Project Deliverable

Project Number:	Project Acronym:	Project Title:
305532	Health-2-Market	From Health Research to Market - Advanced Services and Training Actions for the IPR Management and Business Exploitation of the EU-funded Research results in Health/life sciences

Instrument:	Thematic Priority
COORDINATION AND SUPPORT ACTION	HEALTH

Title

D2.4 SET OF CASE STUDIES

Contractual Delivery Date:	Actual Delivery Date:
Month 36	Month 36

Start date of project:	Duration:
September, 1st 2012	36 months

Organisation name of lead contractor for this deliverable: inno TSD	Document version: v2.0

Dissemination level (Project co-funded by the European Commission within the Seventh Framework Programme)

PU	Public	**X**
PP	Restricted to other programme participants (including the Commission)	
RE	Restricted to a group defined by the consortium (including the Commission)	
CO	Confidential, only for members of the consortium (including the Commission)	

"Health-2-Market has received funding from the European Union's Seventh Programme for research, technological development and demonstration under grant agreement No 305532"

Abstract: This document describes the Health-2-Market case studies development process, including the concept, the types of case studies developed and their use. It also provides all the set of case studies which were deployed during the project.

19 case studies were developed, used in seminars and/or academies and made available on the project's e-learning platform. Furthermore, 9 were transformed into interactive material for the e-learning platform.

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1. Introduction

Health-2-Market (H2M) aimed at providing support to researchers in the field of Health/life sciences in order to boost their competences in the commercialization of research results. One of the main project activities consisted of providing training services in the form of week-long academies on European level, 1-2 days topic specific seminars on regional level and e-learning modules to European Health/life sciences researchers.

The Health-2-Market training materials included, among others, a set of case studies to be deployed in both the face-to-face trainings (academies and seminars) and e-learning. Case studies were proven to be an effective training method that permits to offer, to training participants, an interactive learning based on real-life case examples.

The case studies development was based on outcomes from previous project activity, mainly the Training Needs Analysis and underlying studies, which gathered the needs, the demand and the preferences of health/life science researchers regarding the training offer. This included also information regarding the training concept, material and teaching methods which were taken into consideration for the case studies development.

This document provides information regarding the following aspects related to the case studies:

- **Information regarding the development of case studies**: sources of information, identification of existing material, structure (types) of cases to be developed, timeline for development;
- **Information related to the use of case studies**: efficient use in the H2M training offer (based on needs expressed), online access to material through e-learning and deployment during and beyond the project life time;
- **Indication on the timeline for development and deployment of the case studies**.
- **Provision of the case studies, either available as open source documents or developed by the Health-2-Market project team until this stage**.

1.1. Objectives

A case study is a teaching tool that shows the application of “theoretical” information to real situations. As cases are used to promote deeper understanding, the best cases require trainees to problem-solve and apply disciplinary material.

The aim of the Health-2-Market case studies as training material was to support “theoretical” teaching of specific training topics through real-life case examples that training participants can easily identify with. Both “best case” and “worst case” examples can be useful – the objective was to show different steps of commercialization activities (market analysis, business plan development, IPR issues, business creation, etc.) in the context of real examples.

One of the goals of a case study is to give users an opportunity to see how the guidelines could be applied in the context of a real life, and how it intersects with issues of mentoring, authorship and technical training; a secondary goal is to reinforce the understanding of the real examples which are helpful. The case study also aims to help users identify various temptations and pressures that make misconduct more likely, and to reflect on ways to avoid those temptations.

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2. Development of case studies

2.1. Sources of case information/material

The case studies are composed of existing cases on the one hand and cases developed by the H2M project team on the other hand.

- **Existing case studies**: Several Business Schools (and eventually other partners) of the project already possess complementary case studies, guides and relevant training material that were adapted and utilized for the scopes of the training programme. Indeed, such case studies, even if not necessarily related to the health field can illustrate difficulties that are also relevant to the Health-2-market training topics: entrepreneurship, marketing, intellectual property rights, etc.
  The partners investigated on the IPR issues related to the utilisation of existing material and adapted the material on time for the use in the respective face-to-face trainings (e.g. UGOT academy and IE seminars).

- **Open source case studies**: Renowned institutions, such as Harvard or MIT, have developed an intensive database of case studies, available through internet. Some of this material can be freely downloaded (open source), whereas some of it is protected and requires payment in order to gain access. In order to ensure sustainable use of training material, even beyond the H2M project lifetime, the project team decided not to use case studies which incur fees. However, providing information on open source case studies seemed appropriate to the training objectives, as well as the participants' needs, in order to complete other material. Relevant open source case material were detected which can be made available for the H2M trainings (face-to-face trainings if needed, otherwise in e-learning). Sources are:
  https://mitsloan.mit.edu/LearningEdge/entrepreneurship/Pages/default.aspx; All open source case studies provided have been screened with regard to their quality and coherency concerning the H2M training topics. A summary of the selected material, as well as an overview of their relevance towards each of the seminar or academy topics is provided in the Annexes.

- **Case studies developed under Health-2-Market**: The majority of the case studies designated to H2M trainings (face-to-face or e-learning) were developed by the project team with specific focus to the training topics. The source for these cases is twofold:
  - Existing case information: Some partners had access to data of health/life sciences companies that can be transformed into case studies, in particular information on business plans and company creation (e.g. engage, UGOT, APRE).
  - Case information gathered through project activity and developed as a case study: several project activities were the source to gather information on real-life cases.
    - Academies' and seminars' participants with relevant experience were asked to provide information on their business which were then translated into case studies. According to the extent of information that were gathered, these case studies were extensive or small case examples.
    - In addition, the same kind of information was gathered through the H2M support in the Advanced Services project activity.

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- The Venture Academy on "Entrepreneurship and Business Planning in Health/Life Sciences", in addition to "standard" case studies, brought interesting outcomes that provided as case collection guidebook (see the chapter on case structures for more information on this type of case study material). It is composed of a sample of pitches given through presentations of training participants in front of a jury, including venture capitalists.

2.2. Case structures

In order to offer the best possible training methods and material to the training participants, it was decided to develop different types of "case studies".

Indeed, through the Training Needs Analysis (including feedback through qualitative interviews and round table discussions with concerned target groups), we learned that researchers would highly prefer to learn business aspects through work on their own cases, instead of study of other (external) cases. The reason is of course that they have much better and more detailed insights into their own case context and potential problems which allows them to apply theoretical learning aspects in a more effective and concrete way. The learning effect is also estimated to be higher. Also, they have expressed preference for "praxis-oriented" training material and have shown interest to learn from peers through concrete real-life examples.

The H2M project team has as thus decided to follow the expressed needs and recommendations which allowed adapting the use of the case material to the different training channels the H2M project offers. Previously planned (long) MBA case studies with teaching notes did not seem to correspond to the participants' needs: their reading and discussions would take too much time during the trainings and the participants obviously would prefer to spend such time rather on work on their own cases. Also, for e-learning, long and theoretical case studies were not adapted.

In order to adapt to the expressed needs and interests of the potential participants and to best suit to the training offer, the Health-2-Market project team decided to prepare the case material in several distinctive formats which could then be used for different purposes. As deployment was privileged through the e-learning channel, no teaching notes were prepared, as this would be counterproductive to the learning objectives. However, cases end with some open "thinking further questions" which allow reflexion through users (see case structure in the Annexes).

The structure of the case material is as follows:

✓ **"Pedagogical Case studies"**. This method emphasizes trainees' participation and leadership rather than professor-led lecture and discussion. In a "pedagogical case study", students analyze a business scenario, consider the possible options for action and attempt to recommend the best solution or plan. Besides extensive information on the context of the real-life case, the case study also evokes a (or several) question(s) that should be solved by the training participant, and that was discussed during the course or could lead to further reflection. This methodology prepares participants for actual situations they may encounter in their business environment, teaching them to make measured decisions, consider a problem from all angles, and work effectively with their peers as leaders and teammates.

The pedagogical case studies (length: about 10 pages) are adapted to face-to-face trainings (where useful) and were in particular be made available through e-learning.

✓ **"Mini case studies".** Caselets, or mini cases, are increasingly used as teaching aids in various executive education programmes. Being brief and focused on a specific topic, a "mini case study" is a useful supplement to a lecture. A mini case study is a shorter version of a case study, generally two to three pages in length. Mini case studies are similar to case studies in that they may either describe a sequence of events or put forth an issue or problem that requires decision making. The basic objective of a mini case study is to allow the learner to apply ideas and insights from theory to the real-life issues and problems contained in the caselet. This helps the participant obtain a deeper understanding of all the relevant factors in a particular problem situation as well as gain insights into the finer nuances of a topic in a particular field of management.

The mini case studies (length: about 3 pages) are adapted to face-to-face trainings (where useful) and e-learning.

✓ **"Case collection guidebooks".** Case collection guidebooks are a collection of contributions on a specific topic. In the Health-2-Market training concept which has been developed based on the Training Needs Analysis's results and the experience of involved learning institutions (Business Schools project partners), the outcomes of one academy was used in order to develop such guidebook. Indeed, it contains the training participants' real-life cases on the academies' thematic, such as the Business Plan pitches (from the "Entrepreneurship and Business Planning in Health/life sciences" academies). Sharing such information with other Health/life sciences researchers is very valuable, as these examples stem from peers who face similar situations and problems and can thus provide high learning value. Due to IPR questions, training participants will be asked to agree on the publication of their case information directly through the training registration interface.

The Case collection guidebooks stem from an academy and can be used for other face-to-face trainings (where useful) and are adapted as a reference for e-learning.

2.3. Steps of development

The Health-2-Market case study material was developed on the basis of a detailed concept note, prepared during the second project semester (spring/summer 2013). This concept took into account the outcomes from the Training Needs Analysis and explicit demand/preferences of health/life sciences researchers (gathered through interviews, round table discussions, etc.).

The concept note was developed after multiple discussions with most partners involved in the task, notably those with teaching experience and in charge of trainings and/or consulting expertise, in order to adjust the case material to the concrete training concept and learning objectives.

As for the case studies developed by the Health-2-market project team, their preparation went through a quality validation process: one partner (A) prepared a draft which was revised by another partner (B) regarding completeness, logic and format criteria. After rework, a second draft was sent to the Business School (C) in charge of the training the case study addresses. Indeed, it had to be sure the case study addressed the training topic in a suitable and best possible way. Partner A finalised the case study taking into account comments and potentially needed adjustments.

After finalisation of a case study text and formatting, the case study was uploaded on the Health-2-Market project website and e-learning tool. Here, it was "classed" to the seminar or academy it suited, so training participants had access to the material via their e-learning login.

The case study material is accessible for project partners through the internal project working platform (shared dropbox account).

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3. Use/Deployment of case studies

Case studies, as part of the training teaching material, were used in face-to-face trainings, as well as the e-learning. The use of the different case studies material was as follows:

3.1. In face-to-face trainings

In Academies:

Pedagogical case studies and mini case studies were deployed in the H2M academies; this was more specifically the case for the IE and UGOT academies, the SKEMA academy being based on the concept of own use cases of the participants. Each academy responsible, together with the concerned trainers, decided on the deployment of case studies and how/to what extent they would be used. The case collection guidebook (updated after each academy) stemmed from SKEMA's academies and was used in other (later organised) academies in order to illustrate outcomes from previous academies (when considered useful by trainers).

In Seminars:

Case studies were deployed in the H2M seminars: especially mini case studies which can be a useful support for seminars, as well as eventually also the Case collection guidebook. Each seminar responsible, together with the concerned trainers, decided on the deployment of case studies and how/to what extent they were used.

3.2. In the e-learning

It became obvious that the best option for providing case study material to interested users was through the H2M e-learning tool: they can be thematically classed and adapted to the training subjects (especially seminar topics) and were available to all registered participants. Participants were free to learn from the different case studies whenever convenient to them, in particular as complementary teaching material to the material received through face-to-face trainings.

All types of case studies were published in the e-learning, including the Case collection guidebook.

Furthermore, 9 case studies were further developed in an interactive version, also made available on the e-learning platform.

3.3. Definition of utilisation

- **Printing and distribution of case study text to participants** and trainers in face-to-face training, where applied (in pdf/non modifiable format)
- **Publication of case study text on the e-learning platform** (in pdf/non modifiable format); for "existing" case studies (e.g. stemming from existing Business Schools material), in order to comply with intellectual property rights, it was not possible to publish them on the e-learning platform. They were used in seminars and academies and are available upon request (Annex 2).
- **Publication of interactive presentations of case study on the e-learning platform;** 9 of the case studies were developed as interactive case studies specifically for the e-learning platform.
- **Publication of case study text in the deliverables**; for one "existing" case study (e.g. stemming from existing Business School material), in order to respond to intellectual property rights, it is not possible to

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include it in the deliverable. It was used in seminars and academies and is available upon request (Annex 2).

- The case studies developed through the project are considered as an intellectual property of the Health-2-Market project (as described in the consortium agreement); use by project partners during and beyond the project is possible for non-commercial utilisation only and under respect of excluded background (e.g. use of material provided by partners but not developed through H2M should be approved by the respective partner first). For case studies developed under H2M and published on the web-platform, their content is protected by the Creative Commons license CC-BY-NC-ND 3.0. The Creative Commons licenses CC-BY-NC-ND 3.0 allows user only to download the works and share them with others as long as they credit the source. Users cannot change the course materials in any way or use them commercially and if used, they have to credit the source.
- Published material remains accessible through the project website beyond the project lifetime
- Use of material developed and/or deployed in the H2M project remains at disposal of all project partners after the H2M project end (under the conditions specified above); this insures the possibility to perform similar activities as sustainable outcome of the project.

4. Timeline of the case study development and provision for trainings

Case study development started on the 6th month of the project. A concept note was developed and the structure and use of case studies was determined with concerned partners through intensive discussions on needs for learning purposes, usefulness and feasibility. The first set of cases was prepared for the first version of this deliverable D2.4 “Set of case studies (v1)”, including the description of case development and use, as well as several case examples.

After the deployment of first trainings and Advanced Services, the project team updated the material through training participants’ cases. In total 19 case studies were developed during the course of the project. This includes “Pedagogical case studies”, “mini case studies” and the “Case collection guidebook”.
The SKEMA academies brought a set of material that was published as Case collection guidebook; it includes contents (Business Plan) from the 9 best cases (participants/ 3 per each SKEMA’s academy).

5. Overview of the case study material provided in the Annexes

The Annexes of this document include the project’s case studies. Indeed, this material is composed of two parts:

- 7 open source case studies
- 19 case studies developed by the Health-2-Market project team until this stage

The open source case studies are accessible in full text via the MIT database, but it seemed appropriate to preselect suitable cases for H2M training topics. These are shown in the “open source case studies overview table”, followed by a short summary on each of these cases (Annex 1).

The case studies developed by the project team are displayed in full text in Annex 2.

6. Conclusion

The case studies development for the Health-to-Market training programme allowed maximum tailoring to the specific needs of the Health/life sciences researchers (participants). This included in particular their demand for reinforced use of their own cases in the H2M training, short and praxis-oriented material and case collection guidebooks in order to learn from peers.

19 case studies were developed and 18 were made available on the e-learning platform, of which 9 were also transformed into interactive case studies. The creation of a repository of training material through the e-learning tool on the training web portal ensures that trainees are able to revisit and revise the concepts' techniques, and tools covered in their training programme, whereas other aspiring entrepreneurs have at their disposal high-quality tools that can aid them in their attempt to commercialize their product or technology. They will remain available for at least 5 years on the e-learning platform insuring sustainability.

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7. ANNEXES

7.1. Annex 1: Open source case studies

7.1.1. Open source case studies: overview

The table below provides an overview of pre-selected open source case studies and their coherence regarding Health-2-Market training topics:

Training topic/ Business Schools	Seminar 1: Introduction to Knowledge-Based Business	Seminar 2: Intellectual Asset Management and Knowledge-Based Business Strategy	Seminar 3: Intellectual Property Management and Open Innovation in Health/Life Sciences	Seminar 4: Essentials of Negotiation Behavior	Seminar 5: Marketing of Innovation & Effectual Entrepreneurship	Seminar 6: Cutting Edge Decision Making Tools for Entrepreneurs	Seminar 7: Marketing of Innovative Products in Health/Life Sciences	Seminar 8: Identifying entrepreneurial opportunities and understanding modes of financing
UGOT	Kibernum, Biocon, PPS.tv		PPS.tv					
SKEMA					Biocon, Conexia, Eli Lilly's Project Resilience, I+MED Laboratories			
IE						PPS.tv, Eli Lilly's Project Resilience	PPS.tv, Conexia, I+MED Laboratories	Biocon, PPS.tv, I+MED Laboratories, Sun Power

Table 1: Open source case studies overview table

7.1.2. Open source case studies: short summary of selected case studies

The following are short summaries of the 7 open source case studies, providing information on their main thematic field, the problematic addressed, source, as well as the link to one or several Health-2-Market training topics.

Kibernum

Key thematic area: IT; global entrepreneurship, strategy; decision making, business model

Problem treated: evaluation of improvement options for a startup firm as it seeks to grow exponentially while changing its business model.

Interesting for H2M academy / seminar topic:

- Seminar 1: Introduction to Knowledge-Based Business (Ref: KBB) (by UGOT);
- Seminar 2: Intellectual Asset Management and Knowledge-Based Business Strategy (Ref: IAM) (by UGOT);
- Seminar 6: Cutting Edge Decision Making Tools for Entrepreneurs (Ref: DM) (by IE);
- Academy 1: Intellectual Property, Ethics, and the Utilization of Academic Research in health/life sciences (UGOT).

Summary

Kibernum was founded in 1991 when Mario Araya, Sergio Concha, and two other investors decided to develop an ERP system. In February 1993, the founders decided to change their business model to one that provided IT staffing services.

In early 2008, in response to new labor laws and increasingly complex staffing requests from clients, Chile-based Kibernum was in the process of evolving from an IT professional staffing firm to a full-fledged software factory. A team of MIT Sloan students was helping the company develop its new business plan. But with only three weeks on-site, the team needed to decide where it should focus its efforts in order to be a truly effective partner.

To succeed on this front, a couple of variables had to be considered. For one, no one on the G-Lab team spoke Spanish very well, and except for the CEO, the vast majority of Kibernum's employees understood little or no English. Communication would be a challenge. In addition, Kibernum was currently working with an outside consultant on some elements of organizational design for the software factory, and another MBA student team from the Kellogg School of Management was scheduled to arrive in March to assist with the company's ongoing sales and marketing efforts.

Source

Authors: Benjamin Black, Ajit Dansingani and Dong Min Kim

Website: https://mitsloan.mit.edu/LearningEdge/strategy/Kibernum/Pages/default.aspx

Biocon India Group

Key thematic area: medicine; global entrepreneurship, strategy; business planning

Problem treated: illustration of the Indian pharmaceutical and intellectual property environment; and the trade-offs faced by startups expanding into new sectors.

Interesting for H2M academy / seminar topic:

- Seminar 2: Intellectual Asset Management and Knowledge-Based Business Strategy (Ref: IAM) (by UGOT);
- Seminar 5: Marketing of Innovation & Effectual Entrepreneurship (Ref: ISMA) (by SKEMA);
- Seminar 6: Cutting Edge Decision Making Tools for Entrepreneurs (Ref: DM) (by IE);
- Seminar 8: Identifying entrepreneurial opportunities and understanding modes of financing (Ref: EOF) (by IE).

Summary

Biocon India was established in 1978 by Kiran Mazumdar-Shaw, the Managing Director, as a joint venture with Biocon Ireland to bulk manufacture enzymes. In 1989, Biocon Ireland was acquired by Unilever. As part of Unilever, Biocon began producing enzymes for Unilever's food business. In 1998, Biocon India bought out Unilever's share in the company and became an independent, privately owned entity.

Emboldened by the strength of Biocon India's culture and its two subsidiaries, Mazumdar-Shaw and her senior team developed a vision: to become a fully integrated drug discovery and development company. The Biocon India Group already possessed or was developing the capabilities for conducting research and development, manufacturing pharmaceuticals, and marketing its products. Besides animal testing, Biocon's missing link in the traditional pharmaceutical value chain was the ability to run clinical trials

As a result, Biocon India Group formed a new subsidiary, Clinigene, to provide services in clinical trials. Concerns abound, however, as to whether this new subsidiary could prove to be a distraction or worse to this enzyme and pharmaceutical manufacturer.

Source

Authors: Archana Kalegaonkar, Jonathan Lehrich and Richard M. Locke
Website: https://mitsloan.mit.edu/LearningEdge/strategy/Biocon/Pages/default.aspx

PPS.tv and China's Online Video Distribution Market

Key thematic area: IT/video market; global entrepreneurship, strategy

Problem treated: exploration of the classic growth choice for entrepreneurs in developing markets: a domestic market that is large and immature, an international market that will require fundamental changes to the business model, or a technology market that could threaten intellectual property rights.

Interesting for H2M academy / seminar topic:

- Seminar 2: Intellectual Asset Management and Knowledge-Based Business Strategy (Ref: IAM) (by UGOT);
- Seminar 3: Intellectual Property Management and Open Innovation in Health/Life Sciences (Ref: IPM) (by UGOT);
- Seminar 6: Cutting Edge Decision Making Tools for Entrepreneurs (Ref: DM) (by IE);
- Seminar 7: Marketing of Innovative Products in Health/Life Sciences (R: MIP) (by IE);
- Seminar 8: Identifying entrepreneurial opportunities and understanding modes of financing (Ref: EOF) (by IE).

Summary

Based in Shanghai, China, PPS.tv provided Chinese Internet consumers with professionally-produced online video content in the form of movies, TV shows, and sports, for free. The company's founders decided to focus on this segment to avoid the crowded (100+ companies in China alone) user-generated content space, where content was uploaded by individual users.

By January 2008, PPS.tv had reached a pivotal stage of its expansion, and was under significant pressure to deliver both profitability and a larger user base. In order to do so, the small start-up had to decide which strategic direction made the most sense.

The first option was to focus on the small and relatively immature online advertising market in China, dominated by much larger and more established portal sites. Another option was to attempt to internationalize PPS' service offerings in the United States and other countries where more money was available, notwithstanding the company's lack of expertise, customers, or extensive content provider relationships. Third, the firm could shift its focus to its technical strong suit and patent the company's highly innovative streaming protocol technology, licensing its technology to leading content distributors abroad.

The PPS founders, along with Qiming, had to decide which strategy, or combination of strategies, made the most sense for PPS. PPS needed to raise its next round of financing in the coming months to respond to potential investors' questions.

Source

Authors: Aaron Rackoff, Kevin Anthony, Roger Erdong Chen and Wai Yan Wong
Website: https://mitsloan.mit.edu/LearningEdge/strategy/PPStv/Pages/default.aspx

Eli Lilly's Project Resilience

Key thematic area: pharmaceuticals; strategy; decision making, business model

Problem treated: demonstration of issues inherent in "making strategy" in terms of very significant environmental turbulence; introduction to participants the strengths and weaknesses of scenario planning as a tool; and enable them to practice making strategic choices.

Interesting for H2M academy / seminar topic:

- Seminar 5: Marketing of Innovation & Effectual Entrepreneurship (Ref: ISMA) (by SKEMA);
- Seminar 6: Cutting Edge Decision Making Tools for Entrepreneurs (Ref: DM) (by IE).

Summary

Empowering Lives International (ELI), which by 2009 had operations in four African countries including Kenya, was the brainchild of American Christian missionary Don Rogers. Rogers founded ELI in 1994 not only to minister to Africans, but also to address the physical suffering faced by the communities in which he ministered. In 2009, ELI continued this "holistic work" in "spreading both the Word of God and practical ideas for breaking the cycle of poverty at the village level." ELI was headquartered in Los Angeles, where a largely American staff raised funds for global operations. In Kipkaren and other sites in Africa, operations were run by nationals working with Americans on long-term or permanent missions.

In 2004, Eli Lilly was considering how to alter its business model in order to address the changing face of the pharmaceutical industry brought on by new science and unsustainable cost structures.

Source

Authors: Rebecca M. Henderson

Website: https://mitsloan.mit.edu/LearningEdge/strategy/Resilience/Pages/default.aspx

Conexia: Entering the U.S. Market

Key thematic area: healthcare; global entrepreneurship, strategy; new market

Problem treated: recognition of how power in the value chain can affect the characteristics and barriers to market entry; and understanding the options faced by startups entering new competitive environments.

Interesting for H2M academy / seminar topic:

- Seminar 5: Marketing of Innovation & Effectual Entrepreneurship (Ref: ISMA) (by SKEMA);
- Seminar 7: Marketing of Innovative Products in Health/Life Sciences (Ref: MIP) (by IE);
- Seminar 8: Identifying entrepreneurial opportunities and understanding modes of financing (Ref: EOF) (by IE).

Summary

Since 2003, Buenos Aires-based Conexia had grown successfully by providing electronic billing and reconciliation services to the Argentinean healthcare market. In 2010, the company was preparing to enter the U.S. market, where healthcare, insurance, and payment providers were in rapid flux.

With the G-Lab findings in hand, Navas pondered the various U.S. market entry strategies the team presented:
A. Enter as planned with a full RTA solution
B. Establish credibility through simpler products
C. Establish credibility through services
D. Partner with an existing U.S. IT services company
E. Focus on other Latin American countries while waiting for the U.S. market to mature

Conexia needed to enter the U.S. market if it was to be transformed into the large, public, multinational company Navas, the CEO, had set his mind on creating. Even without the U.S. market, Conexia as profitable and growing. Navas wondered, “Should we leave well enough alone?”

Source
Authors: Katie Barrett, Anand Mohanrangan, Teru Tanaka and Yipeng Zhao
Website: https://mitsloan.mit.edu/LearningEdge/entrepreneurship/Conexia/Pages/default.aspx

I+MED Laboratories: Expanding Beyond Thailand

Key thematic area: biotechnology; global entrepreneurship, strategy; new market, innovative product

Problem treated: exploration of the challenges startups encounter as they go global, particularly when the firm is small, the product novel, and the market vast and complex.

Interesting for H2M academy / seminar topic:

- Seminar 5: Marketing of Innovation & Effectual Entrepreneurship (Ref: ISMA) (by SKEMA);
- Seminar 7: Marketing of Innovative Products in Health/Life Sciences (Ref: MIP) (by IE);
- Seminar 8: Identifying entrepreneurial opportunities and understanding modes of financing (Ref: EOF) (by IE).

Summary

Founded in 2001 in Bangkok, Thailand, i+MED had originally focused on rapid test manufacturing, producing commoditized products such as pregnancy and drug tests. Since the mid-2000s, however, i+MED had made substantial strides in growing its business, expanding into the medical supplies industry and launching two new products, with a handful of new innovations in the pipeline that were scheduled for commercialization in late 2009. Going forward, i+MED hoped to expand its innovative product offerings to become the missing link between Thailand's national research and development laboratories and the global biotechnology markets.

Unfortunately, i+MED had had little experience operating in markets outside of Thailand. To penetrate a new geographic market, the firm would need access to local expertise and connections with prospective suppliers, customers, and distributors, and could not expect to rely on its existing Thailand-based marketing and sales forces.

The task required a significant commitment of finances and human resources. India seemed like a promising market, but one in which i+MED had no experience. But though India might not be the best market to launch CD4 SELECT and i+MED globally, it wasn't clear that sub-Saharan Africa was more promising. Perhaps i+MED should launch AlphaTHAL internationally first, or focus on its proven products, or begin with developed countries, or even wait and see how its commercialization pipeline turned out. i+MED had thrived by seizing every opportunity. Now Khun Komkrit wondered whether he had not too few opportunities, but too many.

Source

Authors: Jennifer Jeng, Laura Rieber, Gautam Shewakramani and Irina Starikova
Website: https://mitsloan.mit.edu/LearningEdge/strategy/IMEDLaboratories/Pages/default.aspx

SunPower: Focused on the Future of Solar Power

Key thematic area: sustainability; technology strategy, strategy; competitive advantage

Problem treated: the focus on the role of the learning curve in building competitive advantage, asking how SunPower can compete against rivals that are many times larger in an industry that is almost certainly subject to significant learning effects; and introduction to participants the challenges inherent in investing in alternative energy.

Interesting for H2M academy / seminar topic:

- Seminar 2: Intellectual Asset Management and Knowledge-Based Business Strategy (Ref: IAM) (By UGOT).

Summary

SunPower was founded in 1987 by Dr Richard Swanson, a professor of electrical engineering at Stanford University. In September 2006, SunPower invested in a joint venture with a Chinese company to manufacture ingots and in December 2006 it acquired PowerLight, a California-based installer that specialized in large installations over 100 kWp, for $335 million. SunPower's competition consisted of 15-20 established cell manufacturers, a handful of silicon-based cell manufacturing upstarts, and a number of thin film solar companies offering potentially disruptive technologies.

In late 2006, SunPower designed, manufactured, and delivered the most efficient solar cells in the world. However, in light of the varied and continually evolving competitive scenario that SunPower had become a part of, company CEO Tom Werner was aware that the road ahead would likely be a challenging one. The key was choosing and formulating the right strategy. At a time when many experts believed solar technology would grow quickly, SunPower needed to decide whether to maintain market share through a strategy of differentiated technology or pricing.

Source

Authors: Joel Conkling, Rebecca M. Henderson and Scott Roberts
Website: https://mitsloan.mit.edu/LearningEdge/sustainability/SunPower/Pages/default.aspx

7.2. Annex 2: Case studies developed by the Health-2-Market project team and pre-existing case studies

The following are case studies, developed by the Health-2-Market project team, following the methodology and quality validation outlined in previous chapters. The case studies are:

1. **"Stentos, identifying opportunities and modes of financing for future development"**, relevant to seminar topic "Identifying entrepreneurial opportunities and understanding modes of financing in the field of health/life sciences".

2. **"GENESE, establishing a marketing strategy for an innovative product"**, relevant to seminar topic "Marketing of innovative products in Health/Life sciences".

3. **"Life Genetics, secondary use of Compounds for the treatment of ageing-related Neuro-Diseases"**, relevant to seminar topic "Intellectual Property Management and Open Innovation in Health/Life Sciences".

4. **"Elchemica, marketing of a novel technology"**, relevant to seminar topic "Marketing of Innovative Products in Health / Life Sciences".

5. **"AHP: Analitic Hierarchy Process"**, relevant to seminar topic "Cutting-edge decision making tools for entrepreneurs".

6. **"Repositioning of an approved drug as a treatment for an orphan disease"**, relevant to seminar topic "Intellectual Property Management and Open Innovation in Health/Life Sciences".

7. **"Terracycle (A): Getting the Cycle Going?"**, mini case study for seminars, relevant to seminars "Marketing of Innovation and Effectual Entrepreneurship" & "Identifying Entrepreneurial Opportunities and Understanding Modes of Financing".

8. **"Understanding Decision Making to Optimize Pricing of a Nutrition Clinic"**, mini case study for seminars, relevant to seminar topic "Marketing of innovative products in Health/Life sciences.
   Due to IPR restrictions, inspection copy available upon request from Professor Dilney Goncalves

9. **"Kinimage: Preparing to license out a novel medical imaging technology"**, relevant to seminars topic "Intellectual Asset Management and Knowledge-Based Business Strategy" & "Essentials of Negotiation Behavior".

10. **"VIDAVO, Matching financing modes with business development stages"**, relevant to seminar topic "Identifying entrepreneurial opportunities and understanding modes of financing".

11. **"Utilizing early stage research results through intellectual asset portfolio management"**, relevant to seminar topic "Intellectual Asset Management and Knowledge-Based Business Strategy".

12. **"Navigating ownership and rights claims in early stage research utilization, the case of Prosound"**, relevant to seminar topic "Intellectual Asset Management and Knowledge-Based Business Strategy"

"Health-2-Market has received funding from the European Union's Seventh Programme for research, technological development and demonstration under grant agreement No 305532"

13. **"Evaluating and drafting term sheets for biotechnology platform technologies, the case of Nemtox"**, relevant to seminar topic "Marketing of Innovative Products in Health / Life Sciences "

14. **"Patent prosecution and claim coverage, aligning patent strategy with corporate goals"**, relevant to seminar topic "Intellectual Asset Management and the utilization of Academic Research"

15. **"Alterniity, Marketing an innovative solution for Alzheimer's disease"**, relevant to seminar topic "Marketing of Innovation & Effectual Entrepreneurship"

16. **"Utilising market research to enhance decision making"**, relevant to seminar topic **"**Marketing of Innovative Products in Health / Life Sciences"

17-19. **"SKEMA's collection guidebook"** (regroups the 3 guidebooks edited after each academy into 1): Entrepreneurship and business planning.

« Stentos*, identifying opportunities and modes of financing for future development »

Case study in the framework of the Health-2-Market project seminar
"Identifying entrepreneurial opportunities and understanding modes of financing" in the field of health/life sciences

*all names of actors have been changed for publication

Author: Inno TSD

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1. Key questions addressed by the case

Stentos is a company founded six years ago in the form of a limited liability company (GmbH) by two doctors in the eastern part of Germany. The company's aim is to develop biodegradable stents for urinary tract diseases. The product development (in an early stage) has so far generated two product lines which have been patented: ureter stents (between kidneys and bladder) and urethra stents (from the urinary bladder out of the body).

So far, the company has not been operating in a very "business-like" manner, for example there had not been a development plan (business plan based on thorough market research, etc.) and most activity was so far concentrated on R&D and technical improvement on the products, as well as some sales activity.

The first years have brought little development due to the fact that the founders couldn't devote enough time to the company's development and didn't have all necessary capacities. They now wish to see the results of their invention and are aware that this would either mean having to devote more effort themselves or searching external support. The company is as thus confronted with two main issues:

- Both partners being doctors, they do not have the time and capacities to ensure a sustainable management of Stentos GmbH.
- Also, the partners' financial resources are limited and it becomes obvious that they will need to develop a strategy in order to attract further funds and/or investors.

Stentos' founders are consequently currently investigating for potential opportunities of development and looking for modes of financing for their company.
They need to answer to the following questions:

- Which stakeholders have to be taken into account for Stentos GmbH's development – what are their interests and how should they be addressed?
- What can be considered an opportunity for Stentos and why would it be attractive?
- Which modes of financing exist – how can they be exploited and how can investors be attracted?

2. Stents market

2.1. Market size

Stents for the urinary tract are used for the dilation respectively for the support of the urethra in the area of the prostate.
Such stents require a licensing according to the German medical devices regulations or the European law (Medical Device Directive (MDD) or Directive 93/42/EEC). The complexity of the licensing significantly depends on the risk classification of the product, as well as the quality assessment of the known clinical evaluation through the licensing authority (Notified Body, NB). For a relatively new product, independently of the risk level, it can be mandatory to carry out clinical trials if the results of similar trials on the product through animal tests cannot be applied for the utilization on human beings.

The market of stents for the urinary tract is difficult to assess, as relevant institutions such as insurance companies wouldn't communicate the numbers of billed treatments with the use of urethra stents.

However, the numbers of currently used urethra stents not being available, another method of assessment can be to count the number of substitute products.
There are two kinds of products which might be substituted by a stent: transurethral catheters and urine bags. For long lasting diseases for which no stationary treatment with the use of a catheter is necessary, a urine bag is attached to the leg. For both products, an estimate of patients per year is possible (estimates for Germany):

- Number of transurethral catheters of the urinary bladder (BVMed, 2008): 2,3 million pieces / year. Divided by 9-12 changes per year → the number of patients with a transurethral catheter of the urinary bladder is 192,000 patients per year.
- Number of urine bags attached to a leg (BVMed, 2008): 4,2 million per year. Divided by 48 changes per year (expenses for 4 changes per month and patient are generally taken on by the social insurance) → the number of patients having urine bags attached to a leg is 87,500 patients per year.

Another indicator for estimating the number of potential clients for Stentos' products, can be the number of patients at high risk: the standard treatment for such cases is a prolonged catheterisation. The number can be estimated of approximately 300,000 patients in Germany (Statistisches Bundesamt, 2008, source: report N04-01 non-medicinal local treatments for BPH).

Per patient, a mix of both above mentioned methods of calculation on substitutable products would result in the utilisation of two stents per patient per year (use during 3 to 6 months). The sales potential in Germany can thus be estimated between a minimum of 176,000 (number of patients estimated of currently having urine bags 87,500 x 2 stents per year) and a maximum of 600,000 pieces (number of high risk patients x 2 stents) per year.

With regard to different EU countries, the following numbers can be applied:

Country	Market potential for urethra stents
Germany	176,000 – 600,000
France	59,000 – 200,000
Great Britain	55,000 – 188,000
Italy	50,000 – 172,000
Spain	44,000 – 150,000
Sweden	9,000 – 30,000
Czech Republic	7,000 – 24,000
Total:	400,000 – 1,400,000

In addition to the market for stents for the urinary tract, other application markets can be taken into account later on, e.g. for blood vessel stents.

2.2. Market potential and stakeholders

Above indicated numbers of potential patients show the market potential in terms of numbers, on national as well as on European level. The market has been analysed on a general level and the marketability of the product seems to be probable. Indeed, during the first years after its creation, Stentos GmbH has not followed a "planned" development (including market analysis, business plan set up, etc.).

Stentos GmbH's founders concerned with the weak development of their company during the last 6 years, now aim to improve the company's development, so they have also tried to identify the main stakeholders they need to address in order to enhance their company's results:

- Users: patients with urinary tract diseases (and other diseases where stents can be utilized)
- Buyers: established doctors (especially urologists), hospitals
- Regulatory agencies: licensing authorities/notified bodies on national/EU level
- Investors: medical devices manufacturers, research valorisation agencies, business angels, seed capital, risk capital, eventually doctors, etc.
- Influencers: national/EU authorities, media, health industry, health professionals
- Others

The various stakeholders sometimes have divergent interests which need to be analysed. Buyers (mostly doctors) are more interested in the scientific characteristics and product quality, whereas regulatory agencies are more focused on coherence to law and medical standards. Investors seek for cost-effectiveness, return on investment and aim to address a high number of clients in a sustainable manner, whereas influencers can be reluctant to support the product simply because there hasn't been done enough promotion on the product. Despite holding some common interests most stakeholders can have divergent objectives all of which have to be taken into account in the company's strategy, product development and placement, future development plans, etc.

Stentos is currently undertaking a more precise stakeholders analysis, including information on needs, priorities, concerns, etc.
For example, even though the market potential for stents for the urinary tract is relatively high and has been confirmed through qualitative enquiries, investigations among urologists have shown a certain reluctance towards the use of stents in comparison to operations/catheters, likely due to the fact that these are more commonly used interventions. Stentos should combat this through targeted promotion activity.

Two kind of substitutable products for urethra stents exist, namely transurethral catheters and urine bags. In order to address the buyers (doctors) and convince them of the urethra stents' advantages, Stentos GmbH needs to prove the strong assets of its stents. This is particularly important as it is an innovative product: its technological characteristics are superior in comparison to other state of the art products (e.g. bioresorbability), advantages for the patients (e.g. there are fewer complications as there are less operations, etc.), proof of application through clinical trials, etc.

3. Stentos GmbH company

3.1. Profile of the founders and of potential future associates

Stentos GmbH currently doesn't have fully established management, with both lead founders being practising doctors they are therefore not always fully available for the company. Dr Kamm is an established urologist, Dr Müller is chief anaesthesiologist, both are in charge of the product (stent) development. In addition, two other shareholders had been part of the founding team: Tull stock corporation (a company active in the field of pharmaceutical products of urological use) and Mr Schuster (managing director of a company producing and distributing medical devices), however they were involved on a pure financial basis, not partaking in the company's operational work, or strategic decisions so far (all names changed for publication).

The founding team has realized that it will not be able to develop the company on its own and the involved parties have started looking for additional investors and/or managers.

One potential investor being 'InVest', a German company specialized in the exploitation of research through support to start-ups and IPR consulting. InVest's role would be to establish a business development plan, to fix clear and tangible objectifs, to take over management functions and to offer some financial support. The company has analysed Stentos' company profile and already shown interest. InVest would sell its shares or part of it after about 18 months to strategic investors, e.g. companies which are active in the field of medical devices.

In addition, the possibility of the Tull stock corporation and Mr Schuster (who both already possess shares of the Stentos GmbH) strengthening their involvement is being explored.

Mr Schuster being a managing director of a company producing and distributing medical devices (urological devices) has a personal interest in the product and support for the Stentos company (however his company is not involved so far). Such support could be provided in terms of market analysis, assistance in the licensing and production, as well as the sales. Financial support is not very probable despite his initial enthusiasm. It can be assumed that he will not provide additional financial contribution, but rather remain in the company and dilute his shares.

The attitude of the Tull stock corporation has for a long time remained unclear. The partners already discussed the option of excluding Tull from the shareholder base. However, first discussions with Tull's board have shown positive outcomes: in fact, it seems to be very positive about being involved in further development and distribution of the stents and current declarations of intent prove their interest in financial engagement. In exchange, the Tull company expects to have more of a say and to receive a higher amount of Stentos GmbH's shares in the future.

3.2. Stentos capital and financial situation

The company had been founded with an initial capital of 25,000 € of which 10,000€ had been paid by each of the doctors (40% of the shares each), whereas Mr Schuster has only provided 3,000€ and Tull 2,000€.

Now, taking into account the probable entry of InVest, as well as additional investment by the doctors and in particular by Tull, the development idea of Stentos' company management and shares is as follows:

	Old (situation at founding)		Target scenario	TOTAL capital after new contributions per shareholder
	Shares	Cash contribution (at founding)	Targeted new cash contribution	
Dr Kamm	40%	10,000 €	10,000€	20,000€
Dr Müller	40%	10,000 €	10,000€	20,000€
Mr Schuster	12,%	3,000€	-	3,000€
Tull stock corporation	8%	2,000€	50,000€	52,000€
InVest	0%	-	15,000€	15,000€
TOTAL	100%			110,000€

If the target scenario was realized, Dr Kamm and Dr Müller would remain responsible for the product development, Tull would become more involved in strategic decisions and commercialisation and InVest would take over the company management. As thus, InVest would receive a comparatively higher amount of shares comparing to their financial contribution (40% of shares).
The two doctors both already having injected main capital shares when founding the company six years ago (and provided their added value for the product development), they now add about 10,000€ each and their respective shares will decrease with the entry of new partners accordingly.

The necessary legal actions for the changes of the target development scenario are planned to be undertaken shortly.

3.3. Stentos GmbH's technology and its regulations / intellectual property issues

Since Stentos' founding, two product lines have been developed: ureter stents (between kidneys and bladder) and urethra stents (from the urinary bladder out of the body). Their niche in comparison to other products is the fact, that these stents are bioresorbable and can dissolve within the human body. As thus, these stents do not grow into the body tissue and will not create later complications (such as necessity of operation).

The urethra stents are of particular interest: the market relevance is obvious, as it is easier to use (local anaesthesia) and it addresses the common disease pattern of prostate enlargement. Also, these have already been protected with a European patent (the opposition period will terminate in few months). In addition, a recent validation (nomination) for several European states has been required. The patent attorney has undertaken the following nationalisations: France, GB, Germany, Italy, Spain, Sweden, and Czech Republic. This has incurred a cost of about 10 000€ for the first year and maintenance fees for the following year are estimated to be about 2 000€.

3.4. Development objectives of the company

Stentos GmbH has started seeking opportunities in order to enhance the company development. Together with their new potential shareholder InVest, Stentos GmbH's founders have established a planning with target objectives to be achieved within the next 18 months.

The development target is twofold:

a) build up a viable company management and shareholder structure and
b) boost the company and product development in order to access the market with a protected product and lead to first sales.

The list of the objectives that should be achieved within the next 18 months is as follows:

- The shareholders should have mobilised the resources planned in the target scenario (around 85 000€).
- The Stentos GmbH should, after 18-24 months, have a licensing and CE-certification for a bioresorbable urethra stent [nearly finalised].
- The product should be secured through a strong (early) patent on the main European markets [nearly finalised].
- The certification should be achieved together with a renowned Original-Equipment-Manufacturer (OEM) which facilitates the market placement (of the product and company) – discussions are opened.
- Venture Capital (VC) investors and potential buyers (trade sale) should have been addressed at an early stage (12 months after InVest's entry) on the basis of the first clinical trials' results and the exit should be prepared.
- In order to further raise the value of Stentos GmbH, it should then be investigated if it is possible to have the costs of the product covered by health insurances (private, public, others) which would be a huge advantage to push doctors for its use.
- Other product lines should be at an early stage after about 18 months.
- The utilisation of the patent which goes beyond the protection of the core product and can be applied for example as blood vessel stents should be analysed in details as a supplementary source of revenue. A corresponding scenario of development should be elaborated after 18 months.

3.5. Seeking for opportunities of development

In order to achieve the different objectives of development, Stentos needs to investigate on collaboration opportunities, access to finance and marketability of its products.

The licensing of Stentos' products in cooperation with a certified medical product manufacturer who also has a close relationship to a licensing authority (notified body) would be advantageous. For example, Schuster's company could be addressed on this issue. This would be a clear opportunity which could permit to delegate all work on documentation to this manufacturer except for the clinical trials which might have to be conducted for the product in particular. Partners would here be predominantly scientific institutions or urologists in practice in the country.

Through the collaboration of the licensing authority with the current favourite partner in the field of medical product manufacturing, the needs in terms of risk classification, clinical assessment, etc. for the licensing should be clarified at an early stage. Within short time, a concept regarding the clinical assessment could be provided to the licensing authority. It becomes clear that collaboration with such manufacturer would be attractive, as it brings collaboration contacts, facilitates the compliance of procedures and reduces the time to market.

The current financial situation of Stentos doesn't permit further development. This is why discussions with several investors have been started in order to acquire additional funds, e.g. through the entry of InVest. A first rise in capital of about 80,000€ seems a minimum to achieve first objectives of development. However, Stentos still needs to prepare a coherent Business Plan, including financial considerations such as the ROI, in order to have a concrete strategy on how to attract investors.

The final objective of development should be to sell the Stentos company, or company shares, to a supplementary investor, in particular a strategic partner in the field of medical technology (less probable, but also possible: another financial investor).

In order to be attractive for a potential buyer, Stentos needs to acquire "market recognition" for its core product, which means that first sales of the product to medical specialists have to be concluded. The following are prerequisites in order to attract investors:

- Licensing of the stent according to the German medical devices regulations or the European law (Medical Device Directive (MDD) or Directive 93/42/EEC for Europe-wide certification), including the determination of the Original-Equipment-Manufacturer (OEM) and the manufacturing process
- Sufficient patent protection in Europe (core markets)
- Initialisation of distribution relationships (shared use of already existing distribution networks)

The Tull stock corporation has shown signals of interest for a takeover of Stentos at a longer stage. Tull is currently undertaking a strategic extension of its product business and could be interested in further investment.

Revenues stemming from the core product are unlikely within the short timeframe of the first 18 months. After the licensing, however, "friendly sales" should take place in order to prove the marketability of the product/company. Revenues arising from these sales could help to address the risk of financial shortfall.

Furthermore, the option of funding of the licensing process through diverse funding programmes is worth analysis: one could be the German programme Inno-Kom OST which specifically supports market-oriented R&D activities of companies in the eastern German regions. Other options could be the support through the patenting and licensing funds of the region or through project promoters such as the TBI technology consulting institute of the regional ministry which offers funding programmes in the fields of technology & innovation, in particular to SMEs.

Another opportunity of development for Stentos would be its possible application to other markets: the licenses for other applications are different and cannot be prepared by Stentos from the beginning, but a preparatory documentation could raise the stents' value. The patent for the urethra stent for example could also be applied for a blood vessel stent which would permit further product development at a longer stage. The potential for increase in value of Stentos GmbH becomes obvious.

3.6. Future actions and decisions to be taken

A planning has been set up for the activities to conduct within the next 18 months in order to clarify what actions are needed for the company's development:

- Overview on relevant specialised literature (studies, results, obvious risks)
- Differentiation towards the state of the art
- Market analysis in order to check whether the initially targeted market (last 6 years) is coherent and / or there might be other market options
- Finalisation of the selection of and coordination with the Original-Equipment-Manufacturer
- Addressing the licensing authority together with the OEM in order to clarify licensing issues at an early stage

After the discussions with the licensing authority, it has become obvious that it is not possible to determine the procedure of licensing in the run-up. On the one hand the risk classification is not clearly defined (discussions with the licensing authority are underway) and on the other hand the question of clinical data or transferability of data from known studies is open. The licensing authority has proposed Stentos GmbH to prepare a conception of the clinical assessment (overview of known clinical data and risks) which could be the base for the licensing authority to draft the requirements for the licensing process in the run-up. In case of doubt, data would have to be gathered through proper studies.

Initial contact with a manufacturer and through him with the licensing authority has thus-far proved successful: the clinical assessment as well as technical documentation as required

documents for the licensing could be done in collaboration with the OEM. The selected manufacturer will have to document the whole process of manufacturing (pilot series significant for the later production in series), as well as the change management procedures and the quality management.

In parallel to the documentation and launch of the pilot series, material tests, test for biocompatibility and animal experiments will have to be conducted. In general this is done through a subcontractor – InVest has good contacts and could try to handle this with local universities. Discussions have also been undertaken with leading institutions in urology and their expertise with bioresorbable material has become obvious, including for stents.
The main questions to be treated by the tests and documentation are:

- Degradation of the stents: what happens when the stent is surrounded by infected tissue?
- Migration of the stents: stability, positioning
- Mechanical design

The results and the methodology should be documented as they are necessary for the licensing process.

With regard to the clinical trials, its planning should be done in combination with a "coordination centre for clinical trials" (KKS): clinical trials competence centres are directly located at a university's Medical Department and offer services primarily to the academic clinicians of the University Hospital, but also to other interested investigators and the industry. Like a small full-service contract research organisation (CRO), a KKS is staffed to provide support in all stages of a clinical trial, from protocol development to monitoring to data management to statistical analysis and reporting. By professionally supporting investigator-initiated trials (IITs), the KKS helps to improve the quality of IITs in Germany and ensures their conduct in accordance with national and international regulations. Such approach via a KKS is significantly less expensive than going through a contract research organisation. However, a close contact to the KKS institution is essential.
Stentos GmbH should investigate on the issue through university contacts.

As for the execution of the clinical trials, it should be organised at the largest and most international level possible. The costs are not proportionate with the number of patients, but depend on the expenses of the external experts/consultants. The duration depends on the optimum placement in the human body, as well as the aftercare of the patients in order to analyse eventual consequences (risks).

Upon finalisation of the documentations process and proof through the licensing authority, it is important to proceed with the publication of the successful trials or its results respectively in a renowned international journal. This is an essential aspect for the marketing of the stent which definitively impacts the sales (and as thus the value of the company).

Once the first preliminary results of the clinical trials become known, Stentos GmbH should target to contact potential investors and also customers of the medical products field. This can be done through InVest.

4. Lessons learnt and thinking further

The Stentos case example elucidates the questions of opportunity identification and exploitation. Also, the case illustrates different modes of financing which can be exploited for a company creation or development.

Some ideas of thinking further are:

- Identify your specificity and competitive advantage, evaluate opportunities
  In the case example: bioabsorbability, early protected product

- You may have developed several products : identify your core product through analysis of marketability, competitive advantage and maturity and privilege its launch.
  In the case example: urethra stents rather than ureter stents as the market relevance is obvious, it is easier to use (local anaesthesia) and it addresses the common disease pattern of prostate enlargement. Also, it is already protected with an early European patent (nearly finalised).

- Identify relevant institutions / cooperation partners and authorities that should be implicated in your process of development from an early stage in order to:
  - Facilitate access to information
  - Gather additional competences for your company
  - Raise funds
  - Strengthen links that may serve / speed up further development
  - Build up networks (for individual steps / activities of the company development, sales, trials, etc.)

  In the case example: early contact has been sought to persons / organisations with diverse competences (scientific / medical competences, IPR issues, regulations, clinical trials, manufacturing, sales, etc.)

- Protect your product at an early stage to benefit from arising competitive advantages
  In the case example: early patent and nationalisation in different European markets.

- Raise the question on funding modes at an early stage and check for diversified modes in order to select the most appropriate one(s) – from the beginning or later on. Not every mode of funding/investment is beneficial for any product or company type and nor at any stage of development.

- Identify the needs, priorities and concerns of stakeholders and take them into account for your business development

- Once the licensing process is finalized and the product is protected, proceed with marketing activities as soon as possible (e.g. publication of results in a renowned journal) in order to positively impact on the marketability of your product and the raise of value of your company.

« GENESE*, establishing a marketing strategy for an innovative product»

Case study in the framework of the Health-2-Market project seminar
"Marketing of innovative products in Health/Life sciences"

*all names of actors have been changed for publication

Author: Inno TSD

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Tables and figures

1. Key questions addressed by the case

GENESE is a company in the field of Direct-to-Customer (DtC) genetic analyses[1] and online evaluation. A personal genetic analysis can be used to reveal individual traits, predispositions, and characteristics, e.g. it can determine if an individual has a higher risk than the general public of developing a specific disease, it suggest ways to best maintain health, and may indicate which treatment options would work best for the individual if it got certain illnesses. Personal genetic analysis involves identifying which variations of particular genes an individual has. The specific combinations of variations then need to be assessed relative to current knowledge about how they affect individual traits. Indeed, an individual may wish to have a genetic analysis done in order to analyze the probability of getting some sort of disease, based on genetic set ups.

GENESE's activity covers two technological fields:

1. Genetic analyses which are provided through external laboratories on the basis of saliva samples. Per person, about 1 Million different Single Nucleotide Polymorphisms (SNPs)[2] are sequenced through external service providers.
2. GENESE compares the results of the SNP analyses with known associations[3] through state-of-the art algorithms and on the same time identifies new genetic markers[4].

GENESE is in fact a data company with online commercialisation, whereas laboratory analyses are rendered by external partners.

Founded at the end of 2011 in Germany, GENESE is the first German company proposing comprehensive genetic analyses for the final consumer.
GENESE co-founder Mr Red is pleased that "GENESE is the leading provider of genetic DtC analyses outside the USA" and that "GENESE enjoys outstanding confidence by its final consumers thanks to its high technical and legal standards". Indeed, public awareness and

[1] **Genetic analysis** is the overall process of studying and researching in fields of science that involve genetics and molecular biology. There are a number of applications that are developed from this research and these are also considered parts of the process. Basic studies include identification of genes and inherited disorders. Genetic analysis may be done to identify genetic/inherited disorders and also to make a differential diagnosis in certain somatic diseases such as cancer.

[2] Single Nucleotide Polymorphisms (SNPs) are the components of genes. A SNP is composed of one base pair. A human being has around 3 billion of such base pairs of which according to actual knowledge about 3% have a control function. Only these 3% are relevant for GENESE's analyses and GENESE only gives the most important ones of these base pairs, about 1 Million, to external service providers (laboratories) for sequencing.

[3] A **Genetic association** is the occurrence, more often than can be readily explained by chance, of two or more traits in a population of individuals, of which at least one trait is known to be genetic. Studies of genetic association aim to test whether single-locus alleles or genotype frequencies differ between two groups of individuals (usually diseased subjects and healthy controls). Genetic association studies are based on the principle that genotypes can be compared "directly", i.e. with the sequences of the actual genomes.

[4] A **genetic marker** is a gene or DNA sequence with a known location on a chromosome that can be used to identify individuals or species. It can be described as a variation (which may arise due to mutation or alteration in the genomic loci) that can be observed. A genetic marker may be a short DNA sequence, such as a sequence surrounding a single base-pair change (single nucleotide polymorphism, SNP), or a long one, like minisatellites. Genetic markers can be used to study the relationship between an inherited disease and its genetic cause (for example, a particular mutation of a gene that results in a defective protein).

confidence is of high importance for a company such as GENESE that acts in an innovative field which is in addition confronted with ethic interrogations regarding privacy issues.

The company has undertaken a marketing analysis and now (6 months after the start up creation) it wishes to establish a marketing plan that is adapted to help attaining the goal of double digit million profits after 6 years business. Is the market research so far undertaken sufficient and adapted to GENESE's product and company objectives? What is needed to establish a coherent marketing plan?

2. GENESE company

2.1. Profile of the founders / of the current associates

GENESE has been founded by three stakeholders, namely Mr Red, Mr Wild and the company Ingeneos, represented by Prof Farway (all names changed for publication).

Mr Red has completed law school and has more than 12 years of professional experience in a start-up environment. He has more than 4 years experience as managing director of technology companies and he is part of the managing board of Ingeneos.
As co-founder of GENESE, Mr Red is in charge of the general management and builds an interface towards the medical-technical competency.

Mr Wild holds a degree in Business studies and has promoted in a thematic related to Venture Capital and technology start-ups. He has already previous experience in company foundation and has worked with venture capitalists. He has acquired additional experience as Chief Marketing officer for a successful German online start-up company before and during the market launch.
Mr Wild is co-founder of GENESE and in charge of marketing and business development.

Ingeneos is a company established in northern Germany which has the aim to implement research results regarding the genetic basis of immune response as well as neurodegeneration. For example, Ingeneos develops and markets diagnostic tests and similar services for immune mediated diseases such as multiple sclerosis or rheumatoid arthritis as well as neurodegenerative diseases. One of Ingeneos key team members, in charge of research and member of the company's supervisory board is Prof Farway, professor in human genetics with more than 15 years of experience. Prof Farway disposes of an excellent network and is founder of Ingeneos.

Regarding GENESE, Prof Farway is part of the board of directors on behalf of Ingeneos.
Besides this, GENESE is also linked to Ingeneos through incubation in their premises. Indeed, Ingeneos plays also a role as provider of ideas and scientific know-how (genetics, genetic analysis, algorithms, etc.). In addition, Ingeneos has participated in the start-up funding (pre-preseed-phase), provides office and back office services during the preseed and seed-phases, as well as networking opportunities and can take over employees during the preseed

phase, in order to use available public financing opportunities. Also, Ingeneos helps GENESE to develop and establish a quality management system.

The Advisory Board of GENESE is composed of a committee of experts in the fields of genetics, medical specialists, bioinformatics scientists, online-marketing experts, privacy protection specialists, as well as an ethics committee.

2.2. GENESE's business model

GENESE's business model is oriented towards 4 types of services/activities:

- Individual genetic analyses, ordered by private customers (major part of business)
- Scientific R&D cooperation with universities / research institutions
- Commissioned studies, ordered by company clients
- Licensing of genetic markers

The individual genetic analyses are GENESE's main field of activity, even though the others support it: scientific cooperation provides the necessary access to new scientific outcomes, as well as public funding, whereas commissioned studies and the licensing of genetic markers are secondary sources of income with direct links to industry.

Individual genetic analyses are the baseline business of GENESE; clients are final consumers. The laboratory analysis is undertaken by external laboratories (partners) and GENESE provides the individual results to the client via its online portal. The results are based on publicly available studies; the diagnostic values are not patentable and as thus cannot be protected. At the current stage, 200,000 genetic studies have been published. GENESE is currently establishing its proper evaluation algorithms (the competence is available through its stakeholder Ingeneos (see profile of founders) and will be established at GENESE within few time). The concept is that the "medical activity" (the genetic analysis on the basis of saliva samples) is provided through external laboratories whereas GENESE compares the results of the SNP analyses with known associations through algorithms, identifies new genetic markers and provides the results to the client through online commercialisation services. Clients can subscribe, at their expense, to a data update afterwards.

GENESE's **R&D cooperation** with researchers is based on access to funding. Indeed, such cooperation schemes permit benefiting from public funding (e.g. through open call schemes from national ministries) which results in the development of new or better products and the acquisition of new clients. For example, GENESE cooperates with the following researchers/universities, collaboration mostly being so far based on personal networks:

- Collaboration with a renowned professor, working at the Ingeneos company in the field of genetic markers for Alzheimer; a cohort of > 1,000 patients is available; the application for funding through a national ministry has been submitted
- Collaboration with a professor active in the field of genetic foundations regarding EEG data; funding through a national ministry is possible
- Collaboration with a professor regarding the development of genetic SLE-markers; funding through a regional programme is possible

- Collaboration with a pharmaceutical association; funding through a national ministry is available.

The advantage of such cooperation for the universities/research institutions is indeed GENESE's vision of the market and its technical knowledge regarding the algorithm development.

Commissioned studies are studies ordered by third parties (e.g. pharma companies) which set the concrete study's question/ the problematic to be analysed. Together with that party, GENESE develops a questionnaire which GENESE sends to its customers. Through this study analysis, GENESE "searches" for possible genetic associations. Third parties can for example come from the pharmaceuticals, cosmetic or agro alimentary field. Companies indeed may wish to analyse certain genetic associations which can for example be a negative predisposition for specific drugs, trigger an allergic reaction, etc. GENESE's role in this activity is its access to data from potential customers who are generally positive towards genetic analysis through the fact that they had done individual analyses before (the client data base is set up through the individual genetic analyses mainly) and may respond to such questionnaire with less hesitation as if the third party (company) had done such inquiry on its own.

Licensing of genetic markers can for example aim to

- Prognosis, prevention or therapy of diseases
- Prognosis or interaction for the metabolism
- Improvement of cosmetics, etc.

Those genetic markers are patented and licensed, e.g. to industry. License agreements include specifications on up-front payments, milestone payments, licensing based on turnover and sales revenues.

3. GENESE's market approach – focus on the genetic analyses market[5]

GENESE main activity relates to providing genetic analyses. This indeed addresses trends which all stand for markets of more than 1 billion € per year:

- Personalized medicine
- Data profiling
- Private healthcare
- Gene diagnostics and –therapy

Personalized medicine or is a medical model that proposes the customization of healthcare - with medical decisions, practices, and/or products being tailored to the individual patient. The use of genetic information has played a major role in certain aspects of personalized medicine. To distinguish from the sense in which medicine has always been inherently

[5] Due to the fact that genetic analyses are GENESE's main business, the case study here focuses on the market analysis regarding this specific activity.

"personal" to each patient, Personalized Medicine commonly denotes the use of some kind of technology or discovery enabling a level of personalization not previously feasible or practical.

Data profiling is the process of examining the data available in an existing data source (e.g. a database or a file) and collecting statistics and information about that data. The purpose of these statistics may be to find out whether existing data can easily be used for other purposes, improve the ability to search the data through keywords, descriptions, or assigning it to a category, etc. The benefits of data profiling is to improve data quality, shorten the implementation cycle of major projects, and improve understanding of data for the users. GENESE addresses this market through its data analysis tool.

Private healthcare or private medicine is healthcare and medicine provided by entities other than the government. Private healthcare generally has a profit motive, but nevertheless has to follow regulations to ensure that it achieves standards set by the state, predominantly regarding safety, value, and efficiency.

Gene Diagnostics is the testing of DNA for mutations that could lead to a number of diseases and or genetic disorders. A very accurate diagnosis can be made on a wide array of genetic disorders by doing a genetic test or screening. **Gene therapy** is the use of DNA as a pharmaceutical agent to treat disease. It derives its name from the idea that DNA can be used to supplement or alter genes within an individual's cells as a therapy to treat disease. The most common form of gene therapy involves using DNA that encodes a functional, therapeutic gene to replace a mutated gene. Other forms involve directly correcting a mutation, or using DNA that encodes a therapeutic protein drug (rather than a natural human gene) to provide treatment.

3.1. Market potential and size

Individual genetic analyses are ordered by final customers.
In order to identify the market potential of genetic analyses and its consumer target groups, GENESE has undertaken a survey among 366 individuals in order to analyse whether a market for DtC genetic analyses in Germany exists. The population addressed by the survey was chosen to be representative of all ages, gender, educational background, profession, etc., to reflect as good as possible the German population in a small sample.
The results are as follows (the table shows most important figures only, other information is provided in the text below):

	Target Group (tight)	Target Group	Target Group (wide)	Rest (against)	Total
Part in %	26%	53%	81%	19%	100%
% who know DtC genetic tests	41%	34%	33%	26%	32%
% of those interested in doing themselves such test	95%	86%	81%	4%	67%
% of those who showed doubt	42%	49%	51%	90%	59%
% of those who consider relevant that the company providing the tests is established in Germany	73%	73%	72%	59%	70%
% of those interested in subscribing to updates	64%	42%	28%	1%	23%
% of those who seek medical advice	82%	79%	73%	24%	64%
% of those who seek discussion within the community	18%	17%	17%	4%	15%
Average age	36,8	36,8	38,8	38,8	38,8
Minimum age	20	20	20	23	20
Maximum age	74	74	80	72	80
% Male	65%	63%	66%	69%	66%

Table 1: Overview of the Market survey (Germany)

The results of the survey (n=366) are classed according to the target groups which were mainly defined on the criteria of interest in individual genetic analyses and willingness to pay for it; the classification of a wider or tighter target group is based on their consent to pay a certain amount of money on an individual genetic analysis. The main objective of the survey was indeed to be able to establish a price for GENESE's product based on these outcomes. More specifically, the groups are defined as follows:

- Target group (tight) = willingness to pay > 200€ ; interest > 10 out of 16 and no specific reserve (doubts)
- Target group = willingness to pay > 100€; interest > 8 out of 16 and no specific reserve
- Target group (wide) = interest independently of the price
- Rest (against) = do not want to undertake a genetic analysis and are not interested in results

As a conclusion of the whole survey exercise, GENESE has identified its typical client as being between 25 and 49 years old, male, well educated and health-conscious.
More precise criteria include:

- Rational
- Well educated
- Innovative
- Online-affinity
- 25-49 years old
- Health-conscious
- Open towards novelties
- More than average income
- Field : health & fitness, life style

The motivation of this target group for ordering an individual genetic analysis seems mainly based on the following 4 reasons:

- Prevention/health
- Drug compatibility
- Life style
- Curiosity

In the contrary, doubts occur regarding:

- Personal data protection
- Psychic consequences
- Quality of the results

A top-down calculation shows that about 9.4 million Germans can be taken into consideration as target group for GENESE. Out of these, just over 1% would have to ask a genetic analysis to GENESE to permit the company to reach a cohort of 100k.
The table below shows a general overview (without considering all elements of the target group' characteristics):

	Numbers	100K
Germans	82.000.000	0,12%
age 18-60	55.000.000	0,18%
of which online affinity (85%)	46.750.000	0,21%
of which with high school level education (38%)	17.765.000	0,56%
of which showed interest (>100€) (53%)	9.415.450	1,06%

Table 2: Top-down calculation of market potential

3.2. Promotion channels

GENESE has oriented its promotional activity towards online channels, as it sees itself as a "data company with online commercialisation".
Besides its own company website, the following marketing channels are used by GENESE:

- Google AdWords
- Banners
- Press distribution lists
- Newsletters
- Blogs
- Referral Marketing
- Etc.

GENESE has indeed created accounts on the most well known and used community interfaces, such as facebook, twitter, google groups, you tube, etc.[6]

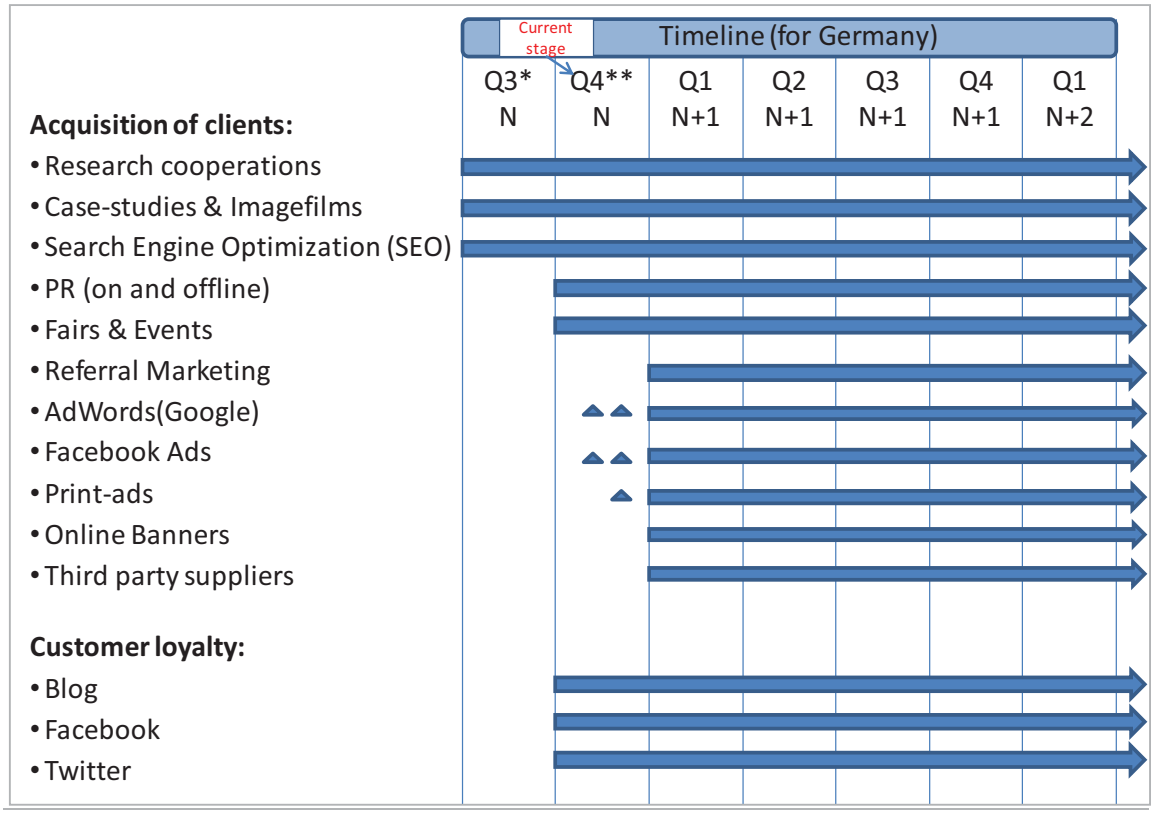
[6] When mentioning company names or brands within this text, the authors do not present any opinion, but only mention tools used by the company.

The most appropriate and beneficial sales channel for the genetic analyses is the online order (DtC) through the end client.

In addition, GENESE uses the following offline marketing channels:

- Cooperation and promotion for example at the following offices/facilities through B2B and B2C activity:
  - Doctors offices
  - Pharmacies
  - Health centres
  - Rehabilitation centres
  - Fitness centres
- Presence in events, e.g. Red Bull sponsored events which can be estimated to attract a public close to GENESE's identified target group
- Participation in conferences
- Publications and articles
- Advertisement (press, radio, TV)
- Partnership in medical studies

The timeline for the marketing activity set up is as follows:



* Test phase
** Initialisation phase
▲ Test campaigns

Figure 1: Timeline for the marketing campaign set up per marketing channel

GENESE has also analysed which promotion channels are the most promising in terms of client acquisition. The results are shown in the table below:

	N+1 (only Germany)				N+2 (only Germany)			
	Clients	Part	Costs	Costs per user	Clients	Parts	Costs	Costs per user
Online	31.805	64%	732.293 €	23 €	41.870	67%	774.341 €	18 €
Google generic (SEO)	7.500	15%	0 €	0 €	9.900	16%	0 €	0 €
AdWords	7.500	15%	360.000 €	48 €	9.900	16%	360.000 €	36 €
Facebooks Ads	900	2%	50.400 €	56 €	1.188	2%	50.400 €	42 €
Banners	375	1%	180.000 €	480 €	495	1%	180.000 €	364 €
Refferal Marketing	4.730	10%	141.893 €	30 €	6.131	10%	183.941 €	30 €
PR (online)	10.800	22%	0 €	0 €	14.256	23%	0 €	0 €
Offline	17.850	36%	620.000 €	35 €	20.490	33%	620.000 €	30 €
PR (Offline)	7.500	15%	0 €	0 €	9.900	16%	0 €	0 €
Advertisement	750	2%	240.000 €	320 €	990	2%	240.000 €	242 €
Fairs & Events	1.200	2%	20.000 €	17 €	1.200	2%	20.000 €	17 €
Third party providers	6.000	12%	360.000 €	60 €	6.000	10%	360.000 e	60 €
Studies	2.400	5%	0 €	0 €	2.400	4%	0 €	0 €
TOTAL	49.655		1.352.293 €	27 €	62.360		1.394.341 €	22 €

Table 3: Promotion channels

3.3. Competitors

Part of the market analysis undertaken by GENESE is a competitor analysis. Indeed, it is important to evaluate who are competitors, in which field they are active and which (geographical) market they cover. The following is an overview of the main prospective competitors identified:

Name	Origin	Number of genetic markers	Comments
23andMe	USA	> 200 different indications	Most important competitor; 220$ for an analysis and update subscription
Navigenics	USA	Probably similar to 23andMe	Together with 23andMe probably the most important competitor, but without the footprint and financing of 23andMe
deCodeMe	Island	47	Nearly 100% of Islands inhabitants are sequenced; had cooperation with Novartis
DNAplus	Munich/ Germany	9 analysis types' packages, about 50 SNPs	Prices per analysis package between 170 and 700€ per package; types of packages are defined according to medical indicators
bio-logis	Frankfurt/ Germany	> 100	Most important German competitor, but still very expensive
humatrix	Frankfurt/ Germany	About 50 SNPs	Price per SNP-analysis 9,90€ (the number of SNPs to be analysed is determined with the client), only individual studies

Table 4: Overview of competitors

Other providers are – among others – Genovia (Leipzig, Germany), Jenagen (Jena, Germany), GenePlanet (Ireland), easyDNA (UK), Cygene Direct (USA), Genome Control (USA), Graceful Earth (USA), Pathway Genomics (USA), TruGenetics (USA), My Genetic Profile (USA). None of them offers a comprehensive service or undertakes, except for 23andMe, active online marketing.

The following overview shows the visibility of the most important competitors through online marketing channels:

	AdWords	Facebook Fans	twitter	Blog	Alexa*-Ranking	YouTube subscription
23andMe	Yes	5.800	11.000	Yes	45.500	1.000
Navigenics	No	400	24.000	Yes	800.000	-
deCodeMe	No	200	700	Yes	1.270.000	50
DNAplus	No	40	-	No	3.945.000	10
bio-logis	Yes	60	-	No	4.025.800	-

*web metrics provider

Table 5: Overview of competitors' visibility

A more detailed analysis on the main competitor's activity has shown:

According to a recent press release, the leading company in the field, 23andMe Inc. (CA, USA) has, within four years...

- Undertaken more than 100.000 analyses for final customers (of which >50% during one year, N-1)
- Analyses initially incurred a fee of 999$, whereas it is only 220$ now (including update subscription 10$/month x 12 months; the initial "test kit" is at 99$)
- 76% of the clients agree to provide their data for research purposes
- 59% of the clients participate in research studies
- 57% of the clients are male
- 47% share or discuss the results with other clients
- 12% have family ties
- The average ago of the clients if 45 years
- 23andMe now has 60 staff members

Investors in 23andMe bring together 30 million USD. They comprise Google Ventures, Johnson & Johnson Dev. Corporation, MPM Capital, The Roche Venture Group, New Enterprise Assoc., etc. The founder of 23andMe is Google CEO's wife Anne Wojcicki.

4. Business development and financial planning

GENESE is currently at an early stage: the business plan has been established, the financial planning and market analysis have been undertaken and the office is set up. First studies have been completed and research collaboration is brought on rails. Now that the market research has been set up, the marketing plan needs to be finalised and concrete genetic analysis activity has to be enhanced. Also, GENESE looks for additional investors (venture capitalists) who should raise the capital, but also bring new networking opportunities and additional experience in the business field.

The following timeline has been set up as a guideline for future business development:

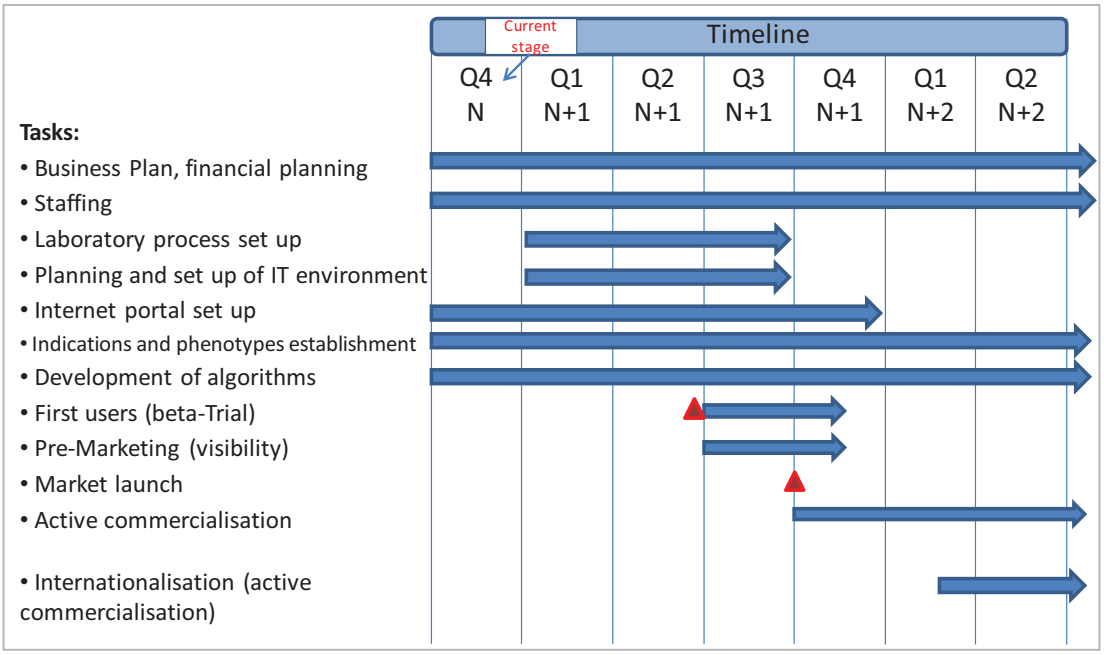


Figure 2: Timeline for business development

The financial planning includes the following figures:

	2012 Plan	2013 Plan	2014 Plan	2015 Plan	2016 Plan	2017 Plan
Revenues						
Turnover analyses and suscriptions	691.500 €	10.876.512 €	28.126.471 €	38.308.925 €	41.727.493 €	43.977.476 €
Studies for third parties	0 €	400.000 €	400.000 €	450.000 €	600.000 €	800.000 €
Licensing for markets (targets) plus licensing incomes	0 €	100.000 €	300.000 €	2.000.000 €	3.500.000 €	5.000.000 €
Other income	0 €	0 €	0 €	0 €	0 €	0 €
Reimbursement of costs through financing of R&D projects	120.000 €	180.000 €	0 €	0 €	0 €	0 €
Sum of turnover	**1.782.287 €**	**12.713.918 €**	**24.925.434 €**	**34.178.321 €**	**36.532.381 €**	**37.943.510 €**
% of raise		1324%	149%	41%	12%	9%
Costs						
Costs of Sales and Delivery Tests	1.116.480 €	11.083.060 €	22.352.950 €	30.825.360 €	32.439.420 €	33.112.031 €
Personnel costs	436.524 €	1.149.408 €	1.662.167 €	2.130.321 €	2.600.157 €	3.014.976 €
Investments office, IT & Labour	14.583 €	91.250 €	117.917 €	120.000 €	175.000 €	242.500 €
Travel costs	9.500 €	40.000 €	56.000 €	85.000 €	115.000 €	155.000 €
Fix costs	133.200 €	155.200 €	236.400 €	260.040 €	286.044 €	314.648 €
Subcontracts	72.000 €	195.000 €	500.000 €	757.600 €	916.760 €	1.104.356 €
Sum of costs	**1.782.287 €**	**12.713.918 €**	**24.925.434 €**	**34.178.321 €**	**36.532.381 €**	**37.943.510 €**
% of raise		613%	96%	37%	7%	4%
Operating profit	**-970.787 €**	**-1.157.406 €**	**3.901.038 €**	**6.580.604 €**	**9.295.111 €**	**11.833.966 €**
% of turnover	-120%	-10%	14%	16%	20%	24%
Interests	31.301 €	191.167 €	71.813 €	0 €	0 €	0 €
Results before taxes	**-1.002.088 €**	**-1.348.572 €**	**3.829.225 €**	**6.580.604 €**	**9.295.111 €**	**11.833.966 €**
% of turnover	-123%	-12%	13%	16%	20%	24%

Table 6: Overview of the financial planning

The break-even is planned to be attaint after the second year, thanks also to low fix costs.

Concretely, turnover, costs, and pre-tax results are visualized in the following figure:

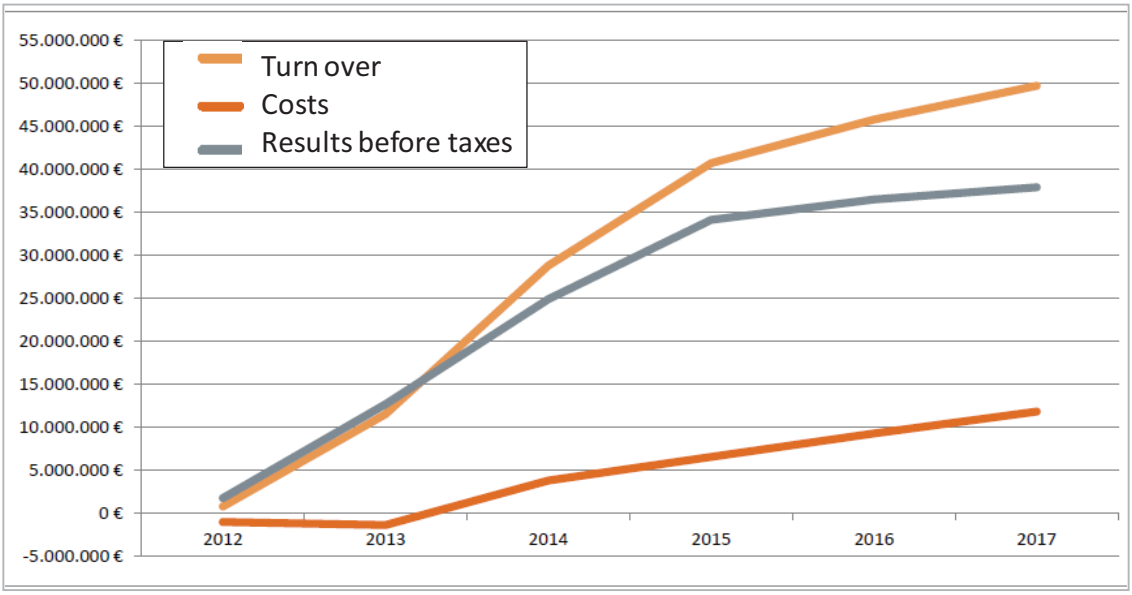


Figure 3: Overview of the estimation of turnover, costs and pre-tax results

GENESE's business planning at a longer stage is a classical one: the exit is planned after 2-6 years of business through sales to a strategic or financial investor. Potential investors could be:

- Competitors which are looking for access to the German/European market (23andMe, Navigenics, etc.)
- Data companies (e.g. yahoo, AOL)
- 2nd stage investors (e.g. intellectual ventures)
- Pharma companies, which wish to have access to personal data (e.g. Novartis, Bayer-Schering)

5. Lessons learnt and thinking further

The GENESE case has outlined the concept of market analysis in a field combining health and new technologies. Indeed, the start up was established following research collaboration activity with the objective to commercialise results and services that can stem from them.

Some ideas of thinking further are:

- How does / can GENESE distinguish its offer and have a competitive advantage?
- What is needed to set up the marketing plan and implementation?
- For the genetic analyses market: make a positioning and provide a marketing mix (product, price, communications, and distribution) decisions or propositions.
- For the other (secondary) potential markets, what other research would you do, and how?

"Life Genetics, secondary use of Compounds for the treatment of ageing-related Neuro-Diseases"

Case study in the framework of the Health-2-Market project seminar

Intellectual Property Management and Open Innovation in Health/Life Sciences

Author: engage AG

Table of contents

1. Introduction

This case study shows an example of a young and financially weak start up developing a new drug suitable for the treatment of ageing-related Neuro-Diseases by implementing a secondary use for a known pharmaceutical compound. A smart IP strategy and cooperations with research institutions and big pharmaceutical companies enable this company to develop a drug without investments from third parties.

The case addresses the participants of the seminar 3: Intellectual Property Management and Open Innovation in Health/Life Sciences (Ref:IPM).

The participants will learn to:

- Identify different types of open innovation and degrees of openness.
- Understand and use intellectual property as a means to govern openness.
- Identify background and foreground intellectual property in collaborative technology development.
- Understand the use of licensing and other contractual mechanisms to manage open innovation for development and commercialization.
- Practice their new understanding on title due diligence, licensing-based business development, and open platform design.

2. Profile of the company

Life-Genetics aims to implement research results regarding the genetic basis of immune response as well as neurodegeneration, i.e. to develop and market pharmaceutical compounds for the treatment of immune mediated diseases such as multiple sclerosis or rheumatoid arthritis as well as neurodegenerative diseases, e. g. Alzheimer's disease and Parkinson's disease.

As the causes for these immune mediated and neurodegenerative diseases have not yet been fully clarified, these diseases are currently not curable and the suitable therapy is to be determined empirically.

The goal is to make predictions on the course of a disease by means of genetic associations, i.e. based on the individual genome of a patient, and thus allow for an individual therapy and medication.

3. Profile of the Management team

Research and development

Prof. Dr. Andy Müller is head of research at Life-Genetics and part of the supervisory board of the company. He studied medical science in Egypt, Finland and in the U.S. (Princeton University). Until December 2008, he was head of a working group at a university institute for Immunology. Subsequently, he was offered a chair at a university. As full professor he is in charge of a group working with dermatology, allergology and venereology. His research focuses on animal models and the transfer of results to humans.

Prof. Dr. Ralf Schneider studied Medicine and Molecular Biology. As a neuropathologist, he is currently leading the Neurodegeneration Research Lab (NRL) at the Center for Mental Diseases that covers basic and translational research on Alzheimer's disease (AD) and other neurodegenerative disorders. Recently, he discovered a new mechanism for sporadic AD. Prof. Schneider is member of the German Center for Neurodegenerative Diseases. He supports Life-Genetics as an external Research Consultant for questioons regarding neurodegenative diseases such as AD and Parkinson's disease.

Management

Erik Seinfeld studied law at various universities and after having completed his studies joined a European management consultancy group. He was in charge of the set-up and management of several subsidiaries before joining the management of another consultancy agency at the beginning of 2006. This agency supports universities and research institutions in the structuring and set-up of research-oriented start-ups in the scope of a defined cooperation. Since 2011, he has been Chairman of the Board of Life-Genetics.

Carlo da Silva, Managing Director at a consultant agency, studied Electrical and Communications Engineering and joined the consulting agency in 1994. Mr. da Silva held several positions in the management of subsidiaries of the group, and his activities mainly focus on the establishing and management of an early-stage technology investment funds. Furthermore, he was responsible for initiating, structuring and managing more than a dozen IP-based high-tech companies. In 2011, he joined the supervisory board of Life-Genetics.

Regulatory Affairs

Stefan Schmidt is a responsible of trainings on Medical Documentary and responsible for Life-Genetics's quality management system according to DIN EN ISO 9001 and DIN EN ISO 13485. Mr. Schmidt additionally supports the research team of Life-Genetics in all questions regarding regulatory affairs, especially documentation and medical approval processes.

4. Collaborative Research and Open innovation as the Fundament of Value Creation (Therapeutical)

Background: Drug Development and Commercialization Strategies

Product repositioning has been used as an alternative to creating novel therapeutics. The main reason for this is the wish to avoid the immense costs and risks associated with drug development from the lab bench to the clinic as a candidate which has already been through (and passed) major tests and trials is used. The following figure highlights the typical risk / cost situation in drug development.

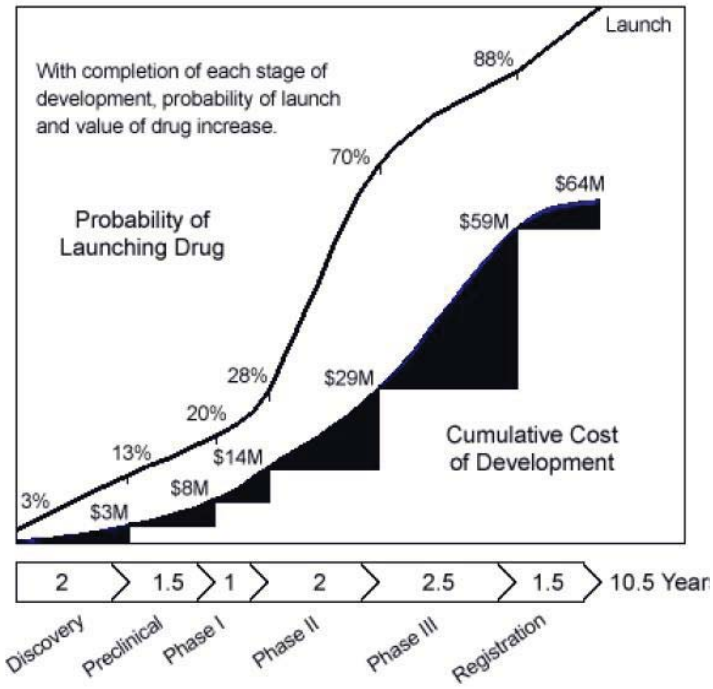


Fig. 1: Drug Development - Costs and Risks (Kolchinsky, 2004)

However, repositioning a known (and certified) drug still is a huge task which can hardly be carried out by a single small start-up.

Typically, such an endeavor was made feasible by a venture capital-backed company which financed the initial clinical trials after the drug discovery and pre-clinical phase had been accomplished. Nowadays it has become harder to get venture capital backing for risky scientific activities. So there obviously is a need for an intelligent model that enables small start-ups to create value without any major VC investments.

Open Innovation is a concept which offers a starting point to create value by combining the strengths, knowledge, and expertise of several players. A mutual understanding of the implications, risk, and reward is necessary in order to conquer this path successfully. The management of intellectual property is particularly crucial when it comes to a collaboration intended to turn into a successful commercialization.

Life-Genetics is using an Open-Innovation approach to market a drug for different uses than it had previously been marketed for. The following process describes how the start-up Life-Genetics created a new previously unidentified use for a pre-existing drug, eventually making it into a market ready product for the therapy of neurodegenerative diseases

Protection of a known pharmaceutical compound for a secondary use

At the beginning of the project, concerns were raised over whether it is allowed and possible to protect a secondary usage (for example another indication for a pharmaceutical compound). According to both international and national, law e.g. the German, patent law stipulates that one can separately protect every single indication or usage of a pharmaceutical compound separately. Other concerns were raised over the rights and laws regarding invention had to be considered, this largely concerned the how the research results would correspond to the existing IP in place. As you can see below, Life-Genetics had to follow a clearly defined route to generate IP and obtain the right to use it.

Reporting of the invention to the university by the inventors

In the case of Life-Genetics, the discovery of the possibility of using a known drug for other previously unidentified purposes required reporting to the German universities whom had created the drugs due to a law called “Arbeitnehmererfindungsgesetz (employee invention law)”. As a result the university has the right to apply for patents based on the inventions of its employees. So if the university decides to claim an invention, it is committed to apply for a patent and is in this case the owner of the IP.

The start-up getting the rights to use the IP

A start-up, which is willing to use this IP owned by the university, has to get rights for its usage granted by the university e.g. by licensing or buying the IP even if the researchers who made the invention/discovery are involved in the start-up. In the case of Life-Genetic,s a choice was made to license the IP.

For the licensing of IP, there were two possibilities: Life-Genetics chose an exclusive license. Meaning only the start-up has the right to use the IP during the term of the contract. Another possibility could have been a non-exclusive license which would allow the university to give away more than only one right of usage, and to various different users.

In the case of Life-Genetics, the license contract between the company and the owner of the IP determined that the university has to pay all cost in relation to the patenting process such as application costs both national and international, maintaining costs and granting costs. In return the university receives payments such as license fees, upfront payments or milestone payments. In addition the start-up is given the option to buy the IP and become the owner whenever they want for a fixed price.

Subject and scope of the IP:

The patent family, i.e. all applications and patents are based on one main application, this includes the protection of both the pharmaceutical compound and its usage as well as the the targeted indications

Realization of a clinical proof of concept via close cooperation with research institutes

In the early stage of development especially for financially weak start-ups, it is important to build a network and use established relationships to cooperate closely with research institutes with the aim to realize clinical proof of concepts in a lean process.

To regulate all kinds of actions and to benefit from a clearly defined working space and processes, a cooperation contract has been set up with each partner. This is a kind of intermediate open innovation. Giving information to external partners and further develop a drug together under the protection of a contract is a secure way of opening up to external partners without the risk of not having any control regarding sensitive information or research results.

However, the minimum objective of any contract should be to clarify the treatment of IP, both foreground and background. In the case of Life-Genetics, the contract clarified that all foreground IP could be used by the partners for the purpose of research but will always be owned by the start-up. The IP which was generated had to be assigned to one inventing facility to avoid patent applications with different assignees, when the start-up had the first right of refusal in case of the IP of the partners. For the case of impossibility, it has been regulated that the start-up and the partners filed patent applications at the same time in order to later on carry out a so called cross licensing. However, the research institutes as partners were given the right to use all generated IP for research purposes.

An important point was the question of how to finance such a cooperation. One possibility is the usage of a public research grant, which Life-Genetics did. Such public funding projects offer the frame to implement such intentions.

The strategic approach to get in contact with Big Pharma – Open innovation with industry partners

As mentioned above, Life-Genetics' approach is to use a compound for a second use. That is why preclinical and Phase I are completed at the relevant point in time. This includes tests with subtherapeutic doses and the tolerability and safety of the drug have been confirmed.

After years of planning and researching, there comes the time to turn a chemical product into a market ready medicine. Before the first Phase I, Life-Genetics considered how the drug's package inserts would read. Furthermore they constructed a model of how they would like to see the drug used in patient care. Because it is a compound for ageing-related Neuro-Diseases, does its pharmacology suite Alzheimer disease or Parkinson's most? Such decisions depended not only on the pharmacology but on the unmet medical need, the potential size of the market and on the nature of current competition. That is why Life-Genetics created a product profile describeing the key features that could potentially be achieved.

It is common for pharmaceutical companies and especially small ones like Life-Genetics to take the development of their compounds one step at a time. Life-Genetics want to see the results of one study before designing the next one. Because human testing is by far the most expensive and time-

consuming part of drug development, the clinical development program must be designed to be as efficient as possible.

For this reason many biotechnology companies, such as Life-Genetics, have no intention of taking their compound through a complete clinical development. The process of filing an investigational new drug applications, modeling the clinical development program with all parameters such as requirements or statistical relevance required capital and expertise which Life-Genetics did not have access to. Therefore they chose a typical strategy and licensed the development rights to a large multinational pharmaceutical company named "Pharma Ltd.". Pharma Ltd. was convinced of Life-Genetics' approach, the product profile and the vision for developing and commercializating the product. The intention of this contract allowed Pharma Ltd. to carry out the clinical trials but Life-Genetics stays involved and gains from the results. Furthermore there are more advantages to sign a contract with a Big Pharmaceutical companies:

- no major VC investments needed
- get access to knowledge and experts
- Life-Genetics acquire a key opinion leader

Because of the contract, Life-Genetics does not depend on further financing through Venture-Capital-investments. Instead of wasting time searching for new financing sources, they combined their strengths in order to get in contact with companies whom would be prepared to spend money on and help to realize a complete clinical development.

Pharma Ltd. with its multinational business, thousands of employees and years of experience educated scientific staff of Life-Genetics, helped to specify the clinical development plan and gave advice to make the design acceptable for the national medicine agency.

Getting a key opinion leader such as Pharma Ltd. Was a very important step for Life-Genetics. Besides the opportunity to realize the clinical trials, the reputation of Life-Genetics in the clinical community rose immediately.

The cooperation contract

Generally in order to build up Life-Genetics successfully the main task was to find the right balance between managing the cost and realizing the value of the product development. So the company chose to share the costs with a partner, which also meant giving up some value. That is why the management team of Life-Genetics, consisting of Mr. da Silva and Erik Seinfeld, had to identify potential partners and successfully negotiate the terms of agreement.

The Partnership

Partnerships can be described as front-loaded (the partner will pay more upfront and in near-term milestones, additionally royalties) or back-loaded (less upfront but higher royalties down the road).

For out-licensing Life-Genetics' compound the management team decided to agree on a front-loaded approach. Pharma Ltd., the company buying into the partnership, made an initial cash payment: 100,000€ for signing the deal, 500,000€ for reaching the pre-clinical mile-

stone and 500,000€ for the successful Phase I. On top of that, Pharma Ltd. will pay 1,000,000€ for initiating Phase II and 3,000,000€ for an approval of the national medicine agency.

The tangible value for Life-Genetics was small, a little more than the sum of the first payments (1.1 Mio. €). In exchange for carrying much of the risk, the partner keeps most of the profits. From Life-Genetics perspective engaging in the front-loaded deal is similar to doing contract research with little or no upside if the drug ever becomes successful. Most of the value of drug development is realized near the end of the process when the risk of the clinical failure has been mitigated with positive data. With positive Phase III data, Life-Genetics will be able to negotiate a deal with a large share of the downstream profits.

R&D Sponsorship

The costs of running a R&D program can be significant. That's why a R&D sponsorship was helpful for Life-Genetics. Having a partner covering the expenses, including the in house labor (measured in Full-Time-Equivalents) and out-sourcing expenses such as those associated with process and clinical development was a good way to build up the company. The agreement of a sponsorship requires experience. Some companies agree to work for their partners in exchange for little more than having their expenses reimbursed. Such arrangements are profit neutral, as they are neither neither harmful nor helpful therefore the costs are covered, but no profit is generated.

In case of Life-Genetics the research sponsorship enabled the carrying out of R&D but provided little incentive to be more efficient since any cost savings benefited the paying partner. An alternative to counting Full-Time-Equivalents is to negotiate for success-based milestones, which reward efficiency.

Royalties

In addition to upfront- and milestone-based payments Life-Genetics negotiated royalties. A royalty is a payment based on product sales. There are two types of royalties:

- a flat percentage of sales
- tiered royalties, for example like US federal tax brackets.

The second type, a tiered royalty might be structured as 10% on annual sales up to 100 Mio €, 12% on sales exceeding 100 Mio. € and 14% on sales exceeding 300 Mio. €.

Life-Genetics negotiated a royalty type 1 with a percentage of 10%. Compared to marketing the compound as their own, the advantage of a sales-based royalty was that Life-Genetics get paid even when the compound or drug is not yet generating profits. So royalties are an effective means of generating significant value in the long-term and each percentage point was worth to negotiate for.

Royalties are larger than they seem. For example: The deal was that Pharma Ltd. pay a 10% royalty on worldwide sales. If the drug generates 500 Mio. € / year Pharma Ltd. will keep 450 Mio. € and Life-Genetics will receive 50 Mio. €. However, after manufacturing, sales and oth-

er expenses, Pharma Ltd. may be left with only 250 Mio. € which would mean that Life-Genetics sales-based royalty represented 17% of the profits.

Profit-sharing

The last point negotiated in the contract between Life-Genetics and Pharma Ltd. was a profit-sharing. That means Life-Genetics agreed to share the ongoing development commercialization costs of the drug, including the high costs associated with first launching a new product, in exchange for also proportionately sharing in the drug's profits. So both partners accepted the risk that the drug might never be approved or become profitable. However, Life-Genetics entered into a profit-sharing arrangement. This doesn't mean, that the company that discovered and partially developed the drug will not be paid upfront and milestones.

Result:

The case of Life-Genetics as described above shows how a start-up company markets a drug with an Open-Innovation approach.

"Elchemica, marketing of a novel technology"

Case study in the framework of the Health-2-Market project seminar

Marketing of Innovative Products in Health / Life Sciences

Author: engage AG

Table of contents

1. Introduction

This case study provides an example of a start-up company in the field of electrochemistry. Using this example it describes how to create a marketing plan for an innovative technology. It addresses the participants of the seminar 7 of the Health-2-Market project: Marketing of Innovative Products in Health/Life Sciences (Ref:MIP). The main contents are:

- understanding the marketing process;
- identification of potential customers;
- handling potential complexities in the above processes that stem from the innovative nature of research;
- creating and implementing a marketing plan.

2. Profile of the company

Company

Elchemica is a leading provider of novel and innovative solutions in electrochemistry and is dedicated to improving Electrochemistry in every field of application.

The basis for this challenging aim are more than 20 years of research experience and a broad international IP portfolio in all relevant areas of electrochemical analysis at heated electrodes.

Founded and funded in 2009 by engage AG, with headquarters in Rostock and Berlin, Elchemica works for and cooperates with leading scientific organizations and private companies from all branches in which electrochemical excellence is needed.

Product

Using the broadly patent-protected and currently unique technology of directly heated electrodes, Elchemica develops, adapts, and continuously enhances tailor-made solutions in cooperation with its customers. The systems provided can be applied for a variety of purposes in electrochemistry. The company develops and markets ultra-rapid and highly sensitive DNA analysis systems, in particular for in-vitro diagnostics. The DNA analysis system is the central platform for carrying the electrochemical detection at heated electrodes. It contains electronics for selective heating and for reading chips as well as the electrodes on the chips. It also includes the mechanics for receiving the chips and the electronics for identifying the chips via RFID (radio-frequency identification). The control of the process is implemented by an integrated microcontroller. The interface between the hardware and the user is realized by an integrated industrial PC.

Figure 1: eDNA analysis system

3. Profile of the Management team

Technical Director

Dr. Fintig obtained his diploma in chemistry at the University of Rostock in 1997, followed by a PhD in 2001 and a postdoc studies ("Habilitation") in 2006, through working on the field of analytical chemistry. His research is mainly focused on electroanalytics with heated electrodes and biosensors for genes and proteins. For his works, he received a Metrohm award in 2003. In 2008, he obtained a Heisenberg fellowship from the German Research Foundation (DFG). Currently he researches and teaches as a Senior Researcher at the Institute of Chemistry at the University of Rostock.

General Manager

Mr. Karmer studied Industrial Engineering and Management with a focus on Electrical Engineering/Computer Engineering and Financial Management at the University of Rostock and graduated as the top student of his class in 2005. During his research visit at the Instituto de Pesquisas Tecnologicas (IPT) in Sao Paulo (Brasil), the leading public research centre in Latin America, he dealt with the problem of technology and knowledge transfer from public research to industry. During his time at engage – Key Technology Ventures AG, he has been involved in the development, evaluation and realization of a variety of technology-based corporate concepts. This gave him the opportunity to apply his broad experiences in the field of the protection and the valorization of intellectual property.

Engage Key Technology Ventures

Engage AG is an early stage investor and has been involved in the business development of Elchemica from the very beginning. The commitment of engage AG regarding the operational business, strategic focus and the connection to investors is a crucial factor for the success of Elchemica. The main reason for the importance of the commitment is the lack of business experience of the scientists. Thus, the main objective of engage AG is to support the scientists of Elchemica with complementary competencies which are needed for the business development and the product marketing of the company. Besides the personal dedication, engage AG holds a company share of 45-50% of Elchemica.

In general, the key competence and tasks of engage AG is to create value from intellectual property. The identification, support, further development and valorization of inventions with high market potential and relevance are the basic concepts of engage AG. In the area of portfolio holding, engage AG partners up with key researchers providing cutting edge technologies to found growth-oriented high-tech companies. As a shareholder, engage AG takes on entrepreneurial responsibility and commits itself to develop a sustainable business model which generates revenues for the benefit of all parties involved. Almost all of engage AG's portfolio companies are based on cutting edge technologies, which are protected by international intellectual property rights.

4. Marketing of an innovative solution for Health Care purposes

The marketing of an innovative solution for health care purposes needs to analyze the initial situation, to develop a marketing strategy and to implement and manage the marketing process.

4.1. Analysis of the Situation

In order to create the right marketing strategy, an analysis of the initial situation of the business is needed. In this case, it had to be clarified as to what the technical features of the eDNA-Approach are to define the right keywords and investigation strategies for situation analysis, market studies and competitor analysis. The aim was to derivate potential customer benefits in health care applications, to identify potential customers for the eDNA-approach-based technology with its possible applications and the relevant competitors.

Technical features of the eDNA-Approach

The subject of the eDNA-Approach is an alternative electrochemical / electronic method for the detection of DNA. Compared to conventional optical detection approaches, this alternative method for the detection of DNA represents a technology that is suitable both for conventional and new applications which could not be done before, due to longer process durations and less sensitive measurement results. Especially because it is faster, more sensitive and more cost-effective, this method seems to improve the opportunities for DNA-detection activities in comparison to conventional methods. In order to arrive at these conclusions, the relevant conventional methods had to be compared to the eDNA-Approach, based on specific process parameters such as analysis duration, analysis costs, analysis sensitivity and other typical characteristics.

Derivation of potential customer benefits in health care application

In the field of DNA analysis, applications which require a fast, sensitive and cost efficient technology in comparison to conventional methods had to be identified. The results of the investigations provided the detection of infections whose diagnosis should be completed in the shortest possible period of time as a main application for the eDNA-Approach. There the usage of said technology should be able to shorten the diagnosis process and should help saving the life of affected people. In detail, it would be possible to determine species accurate pathogens of mortal diseases safe and in a shortest possible period of time. So the value proposition of the company is to provide a method for the detection of infections that cause serious and possibly fatal diseases efficiently, both in analyzing and in respect to costs and improving process parameters of conventional methods like analysis duration, analysis costs, analysis sensitivity and other typical characteristics.

Customers

Every successful business that is based on a product which should be sold needs to know the relevant market field and especially possible customers. In this case, the customers who have a demand for technologies, methods and systems for detecting and analyzing serious diseases causing infections and their associated pathogens as quickly as possible in order to save the lives of affected people had to be detected. Typical customers are ambulances, medical facilities such as hospitals and research institutes working with infections and their pathogens and offering medical services to affected people.

Competitors

To place a product on a market, there is both the need to know the customers and their requirements and the competitors to gain market shares. For this purpose, a competitor analysis had to be performed. The questions that had to be answered were who the competitors are and what kind of products and solutions they offer solving the targeted problems and applications. In a next step, the identified, relevant products and solutions were analyzed in order to clarify the main characteristics and parameters like process duration, costs and usability.

To identify pathogens of infections, there are different methods. One method is cultivating pathogens in cell solution as a proof of their occurrence. The problems or disadvantages primarily are the long period of time needed for cultivating which usually takes about three days and the fact that some pathogens cannot be grown. However, the advantages are cheapness and establishment of this method. The method seemed irrelevant for further analysis.

Conventionally immunological diagnosis employs the usage of antibodies. This method is both inexact and takes a long period of time to perform. The advantage of this established method is its cost efficiency.

Another method to identify pathogens is DNA-based solutions. The detection of specific pathogens is achieved by using DNA sequences. This method is established and exact, but produces high costs and cannot be used at the point of care, but only in central laboratories.

Figure 2 below shows the results of the analysis. The competitors in their relevant activity fields are represented.

The shown figure 2 is only a final summary for visualizing the results. On the way there, every company or product that seemed to be relevant has been analyzed in detail to get an overview as complete as possible on all relevant facts regarding the companies and their products and solutions.

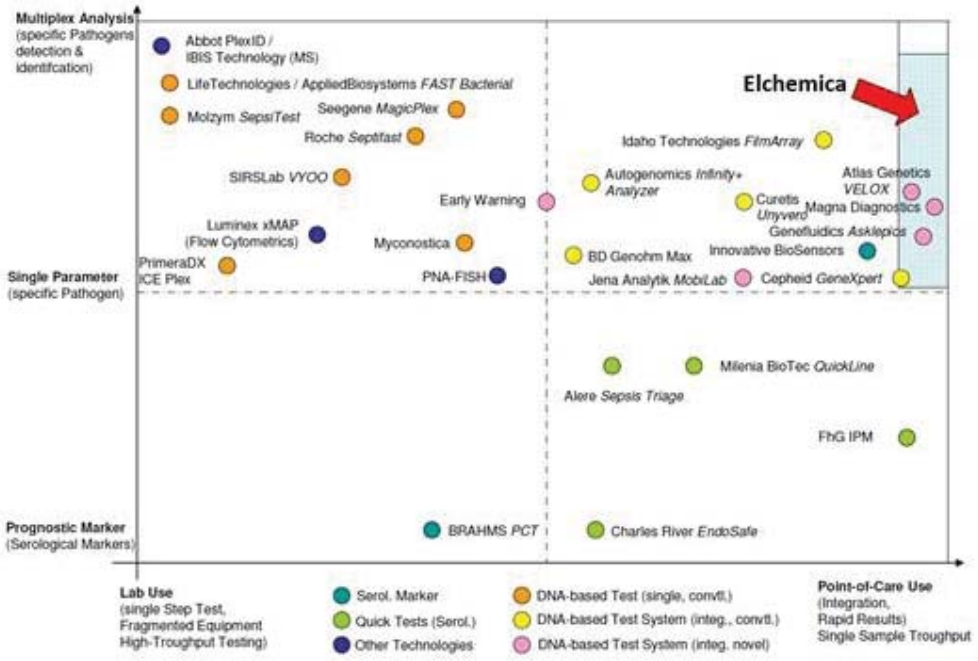


Figure 2: Results of the competitor analysis (source: Elchemica)

Results:

The results of analyzing the situation are a value proposition. Additionally the knowledge of the relevant customers with their requirements regarding such products and solutions and competitors with detailed information about all relevant facts to create a fence against the opponents have been worked out.

4.2. Marketing Strategy

In the figure below, you can see the marketing process which Elchemica planned.

Questions:

How can you create a product that customers want to buy?

In case of Elchemica, which are methods you could use?

How to create a product?

"Spend 10 % of time on product creation and 90 % of time on marketing the product"

– Dan Kennedy, marketing legend

A great product launch starts with a great product – but being "great" just isn't enough. You have got to know how to make your product perfectly suited to your market's needs. The very first thing you need to do when you are developing your product or service is to get objective. This can be hard to do because you are the expert, and you naturally assume you know what your potential customers need. That is why you carried a market research defining your unique selling points and a competitor analysis. A simple method to create a product that customers want to buy is the lead user method. Lead users are users of a product or service who currently experience needs still unknown to the public and who also benefit greatly if they obtain a solution to these needs. In case of Elchemica, they created a product together with clinical members, scientists and research institutions. One of the lead users was Dr. Fintig from the University of Rostock. For many years, he worked in the field of analytical chemistry with heated electrodes. Furthermore Prof. Dr. Müller, working at the hospital of Heidelberg, was involved to identify needs and trends. In collobaration with Elchemica, he also conceptualized the design of the product to reach goals like "usuability" and "reduced work space". These experts used their experiences on how to solve problems or gave advice on which features are missing. Using the lead user method may help to find out, for example, how much money consumers are willing to spend for a product.

Further methods to get in contact with potential customers are for example open innovation platforms.

Questions:

Which market barriers may exist?

Are there any specific regulations you have to regard?

Is a production in-house possible?

How to get market access?

For getting an access to the market, Elchemica had to think about three main facts:

- Regulations: What national and international regulations have to be considered?
- Production: What's our product and how could it be realized? How to manage good quality? How much should it cost?
- Logistics: How should the products get to the customers?

- Regulations

  In order to be perceived as a serious competitor, both for the production and distribution of tests for environmental analysis and in the subsequent in vitro diagnostics sector, a certification of quality management is in fact necessary. This includes in particular the implementation and maintenance of a quality management system according to DIN EN ISO 9000: 2000. This system is not product-related, but will be guided by the processes of development, production and customer service. Elchemica intended to implement such a quality system. Similarly, the industry-specific certifications are Good Laboratory Practice (GLP) reached (necessary for the implementation of analytics services) to be perceived as serious. Further steps included a certification for Good Manufacturing Practice (GMP).

  Complementary to the QM system, for the in vitro diagnosis an authorization according to the in-vitro diagnostics directive of the EU (IVDD 98/79/EC) is necessary, to get an access to the European market. Elchemica intended to start working on the admission as soon as possible and acquired it parallel to the technical development process. For the distribution of the test system in the U.S. an approval by FDA (510k-clearance) is required. This was pursued based on the results of the European authorization procedure.

- Production

  Elchemica analyzed its product and developed work packages. These packages include to do´s and who should realize them.

  Generally to be able to market with both, the DNA analysis system and the tests, development work is necessary. This focus included work in the field of molecular biology, electrochemistry, electronics / electrical engineering and software.

  The aim of the work package electronics / electrical is to realize the actual DNA analysis system as well as the DNA chip circuit, as a microelectronic technology system and the integration of finished components and assemblies as a functional and marketable device. These works are expected to be provided by an external engineering service. This will enable both the development and the documentation up to the production stage.

  The management of the analytical process and the communication between the technical components, the detection and evaluation of electrochemical processes and the analysis and visualization of results are to be realized by a specially developed software. As a development partner, the company Soft-web is available, which offers a software platform with its own software solution, suitable software to capture data from heterogeneous scientific-technical processes and analyze it. This modular and very flexible and adaptable software is the basis for the development of the Software of Elchemica. The development is driven by company Soft-web on behalf of and distributed as a licensed product in the package with the technical DNA analyzer.

  The work packages for molecular biology and electrochemistry could be realized by an in-house production.

Regarding own works and products of the development partners, Elchemica was able to evaluate the quality of the product. Furthermore the production costs could be determined and compared to competitors.

- Logistic:

  The main question is how the products reach the costumers?

  Many ways seemed to be possible for Elchemica and were realized. So they got in contact with potential customers directly. On top of that, distribution ways like an online-shop, collaboration with distributors or locally situated sales agents were set up to reach customers.

Questions:

How can you raise your credibility or reputation?

Do you need further analysis?

How to reach customers?

In a first step, Elchemica wanted to reach new customers to buy the products. So awareness needed to be raised among the specific audience for this new diagnostic approach in scientific publications (e.g. on the effectiveness of tests or the effectiveness and favorability of the DNA Analysis System). This would be done by the inventors and lead users by conferences, publications and networks. Potentially supportive audiences, such as representative scientific partner institutions (Universities of Rostock or Heidelberg), which had shown great interest in this system, had already been addressed. This approach is supported by the presence of Elchemica at relevant scientific conferences and trade fairs.

In case the products had been fully developed and approved as an in vitro diagnostic device, Elchemica focused primarily on the large and university hospitals in the German-speaking countries as potential customers. Elchemica analyzed the supply chain of hospitals to get more information about procurement processes. Primary contact was the head of the diagnostics department. By a personal visit, the device and its operations were presented to these decision makers. In addition to the operation of the doctors and scientists xx provide evidence and reasoning support for potential cost savings of the new approach presented and made available. Potential partners in the non-German speaking countries were addressed by flanking and secondary marketing activities. A direct on-site response, as in the German-speaking area should be started by finding a distributor in each country.

Furthermore to achieve more reputation, an advisory board was established. By acquisition of significant opinion leaders, the credibility of Elchemica was raised additionally to the other marketing actions.

How to keep in touch with customers?

To stay in contact with costumers and convince them to buy more products, Elchemica set up a Customer loyalty program. This includes:

- Trainings;
- Discounts;
- Updates;
- Services.

Because of that, customers get the latest information about new developments or products, can receive a discount when buying new products and get a regularly updated software.

On top of that, existing customers were involved in new developments. According to the lead user method, they can get a specific product for their own requirements suggested.

Additionally it is very important to monitor the competitors. So Elchemica is able to react to product or market changes and can develop equal pull or adjust his marketing mix.

Question:

Is there any part of the marketing mix missing?

Who should be responsible for the implementation of the marketing process? How should it be managed?

Which ways are possible to control the process?

4.3. Implementation and control

In the previous chapter, you can see how Elchemica planned and implemented its marketing process.

Companies that have already implemented a marketing process have created the first requirement. It is important that the marketing department is regarded as a management task. The Marketing Manager should pull the strings and responsibly integrate the various divisions under the leadership of marketing. As Elchemica is a start-up, the management task is carried out by Engage Key Technology Ventures. The main and important task is to coordinate all the processes. For this purpose, the timing, responsibilities, and a contingency plan for emergencies should be developed. Thus you need to define business processes. According to the quality management system, Elchemica defined processes how to realize the marketing. In detail, operating procedures were determined, e.g. how to contact customers or how to react to requests.

After implementing the marketing process, it is important that it is managed by responsible persons. This means a results-oriented review of the marketing regularly. There are two steps to handle this:

1) Measurement of the results based on a target-performance comparison

In case of Elchemica, parameters like the number of customers or sold products were measured and compared to the planned sales suggested in the business plan. Additionally revenues or the amount of discomforts are excellent parameters to manage the marketing.

2) (critical) analysis of possibly occurring deviations to determine starting points for the use of improving marketing instruments.

In case of Elchemica, the above named marketing instruments were evaluated regularly. In this early stage of Elechemica, there is no need to change the existing marketing strategy. In spite of this fact, the evaluation of the process should continue to react to deviations immediately.

« AHP: Analitic Hierarchy Process »

Case study in the framework of the Health-2-Market project seminar
"Cutting Edge Decision Making Tools for Entrepreneurs"

*all names of actors have been changed for publication

Author: Massimo Borriello - APRE

Table of content

1. Key questions addressed by the case

This case study provides an example of a decision making tool of a company in the field of medical devices.
Using this example it describes how to use a cutting edge tool for decision making. It is developed for the seminar 6 of the Health 2 Market project.
The main content is: understanding the decision tool

2. Nitillium market

2.1. Market size

The marketing of an innovative device for health and surgery needs to be analyzed since beginning of the idea till the final step. To develop a marketing strategy and manage the marketing process is necessary to take decisions and have clear ideas about time limits and priorities to take the right choices

Analysis of Situation
It is necessary to study the state of the art of the market to develop a business and marketing strategy. It has to move around some specific keywords as Market Situation, Technical features, Customers and Competitors. The aim is to clarify the customers benefit by using the devices, field of application, social impact, technical features and competitors products. The market is mature and has several miles of potential customers every year only in Italy.

Technical features
The subject of this study is the utilization of an innovative material applied in spinal surgery. This material has unique mechanical and biocompatibility characteristics. The ductility and flexibility of nitinol is well known. It allows to do surgeries respecting delicate tissues such as the periosteum. Innovation is not in the material but in its use associated to anchoring dynamic system.

Customers
The customers are some thousands each year only in Italy. Last epidemiological studies shows the increasing market in the spinal surgery due to new techniques and materials used in this delicate field. There are three sides to monitor: 1) Customer satisfaction : It depends from result, pain and healing time to come back to a normal life; 2) Commercial viability depending of costs and market; 3) Sustainable for society economic resources .

2.2. Market potential and stakeholders

Competitors

Since the nitinol was developed, arose a lot of health application with a lot of producers and distributors. Among these producers and distributors, there are at least four big international enterprises. Obviously for these producers it is easier to made devices with low cost of production. Every device has something unique and something common. In this period, with economic conjuncture and the lack of a strict control about devices made in Asia, it is becoming a problem for little firms that are the real pioneers. So the competition about a product has to be fight on cost and quality.

3. Nitillium company

3.1. Profile of the founders / of the current and potential future associates

Company

Nitillium Research Srl is ISO 9001 – ISO 13485 certified enterprise. It produces and distributes all over the world medical devices for neurosurgery. Nitillium was founded in 1997. Since its foundation, Nitillium established a wide collaboration with the Research Laboratory at the University of Engineering in Moscow, the Implantitalia's Research Center that operates in the field of medical devices for maxillofacial and orthopedic prostheses and the Animal Experimentation Center in "Cardarelli" Hospital in Naples.

This collaboration among surgeons and engineers generated new medical devices for heart and chest surgery, neurosurgery and spinal surgery.

Founder

Dr. Sergio Acampora is a neurosurgeon. He was the chief of the department of experimental neurosurgery in IRCCS Neuromed. Due to his surgical experience and needs, he had the idea to develop a new device that could help to obtain faster and more effective surgeries in the neuro and spinal surgeries with great advantages for patients (less pain) and hospital costs by reducing intraoperative time and the number of postoperative hospitalization days. He developed his idea in 1998. The first scientific publication dates 1998 and many others have been published in the years. Now Dr. Acampora is retired but continues to follow the evolution of his firm and the development of the devices for new surgery applications collaborating in R&D.

General Manager

Eng. Francesco Acampora is Dr. Sergio's son. He is a biomedical engineer graduated in University of Naples "Federico II". He studied technical applications in the medical/surgery field before and after graduation. In the same time he had opportunity to experience the reality of hospitals and surgeries due to the father's job. He takes cares about all technical aspects and is responsible for Quality Assurance.

Account Manager
Eng. Nadijara Alves Acunzo is a managing engineer. She developed some analysis tools for activities monitoring in several enterprises. In Nitillium she is responsible for management by projects, information technology and marketing.

Legal Representative
Dr. Assunta Angela Troisi is a physiatrist. She was the chief of the department of neurorehabilitation in IRCCS Neuromed. She has several years of experience in the post-operative managing of patients. She is the Legal Representative of Nitillium since 2011 and she cooperates in Quality Assurance.

3.2. Nitillium's development: the technology and its regulations / intellectual property issues

Product
These devices are made by "nitinol", a nickel-titanium alloy. Mechanical (shape memory and superelasticity) and biocompatibility characteristics make it suitable for medicine application in several fields.
Nitinol was created in 60's and still now, every year, are developed new medical devices for new applications in surgery field.

Nickel titanium (NiTi) is certainly the most surgically used shape memory alloy. It has a polymorphous crystalline atomic structure, capable of assuming two different atomic structures according to the temperature or pressure to which it is exposed. The main characteristic of this intermetallic compound is its "shape memory", which was discovered in 1961 at the Naval Ordnance laboratory in White Oak, Maryland. Nitinol means "NichelTitanium Naval Ordinance Laboratory".
The sensational discovery, however, was made by chance when Dr. David Muzzeytook a rod of nickel titanium that had previously been deformed to remove the tobacco from his pipe and to his great surprise discovered that when it was heated, the metal assumed a different shape, i.e. returning to its original shape. After various studies, it was confirmed that the memory effect was connected to a thermo-elastic transformation of the atomic structure in a martensitic phase.

Its other main properties include its superelasticity and absence of elastic fatigue.
Nickel titanium's constant elasticity is almost ten times greater than that of steel.
The properties of nitinol can vary, depending on the composition of the two elements, the mechanical work and its heat treatment.
Its superelasticity allows vertebral column supports that preserve the physical mobility of the spine without functional limitations and cranial flap fixations that adapt to variations in bone thickness.
Its shape memory significantly facilitates surgical application and, in some cases, is used to exert a controlled working force on the anatomical structures to which it is applied.
Nitinol, thanks to its particular polymorphous crystalline structure, has two different atomic structures, which change according to the temperature.
In almost-freezing physiological solution (2-3 °C), the material temporarily loses its elasticity (martensitic phase) and becomes plastic, allowing its shape to be easily modified.
This shape is maintained, even when the material is no longer plastic, up to 27°C, after which there is a progressive return to the initial state (austenitic phase) due to the shape memory effect, with the production of mechanical energy until the recovery of its superelasticity at 37°C.

In medical field the most important application of nitinol are in Bariathric Surgery, Cardiac Surgery, ENT Surgery and Neuro/Spinal/Orthopedic Surgery.

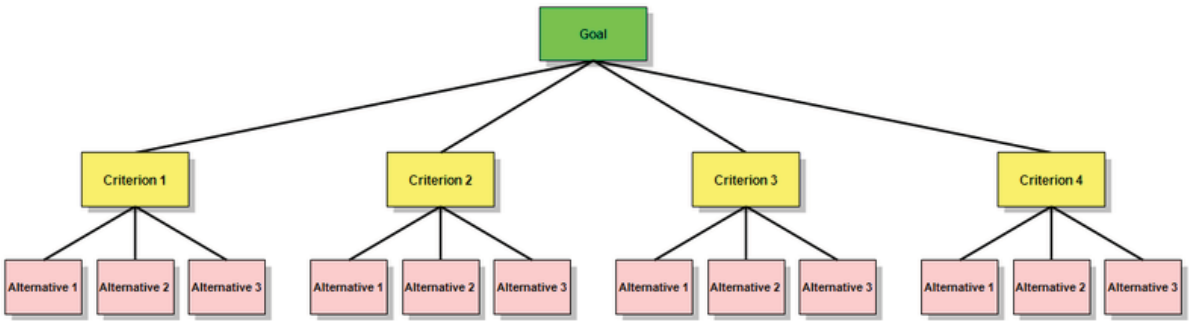
In the specific field of Neuro/Spinal Surgery the Nitillium devices are used to to correct and support column illnessdue to post-traumatic, degenerative and chronic instability.

4. Lessons learnt and thinking further

DECISION TOOL

Cutting edge decision making tool: AHP

The analytic hierarchy process (AHP) is a structured technique for organizing and analyzing complex decisions, based on mathematics and psychology. It was developed by Thomas L. Saaty in the 1970s and has been extensively studied and refined since then.
It has particular application in group decision making and it is used all around the world in a wide variety of decision situations, in fields such as government, business, industry, healthcare, and education.
Rather than prescribing a "correct" decision, the AHP helps decision makers find one that best suits their goal and their understanding of the problem. It provides a comprehensive and rational framework for structuring a decision problem, for representing and quantifying its elements, for relating those elements to overall goals, and for evaluating alternative solutions. Users of the AHP first decompose their decision problem into a hierarchy of more easily comprehended sub-problems, each of which can be analyzed independently. The elements of the hierarchy can relate to any aspect of the decision problem—tangible or intangible, carefully measured or roughly estimated, well or poorly understood—anything at all that applies to the decision at hand.
Once the hierarchy is built, the decision makers systematically evaluate its various elements by comparing them to one another two at a time, with respect to their impact on an element above them in the hierarchy. In making the comparisons, the decision makers can use concrete data about the elements, but they typically use their judgments about the elements' relative meaning and importance. It is the essence of the AHP that human judgments, and not just the underlying information, can be used in performing the evaluations.



The decision maker has to identify all criteria that can influence his decision. After that a weight (that represent the impact of the criterion on the final decision) has to be assigned to each criterion. Applying a pairwise comparison approach, all criterion will be compared each other, giving redundant results too. A matrix of pairwise comparison will be created of which its eigenvector gives the weights of criteria and its eigenvalues represent the consistency ratio of the judgments.
The decision maker has now identify every decisional alternative and valuate how each alternative fits the criteria. For each criterion, a specific measure of satisfaction grade an be performed in order to compare the decisional alternatives for all criteria.

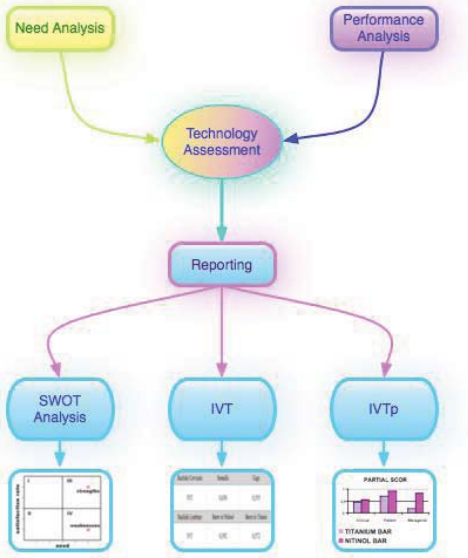
1. Application in Health Technology Assessment (HTA)

NITILLIUM APPROACH

Nitillium applied AHP to allow surgeons to design a hierarchical structure for multi-criteria decision-making, by breaking problem down, and then aggregating the solution of all the subproblems into an analytic conclusion. Overall the most important skill of this methodology is the possibility to run through the process of decision; this is a crucial point especially in a public health system. Health Technology Assessment (HTA) can be an appropriate method to support such decisions. It is an inter/multi-disciplinary and multi-dimensional process to evaluate different technologies, alternative and competitive between them.

The aim is to support the decision makers in health policies with technical-scientific evaluation.
In this paper the authors deal with a main decision problem in cervical spine surgery: fusion or non fusion
systems for cervical herniated disc at one level.
This study analyzes four technological solutions: two kinds of cage, in titanium and carbon, induce intersomatic arthrodesis (fusion); Discovery, disc prosthesis (non fusion); Somafix, shape memory superelastic fixing (non fusion).
The results show that the non fusion technologies satisfy clinical and patients needs better than the fusion
ones. On the other hand, fusion technologies have less impact in the management of health structure. That
is because the fusion methods are well established in clinical practice, while the non fusion methods, in particular the Somafix, constitute an entirely new approach to this disease.

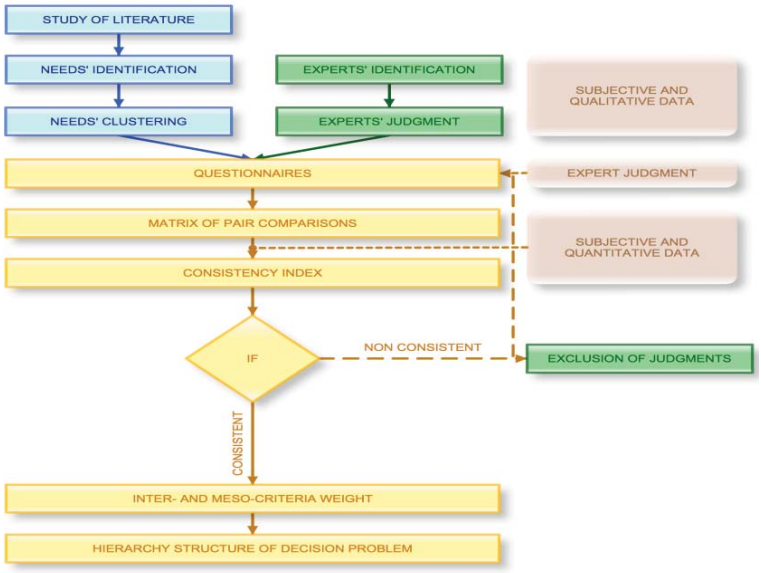
The schematic structure of method is represented in the following algorithm.



The main four steps (Need Analysis, Performance Analysis, Technology Assessment and Reporting) are explained one by one.

Need Analysis: This is the first step of the proposed method. It is a crucial point because every need has to be identified and clustered and it requires a deep knowledge of both disease and managerial problem.

The algorithm of need analysis is represented in the following.

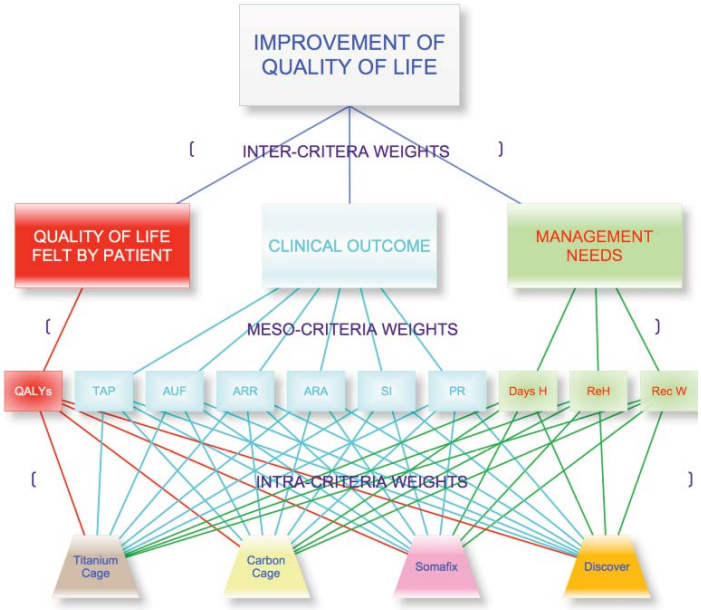


The judgment of experts is weighted using a specific function (Wexp) which considers years of specialized activity (Ysp), experience in the spinal surgery (Yss) and the interest area (Ai).

Experience weights			
Years of activity (specialized in spinal surgery)		Interest area	
Years	Weight	Area	Weight
>15	0.61	Spinal surgery (chief)	0.67
7-15	0.25	Neuroreabilitation	0.22
3-6	0.10	Spinal surgery (assistant)	0.11
0-2	0.04		

$$W_{exp}=Y_{sp}+ (Y_{ss} * A_i)$$

Furthermore, using the Consistency Index method proposed by Saaty and based on the Random Index method proposed by Forman 1990 has tested the coherence of their answers.
Finally, a hierarchical structure of the decision problem was obtained.



Performance Analysis. The performance of technology is the satisfaction's degree for each need. This analysis is performed in a simple of 16 patients, which received surgery for cervical herniated disc at one-level in the same Hospital: IRCCS Neuromed in Pozzilli (IS), Italy. The performance analysis is the measuring of satisfaction's degree in the simple of patients for each need identified in the need analysis. Specifically, radiological parameters pre- and post-surgery are measured in order to calculate the intercriteria weight for clinical need.

Technology Assessment. After weighting every criteria (inter- and meso-criteria) and estimating the satisfaction's degree for each need (intra-criteria), the scores for every alternatives are calculated.
Reporting. The results are showed on different scale. A total score is calculated in order to synthesize the whole analysis. The formula is the following.

$$\text{TotScore}_{A1} = \sum_{j=1}^{m} W_{Cj} \; * \; \sum_{i=1}^{ncj} W_{Bi}^{Cj} * W_{A1}^{Bi^{Cj}} \quad (1)$$

m = *number of clusters of need*

n_{Cj} = *number of needs which compose the cluster* C_j

W_{Cj} = *inter-criteria weight of the cluster of needs* C_j

W_{Bi}^{Cj} = *meso-criteria weight of the need* B_i *in the cluster* C_j

$W_{Ai}^{Bj^{Cj}}$ = *intra-criteria satisfaction degree of the alternative A respect to the need* B_i *in the cluster* C_j

By applying the Mu.S.Me.T.A. to AHP it is possible to provide graphically the fitting of any alternative with any need. This representation is obtained by using a Strengths, Weaknesses, Opportunities, and Threats (S.W.O.T.) analysis. This representation can be easily presented to decision makers not well skilled in mathematical methods.
Another representation consists in evaluating the partial score of an alternative A with clusters of needs.

The score is calculated using the following formula:

$$\text{Score}_{Ai}^{Cj} = \sum_{i=1}^{n_{cj}} W_{Bi}^{Cj} * W_{Ai}^{Bi^{Cj}}$$

n_{Cj} = *number of needs which compose the cluster* C_j

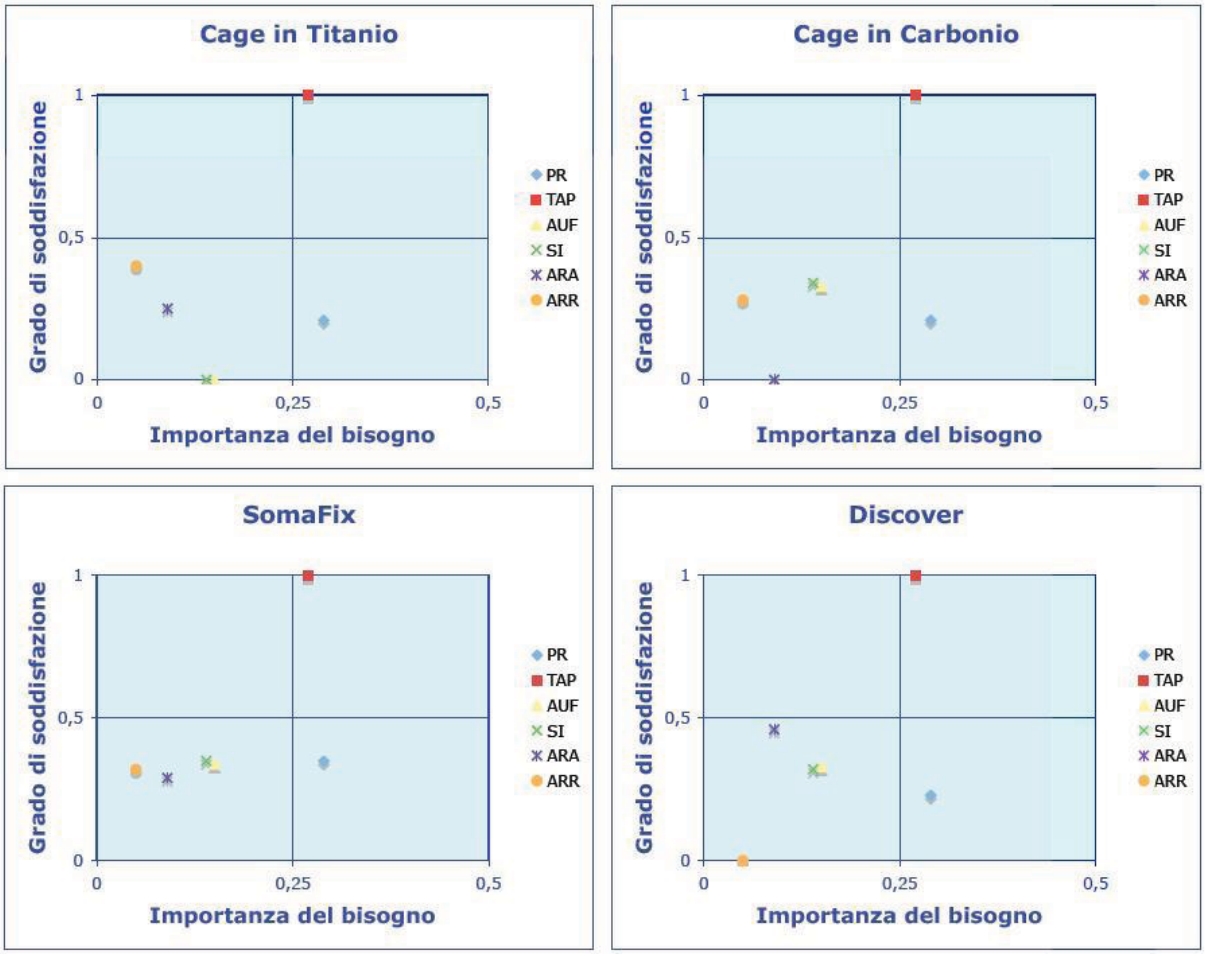
W_{Bi}^{Cj} = *meso-criteria weight of the need* B_i *in the cluster* C_j

$W_{Ai}^{Bi^{Cj}}$ = *intracriteria satisfaction degree of the alternative A respect to the need* B_i *in the cluster* C_j

In the described problem it is possible to evaluate *m* partial scores for any alternative A that means one for each cluster of needs. Finally a bar representation can easily compare the fitting of any alternative with any clusters of needs.

Results

The analysis of case study drives to the results showed in the following SWOT (Strenghs, Weaknesses, Opportunities, Threats) analysis for clinical needs which is represented in the first graphic; the partial scores are given both in the tables and through the diagram chart; the total score in the last table synthesizes this study..

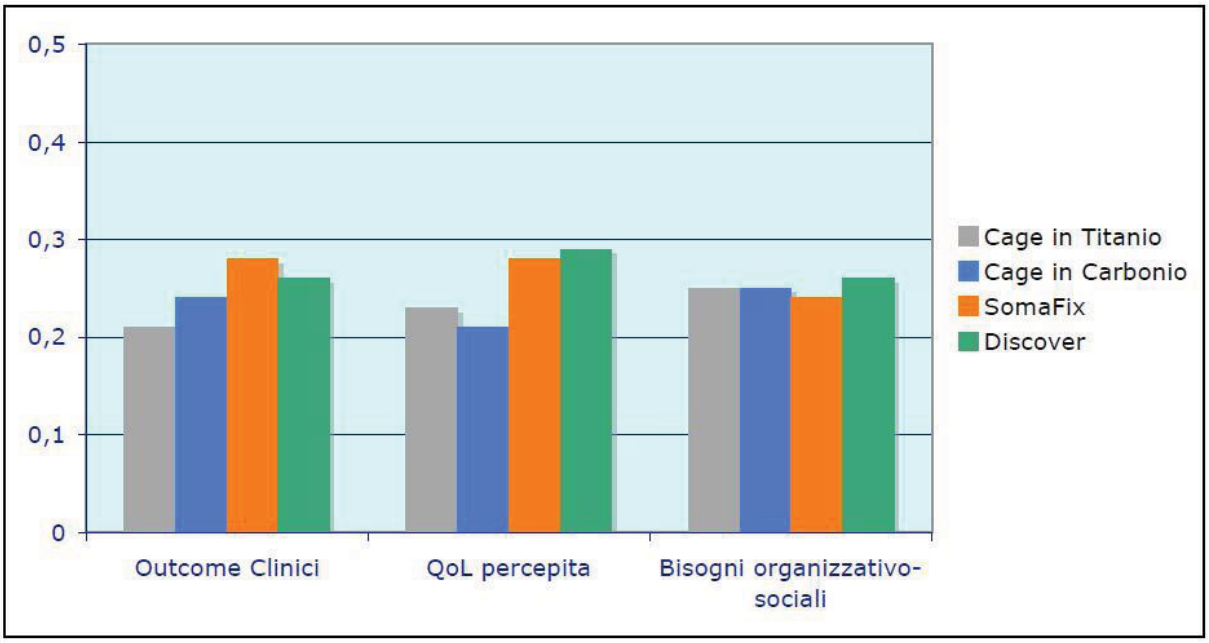


PR, TAP, AUF, SI, ARA, ARR are the mesocriteria weights.
"*Grado di soddisfazione*": Satisfaction
"*Importanza del bisogno*": Importance of the need

Partial score for clinical outcome				
	Titanium Cage	**Carbon Cage**	**SomaFix**	**Discover**
Score	0.21	0.24	0.28	0.26

Partial Score for managerial needs				
	Titanium Cage	**Carbon cage**	**SomaFix**	**Discover**
Score	0.25	0.25	0.24	0.26

Partial Score for felt quality of life				
	Titanium Cage	**Carbon cage**	**SomaFix**	**Discover**
Score	0.23	0.21	0.28	0.29



Total Score				
	Titanium Cage	**Carbon cage**	**SomaFix**	**Discover**
Total Score	0.22	0.23	0.28	0.27

Some ideas of thinking further are:

The method under examination, and particularly with SWOT analysis, outlined and compared the strangeness of different technologies for every identified need. The graphical representation may be easily understood and may be a good support to decisions makers. Besides, the representation of the partial score allows evaluating the satisfaction rate reached by each technology under comparison and for every categories of need. The final decision is obtained considering the judgments of the interviewed experts and the health state of a simple of patients.

In conclusion, the total score gives an indication that the non-fusion technologies are generally preferred over fusion. By analyzing the partial scores is clear that the fusion technologies have less impact in the management and this is understandable considering that these technologies are already in use for many years. On the other hand, the net clinical benefit and improved quality of life perceived by patients, drive the choice to the most innovative non-fusion technologies.

This case is about a criteria of choise using the tool AHP (Analytic Hierarchy Process) to drive to an Health Technology Assesment (HTA). The teaching is on the tool AHP that aid to take important decisions in every field. It may appear not easy in the beginning but a lot of exemples are avaible on line to understand how to manage it.
It is possible to watch a video guide on this link: http://www.youtube.com/watch?v=G1xrL59RsBM
or http://www.youtube.com/watch?v=18GWVtVAAzs
What have to be clear is that AHP is decision tool based on subjective opinion (satisfaction, feeling, preferences, etc.) that is filtered by a ratio scale that gives an output as a consistency decision index.
It works doing few steps: 1) Define objective; 2) Structure elements in criteria, sub criteria, etc.; 3) Make a pair wise comparison of elements in each group; 4) Calculating weighting and consistency ratio; 5) Evaluate alternatives according weighting

« Repositioning of an approved drug as a treatment for an orphan disease »

Case study in the framework of the Health-2-Market project seminar
"Intellectual Property Management and Open Innovation in Health/Life Science"

*all names of actors have been changed for publication

Author: APRE

Table of content

1. Key questions addressed by the case

This case study provides an example of intellectual properties management about pharmacological transfer. It means the implementation of a secondary use for a known pharmaceutical compound.
How to use a patented drug on other disease, creating a new patent application.
It is developed for the seminar 3: Intellectual Property Management and Open Innovation in Health/Life Sciences (Ref. IPM) of the Health 2 Market project.
Participants will learn to:

- Manage an intellectual pharmaceutical property
- Manage open innovation for development, production and distribution of new drug
- Check the market potentials
- Manage the new IPR on other application of the drug

2. Market

2.1. Market size

The market analysis is a typical "orphan drug" case with no huge market, but with a mature market.

Analysis of Situation
The market is urgently waiting for a therapeutic solution for FA.

Technical features
Preclinical studies were done on the murine model for the disease and the results were encouraging. Phase II clinical trials are underway.

Customers
There is one patient every ~50.000 individuals. There are more than one thousand FA patients in Italy and 20-25 thousands FA patients in EU, USA and Canada collectively.

Financing
Funds for supporting this program has been provided by FA patient associations and charities.

2.2. Market potential and stakeholders

Competitors
There are many competitors searching for a therapeutic solution for FA . Different companies are using different strategies. No one is doing R&D using γ-interferon. Obviously it is hard to know in which phase the competitors are, but of course no one has reached the final step of registration.

3. Company

3.1. Profile of the founders / of the current and potential future associates

CEO

Rob Stark, M.D., is full Professor of Immunology at the School of Medicine, University of Rome "Tor Vergata". He has more than 30 years of experience in research and more than 12 years in FA disease. He trained at the Dana Farber Cancer Institute, Harvard University, Boston MA, USA, then at the Monoclonal Center, Becton Dickinson, Mountian View CA, USA. He was also appointed Research Assistant at the University of California San Francisco, San Francisco CA, USA. In 1994 he started the Laboratory of Signal Trasduction (LABST) at the University of Rome "Tor Vergata".

In the past 20 years the research group led by Prof. Testi has been funded by several European Commission Framework Programs, by the European Research Council, by Telethon Italia, Ataxia UK (UK), Friedreich's Ataxia Research Alliance (USA), National Ataxia Foundation (USA) and Association Française de l'Ataxie de Friedreich (France). Prof. Testi served as biotechnology consulting expert for SKGF Attorneys at law, Washington DC, USA (2006-2008) and was the founder and chairman of BioTech Value, a biotech asset valuation firm.

In 2012 he founded Romax Therapeutics LLC, a company committed to develop a therapy for Friedreich ataxia. Dr. Testi serves as CEO for Romax Therapeutics.

CSO

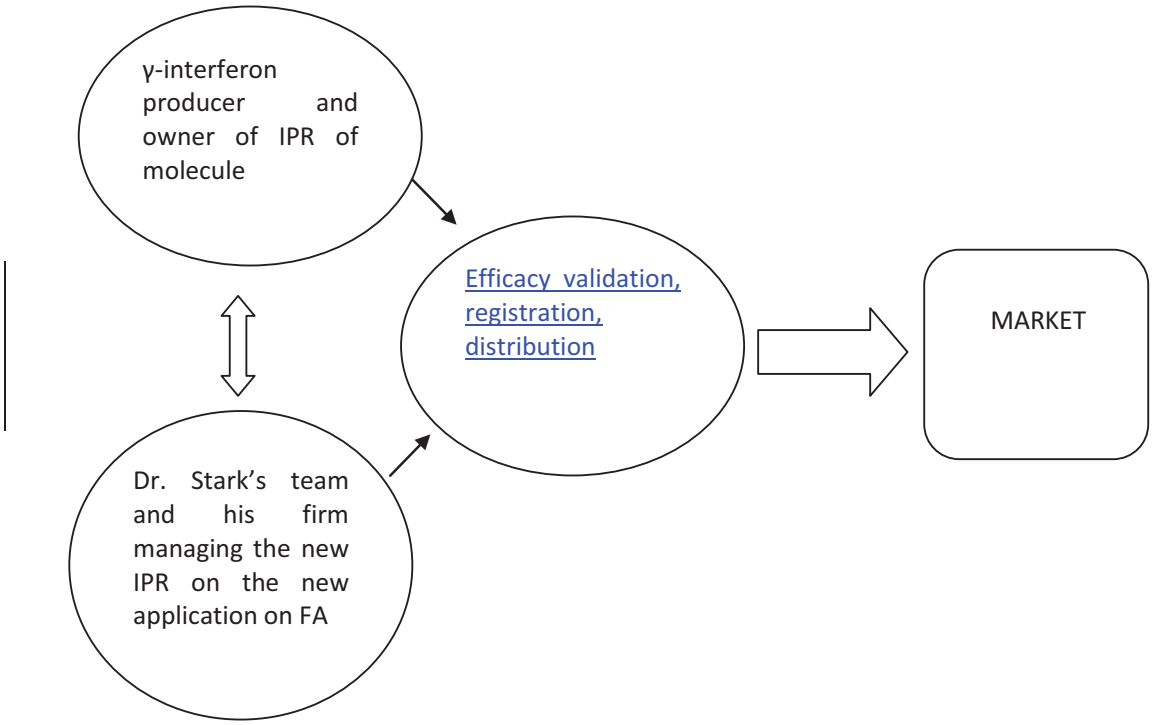
Airyn Lanny PhD., is a close Dr. Stark's collaborator. She has more than 20 years' experience in R&D, more than 10 years' experience in FA research and currently coordinates a team of 15 researchers. Dr. Rufini serves as CSO for Romax Therapeutics.'s development: the technology and its regulations / intellectual property issues

3.2. Opportunities for development of the company

This case is about repositioning of an approved drug as a treatment for an orphan disease. Drug repositioning occurs when a new indication is found for an approved drug. Repositioning is an alternative to creating a novel drug in introducing a novel treatment. There are three main motivations to do this: 1) Reduce the immense cost and risk associated to the development of a new drug; 2) Reduce time to launch the drug in the market; 3) Generate a new opportunity of business for the owner of the molecule of the drug.

In drug repositioning, generally the IP on the molecule remains to the owner of the drug, but a new IP is generated for the new application of the drug. In this particular case, the IP on γ-interferon belongs to the owner, while the IPR for the new application, that is for the use of γ-interferon as a treatment for FA, belongs to Prof. Stark and will be managed by Romax Therapeutics.
The owner of the drug has an interest in extending the label of the drug to the new indication, as this would expand its potential market. In this case, moreover, the new indication of "orphan" disease,

the owner of the drug would benefit from the financial facilitations and leaner regulatory constrains that are granted for the developing of orphan drugs compared to common drugs.



3.3. Identifying modes of development and financing

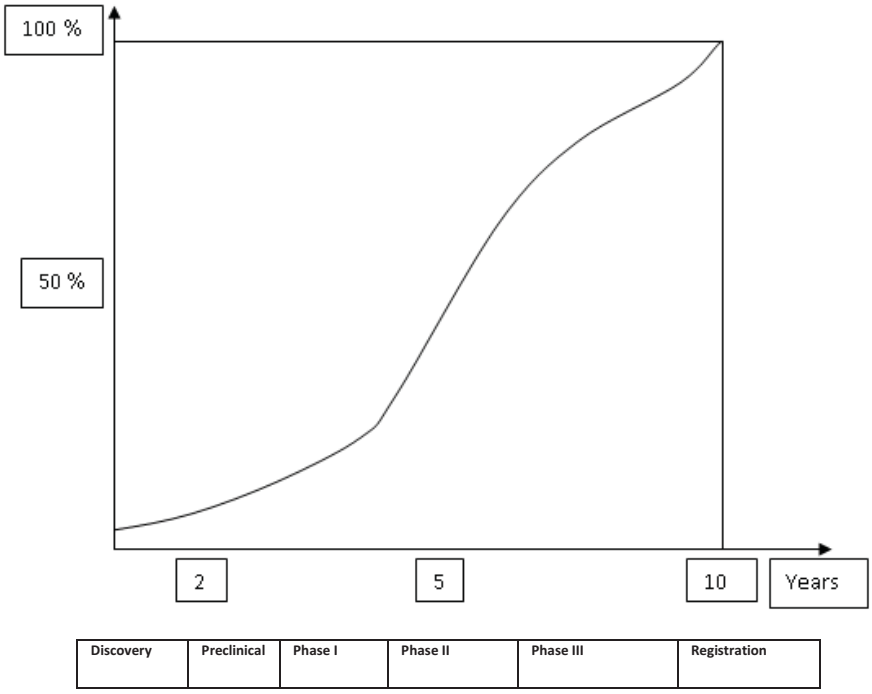
Funds for supporting this program has been provided by FA patient associations and charities.
In the next future the owner of the IPR of the drug will participate in a part of the costs.

3.4. Future actions and decisions to be taken

Friedreich ataxia (FA) is a rare genetic disease with no available therapy (orphan disease). FA affects children and young adults and it is characterized by progressive loss of coordination and motor skills as well as by severe cardiovascular problems. The idea is to develop γ-interferon as a therapy for FA. There are currently two Phase II clinical trials ongoing in Italy and in the US aimed at verifying the tolerability and biochemical efficacy of γ-interferon in FA patients.

3.5. Objectives of development to be achieved after 18 months

In the next months will start the human experimentation in large scale. At the end of this step it will reach the third phase and the drug will be ready to be commercialized. The phases of development are shown in the following graph.
Reduction time to lunch a drug by repositioning is about 50% .



4. Lessons learnt and thinking further

This case shows how a drug repositioning works and how is possible to manage the agreements on IPR for the new application.
There are always three actors in this kind of business:

1) The owner of molecule
2) The Research Team
3) The Pharma enterprise that cares about larger clinical trials, registration and distribution.

Beyond the specific agreements, the important message is how to identify a business opportunity and how to manage the process of developing, funding research, and IPR management when a new possible use is found for a drug that is different from those indicated in the label.

Terracycle (A): Getting the Cycle Going?

Key thematic area: entrepreneurship; technology & innovation; financing for startups

Problem treated: what are the different sources of financing for startups and how should a startup choose investors

Interesting for H2M academy / seminar topic:

- Seminar 4: Marketing of Innovation and Effectual Entrepreneurship (Ref: ISMA) (by SKEMA);
- Seminar 7: Identifying Entrepreneurial Opportunities and Understanding Modes of Financing (Ref: EOF) (by IE);
- Academy 3: New Venture Creation and Marketing (Ref:NVC) (by IE)

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Summary

Terracycle was founded in 2001 by Princeton undergrad Tom Szaky and his classmate, Jon Beyer with the goal of turning organic waste into organic fertilizer through the process of vermicomposting.

The case is set in March 2003. Terracycle has proven that the use of vermicomposting for the industrial-scale production of organic fertilizer is feasible. However, despite having won a few business plan competitions and used funds from friends and family willing to help, the Terracycle team has not secured any markets yet and is running out of money.

Terracycle has just won one more business plan competition organized by Carrot Capital, which has promised to invest $1,000,000 in the startup if their stringent terms are met. Tom Szaky, however, is worried that accepting Carrot Capital's terms might compromise Terracycle's environmental identity and the interests of early investors and supporters. He is thus willing to consider other financing options including friends and family, angel investors, and corporate investors.

The case examines the different motives, interests, and priorities of different kinds of investors, as well as their different (financial and non-financial) contributions for a startup. The advantages and disadvantages of choosing any kind of an investor over others are discussed though a hands-on, in-class role play.

Source

Authors: Hana Milanov & Cristina Cruz, IE professors of entrepreneurship

Website: http://www.ie.edu/eng/claustro/claustro_casos2.asp?id=9709

"Health-2-Market has received funding from the European Union's Seventh Programme for research, technological development and demonstration under grant agreement No 305532"

« Kinimage: Preparing to license out a novel medical imaging technology* »

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Case study in the framework of the Health-2-Market project

*all names of actors have been changed for publication

Author: Q-PLAN INTERNATIONAL

"Health-2-Market has received funding from the European Union's Seventh Programme for research, technological development and demonstration under grant agreement No 305532"

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"Health-2-Market has received funding from the European Union's Seventh Programme for research, technological development and demonstration under grant agreement No 305532"

Key concepts addressed by the case

Knowledge and technology have become an integral part of the European economy. Companies ranging from budding start-ups over to large multinationals are increasingly leveraging the licensing of intangible assets, such as patents, utility models design rights, trade secrets and know-how, in order to generate revenue and grow within a framework of open innovation.

However, technology licensing, more often than not, implies undertaking intricate negotiations aimed at achieving an agreement on a complex set of terms. In this respect, the lack of proper preparation can be a major reason for negotiation failure especially when stakeholders cannot handle deviation from “what should have happened”.

Therefore, preparing in advance is crucial. Prior to the negotiation of technology licensing agreements and before approaching the other party, you may have to spend a long time, spanning from a few weeks to several months, determining your business objectives, collecting intelligence on the other party, identifying any leverage you might use during the negotiations, defining your position on key terms of the potential agreement and protecting your valuable intellectual property, among other tasks.

In this context and in order for you to develop an introductory understanding of licensing-based business development, the current case study provides you with valuable insights on how to prepare yourself for engaging into negotiations with prospective licensees, as experienced through the perspective of Dr György Horváth and Dr Zoltán Oláh, two Hungarian researchers aiming to valorise their promising medical imaging technology.

“Health-2-Market has received funding from the European Union’s Seventh Programme for research, technological development and demonstration under grant agreement No 305532”

1. Introduction

Dr György Horváth and Dr Zoltán Oláh have been working together on several research projects in the fields of diagnostics and medical imaging since 1997. The culmination of their joint efforts, however, came 13 years later with the successful development of an innovative and dynamic imaging technique that can effectively depict motion on one single image. This kinetic image, as they call it, holds promising potential to open up new possibilities in medical applications. Indeed, the kinetic image can provide several existing imaging techniques (e.g. electron microscopy, X-ray projection radiography, X-ray angiography, etc.) with movement-related functional information by installing a simple and inexpensive firmware/software upgrade to relevant medical imaging equipment.

In 2011 and with a view to commercialising their promising technology, György and Zoltán contacted several large medical equipment manufacturers after filing a Provisional Patent Application[1] (PPA) in the US. In fact, during May of the same year, they had personal meetings with the leaders of four different R&D departments of four respective large medical equipment manufacturers. They all seemed to be quite interested in the potential of licensing in the novel technology so as to integrate it into their medical imaging equipment, but eventually discussions did not lead to any fruitful results. At the time, the PPA was just filed and as no examination report of any kind was available yet, many details of the technology were not possible to be revealed. Furthermore, the researchers had no clear idea of any medical indication in which their technology could be of use or in what instruments exactly could prospective licensees integrate the novel technology. It was evident that they had to prepare a lot better before negotiating further with their potential licensees.

Four years later, in 2015, the situation has improved considerably. A legal entity, Kinimage Ltd. (i.e. a limited liability company), has been set up by György and Zoltán to commercialise their dynamic imaging technology. An international application under the Patent Cooperation Treaty[2] (PCT) has been filed for the US and several EU countries within the timeframe required by the PPA (i.e. 1 year from filing the PPA). A Hungarian Intellectual Property law firm has been commissioned to undertake the patenting of the technology and the patents are expected to be granted within the year. The lawyers have also helped the researchers with all the necessary documents and contracts ensuring that Kinimage has all the Intellectual Property Rights to the technology and no other party can make any claims to its Intellectual Property. Furthermore, the PCT international search report on the

[1] According to the US Patent and Trademark Office (USPTO): "A provisional patent application allows you to file without a formal patent claim, oath or declaration, or any information disclosure (prior art) statement. Typically, a provisional application for patent in the US has a pendency lasting 12 months from the date the provisional application is filed. The 12-month pendency period cannot be extended. Therefore, an applicant who files a provisional application must file a corresponding nonprovisional application for patent (nonprovisional application) during the 12-month pendency period of the provisional application in order to benefit from the earlier filing of the provisional application". Available at: http://www.uspto.gov/patents-getting-started/patent-basics/types-patent-applications/provisional-application-patent

[2] According to the World Intellectual Property Organisation (WIPO): "The Patent Cooperation Treaty (PCT) assists applicants in seeking patent protection internationally for their inventions, helps patent Offices with their patent granting decisions, and facilitates public access to a wealth of technical information relating to those inventions. By filing one international patent application under the PCT, applicants can simultaneously seek protection for an invention in 148 countries throughout the world". Available at: http://www.wipo.int/pct/en

"Health-2-Market has received funding from the European Union's Seventh Programme for research, technological development and demonstration under grant agreement No 305532"

technology is now available and detailed descriptions have already been published (i.e. the patent application has been disclosed as well as a paper in a relevant scientific journal has been published). Moreover, the researchers have finally identified a specific medical indication on which their innovative imaging technique can be applied with promising business potential. Therefore, now, they can start approaching potential licensees anew, specifying the instruments on which they could implement their technology with an attractive value proposition. They have also conducted some market research so as to collect information on large medical equipment manufacturers and identify potential opportunities that they can capitalize on, in order to valorise their novel medical imaging technology.

However, both György and Zoltán are aware that further preparation is required before meeting and negotiating with potential licensees, given that all of them are large multinational companies with an equally large bargaining power and 'menacing' legal departments. As such, the researchers decide to contact Melina Tóth, a licensing expert with extensive experience in the healthcare sector. With the support of Melina and before they start making any contacts with potential licensees, they will have to take important decisions regarding some key issues:

- What are the business objectives to be achieved through the out licensing agreement?
- How much should they price their innovative technology?
- Is an exclusivity commitment the way to go? If so, what means could they utilize to minimize the risks implied?
- What else could they offer to make their technology more appealing to prospective licensees?
- What are their main and fallback positions on key terms of the licensing agreement?
- Who will be part of the negotiating team and which strategy will they follow during negotiations?
- Will there be a need for any preliminary agreements (e.g. confidentiality agreements)?

The section that follows provides an overview of the problem that Kinimage is trying to address as well as the solution it is offering to this end, along with important insights that were revealed by the market research conducted by György and Zoltán.

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2. X-ray radiation - implications and the market for imaging solutions with reduced dose

2.1. The problem

Fluoroscopy and mobile C-arms are widespread medical diagnostic tools that utilize X-rays to visualise motions that transpire inside the organism of a patient. They provide valuable information and guidance to physicians in many common medical procedures, such as liver biopsies and orthopaedic surgeries. However, despite their benefits, fluoroscopy and mobile C-arms imply exposure to X-radiation, which increases the risk of cancer. In fact, studies reveal that medical imaging may account for 1 – 3 % of cancer occurrences worldwide[3].

Given that the risk of cancer from X-ray exposure increases as radiation dose increases, there is a growing demand from the healthcare industry for technologies that could significantly reduce radiation dose during medical examinations that utilize X-rays. Indeed, when researching their target market, György and Zoltán found several evidence indicating that lowering X-ray dose to the minimum possible level, while being able to obtain the required diagnostic information, is a major goal of medical imaging equipment manufacturers. This growing demand for medical imaging solutions that imply a significantly reduced dose of X-radiation presented the researchers with a great business opportunity to profitably valorise their dynamic imaging technique.

2.2. The solution

The cutting-edge imaging technology developed by the Hungarian researchers enables fluoroscopy and mobile C-arms medical devices to capture motion-related diagnostic information in a single image and thus has the potential to drastically reduce the radiation dose involved in X-ray based medical examinations (i.e. 10 to 20 times). In particular, it collects several underexposed X-ray images, while keeping the overall radiation dose and measurement time about the same as required to produce a single correctly exposed image. A statistical analysis of the data provides four images at once, the most important of which is a new kinetic image that represents motions inside the patient. Besides the kinetic image, the new technology also reconstructs static images which are practically identical to the existing conventional X-ray images. The error images of both static and kinetic images are also calculated.

In result, Kinimage has the potential to provide fluoroscopy and C-arms equipment manufacturers with a promising solution which can be inexpensively implemented on their existing fluoroscopy and C-arms setups via a simple firmware/software upgrade, allowing them to address the growing demand of healthcare professionals for X-ray imaging techniques that are not as harmful to the long-term health of their patients.

[3] de González, A. B. & Darby, S. (2004), "Risk of cancer from diagnostic X-rays: estimates for the UK and 14 other countries", *The lancet*, 363(9406), pp. 345-351.

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2.3. The market for the solution

In order to efficiently get a quick overview of the current situation of the market for their solution, György and Zoltán employed a targeted internet search. They found out that the market for fluoroscopy and mobile C-arms X-ray imaging devices, in 2012, was estimated to be worth $1.7 billion in terms of revenue. Fluoroscopic equipment represented the biggest share (56%) of the market, generating revenues of $943.9M, in comparison to mobile C-arms which accounted for $751.5M. From a geographic perspective, the most promising markets identified, were those of North America and Europe which, combined, represented 71% of the global market.

A promising finding which the researchers unearthed, was that the market appears to be growing over the past few years and it is expected to continue as such in the future as well. In fact, the fluoroscopy and C-arms market is estimated to grow with a 3% Compound Annual Growth Rate[4] (CAGR) over 5 years reaching almost $2 billion in 2017. The growth of the market is mainly driven by (i) the need for lower X-radiation dose which calls for the development and commercialization of innovative medical imaging solutions; (ii) a growing pressure from public bodies for new methods to reduce X-radiation exposure to patients as well as medical staff[5]; and (iii) an increasing preference of patients for minimally invasive medical practices that employ medical imaging devices over open surgeries.

With a firm grasp of the current situation and future potential of their target market, György and Zoltán then focused on potential licensees. Once again, through a quick internet research, the researchers were able to access the public annual reports of large medical equipment manufacturers and learn more about them. In fact, the top 3 manufacturers, globally, are subsidiaries of multinational corporations, namely General Electric Healthcare, Siemens Healthcare and Phillips Healthcare, which together hold 66% of the entire market. It was evident that if the researchers wanted to “play ball” with these big players of the market they would have to be properly prepared.

Finally, it was time to have a look at competing technologies. In this respect, their market research revealed that the need for X-radiation dose reduction in medical imaging is currently being satisfied mainly through small incremental improvements of existing fluoroscopic and C-arms equipment, developed either by innovative companies (e.g. start-ups and university spin-offs) or by medical imaging equipment manufacturers themselves. Despite the aforementioned improvements, however, the risks remain severe and concerning, as radiation dose still stands at high levels, posing a threat for patients as well as for the user(s) of the device.

Based on the findings of their market research, György and Zoltán were assured that there is a growing demand for medical imaging equipment and technological innovations that reduce X-radiation at global level, which in turn would provide a fertile ground for the market uptake of their novel solution.

[4] The Compound Annual Growth Rate describes the rate at which an investment would have grown if it grew at a steady rate over a certain time period (e.g. years).
[5] For example in the US both the National Council for Radiation Protection and Measurements (NCRP) and the Food and Drug Administration (FDA) have launched relevant initiatives.

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3. Preparing for negotiations

Equipped with a better understanding of their target market, customers and competition, György and Zoltán were optimistic about the business opportunity that was presented to them in view of the commercialization of their innovative technology via out licensing. However, it also became apparent to them that they were up for a great challenge which might not end well without professional support. They were both well-experienced and dedicated researchers but lacked the necessary expertise to negotiate and achieve a mutually beneficial licensing agreement with a large medical equipment manufacturer. Therefore, they decided to enlist the help of Melina Tóth, an old acquaintance of Zoltán and seasoned licensing expert in the healthcare sector.

In order to properly prepare György and Zoltán for technology licensing negotiations, Melina focused on some key issues, which had to be properly addressed before approaching any prospective licensee(s).

Defining the business objectives of the licensing agreement

Melina explained that György and Zoltán will have to determine how Kinimage will generate revenue through the out licensing agreement based on its dynamic imaging technology. In this respect, the most likely out-licensing model that the researchers are currently thinking of adopting is charging licensees with an upfront payment followed by annual royalty payments. In particular, this model implies: (i) an upfront payment made by the medical equipment manufacturer in order to acquire the use of the Intellectual Property Rights for the patent and (ii) subsequent annual royalty payments based on increased revenues that will stem from the installation of the novel technology to the medical imaging equipment of the licensee.

In order to increase the appeal of their novel technology as well as their profitability, György and Zoltán are willing to provide a prospective licensee with exclusive rights to use the technology in the field of medical imaging (i.e. field of use licensing), a strategy that can provide substantial benefits to both sides: Kinimage will benefit from higher payments that will enable the company to dedicate more funds to continue their R&D work on other fields of application, whereas the licensee will obtain exclusive rights to employ a pioneering technology that will boost its competitiveness against other medical equipment manufacturers. However, Melina warned them that this way the researchers will be "putting all their eggs in one basket", relying solely on the revenues generated by a single licensee. If the researchers decide to go with this exclusivity commitment, what could they do in order to minimize the risks implied? For instance, they could tie the exclusivity of the rights on the capacity of the licensee to achieve a certain amount of annual product sales or limit the exclusivity to a shorter time period providing the licensee with a head start against its competitors. As means to make their offering more appealing, Kinimage could also provide prospective licensee(s) with know-how and support to implement the technology. However this may require them to hire additional personnel to undertake the increased work required. What else could they offer in order to make their intellectual property more appealing to their potential licensee(s)?

Finally, György and Zoltán will need to consider how much revenue the agreement should generate to be considered as viable business for their company. In other words they will have to determine a

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proper methodology to place a suitable value to their technology. In this respect, they have to carefully calculate how much they expect their licensee to earn by licensing their novel technology. To this end, Melina suggested that commissioning the help of an accountant or financial expert with background on intellectual property valuation could prove essential for concluding on a proper price for their dynamic imaging technology.

Determining the desired position on key terms of the licensing agreement

The key terms refer to the crucial business and legal terms of which a licensing agreement is comprised. In order to work through these key terms with the researchers of Kinimage and help them decide on their positions, Melina decided to use a term sheet (see Appendix). A term sheet is a brief outline (1 or 2 pages maximum) of the key issues pertaining to a licensing agreement along with a provisional statement under each key term indicating the position of the authors. It has many functions, the most crucial of which is to help the authors sort through the many complex issues that a technology license involves, while at the same time ensuring that none of them goes unaddressed.

Melina explained that György and Zoltán would have to draft both an internal term sheet, to be used only by the researchers as well as an external one to be provided to prospective licensees during negotiations with a view to facilitating the agreement. The first step, of course, would be the preparation of the internal version. The researchers will have to define their position on each key term based on their business objectives as well as to carefully consider potential fall-back positions in order to effectively prepare for any deviations from their ideal planning. Melina will then review the sheet and propose edits, before proceeding on drafting the external version of the term sheet to be used on future negotiations.

Deciding on the members of the negotiating team and the strategy to be employed

A crucial aspect of preparing for technology licensing negotiations is deciding on the individuals that will comprise the negotiating team. This includes appointing the main spokesperson of the team as well as at least one member who will serve a supporting role. Melina volunteered to be part of the team providing legal counselling as well as be responsible for drafting the agreement later on if negotiations progress favourably.

During the negotiations, the term sheet will guide the team and enable them to keep track of their business objectives. As part of their negotiating strategy György and Zoltán in cooperation with Melina, will have to prepare a 'first' as well as a 'bottom' liner for all terms in the term sheet. First liners are the terms that are set first in the negotiations and correspond to an aggressive and ideal position, whereas bottom liners refer to the minimum terms that should be agreed with the licensee in order for the business objectives of the agreement to be achieved. Melina highlighted that bottom liners should never be included in the term sheet (neither the internal nor the external version) for confidentiality reasons and in fact should not be disclosed unless necessary, a case which typically only happens when negations have progressed quite a lot.

However, what should be the strategy of the researchers if their bottom liners are not possible to be gained? In this respect, Melina advised the researchers to avoid any standstill agreements or

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agreements to negotiate on an exclusive basis as they impede the option of turning to an alternative licensee if negotiations prove to be unsuccessful.

Identifying the need for preliminary agreements

Given the nature of the licensing agreement, Melina highlighted that the researchers should be ready to sign confidentiality agreements with potential licensees prior to negotiations. The reason is that potential licensees may wish to evaluate the technology in advance to the negotiations and this should only be performed under a proper confidentiality agreement. Indeed, confidentiality agreements (also known as non-disclosure agreements) are vital when it comes to safeguarding business and/or technical disclosures which are realised during negotiations.

In this respect, Melina also warned the researchers not to agree on signing any Letters of Intent (LoI) or Memoranda of Understanding (MoU). These do not constitute agreements and their vague nature makes them insufficiently concrete for business objectives especially when the disclosure of highly sensitive information is involved.

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4. Lessons learned, next steps and thinking further

As György and Zoltán came to realise from their interactions with Melina, negotiations aimed at achieving mutually beneficial technology licensing agreements are undoubtedly complex. Important decisions have to be made on a wide variety of key issues with many alternative positions being possible, ranging from the most over to the least advantageous for either party.

Indeed, successfully realising transactions based on intellectual property licenses involves more than just determining a suitable price. The ultimate goal is to strike a good balance of value so that the agreement becomes a "win-win" transaction for all parties involved. In this respect, defining the business objectives to be achieved through the out licensing agreement and utilizing a term sheet to sort through the various key issues as well as guide negations with prospective licensees can prove invaluable. Furthermore, it is important to involve lawyers with licensing expertise from the beginning of the negotiations till the end. Frequent communication with a legal counsel who will also review the term sheet and provide support prior to drafting the agreement as well as during the drafting process are vital for success.

In the case of Kinimage, Melina has already laid out the next steps that are required in order to start preparing for negotiating the out licensing agreement of their novel technology. However, this is by no means the end of the line. In fact this is where some heavy thinking and careful decision making is required by György and Zoltán if they are to successfully complete their quest to valorise their research outcomes.

Questions and ideas for further thinking

- *Leverage is an important element of any negotiation. It refers to anything that a party has and can use during negotiations in order to make the other party more likely to agree to its terms. What leverage can György and Zoltán utilize to their advantage while negotiating the out licensing agreement of their innovative medical imaging technology?*

- *When preparing for negotiations, it is crucial to consider the strengths of the other party and what is likely to be their position on each key term. György and Zoltán have already identified some of their potential licensees' strengths through their market research. What means could they employ to gather further information and which ones would you choose to this end?*

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Appendix

Sample Term Sheet *	
Contact info of licensor(s)	
Subject matter	*Specification of use, technical description of the technology, patent numbers, any applicable standards, etc.*
Related agreements	*Development, consulting, training, service, etc.*
Development	*Is the technology completed and fully functional? If not who will complete it, do further research, correct design flaws, etc.*
Scope of license	*What rights are being licensed? Are they non-exclusive or exclusive?*
Derivative works and improvements	*Will the licensee have the right to modify in any way the technology or make new products based on the technology?*
Sub-licensing	*Will the licensee have the right to sub-license? If so, what rights will the sub-licensees get?*
Geographic territory	*Where can the licensee use the license?*
Field of Use	*Are there any limitations with respect to the technical fields of use?*
Financial	*What fees are to be paid by the licensee? What royalties and/or other payments? Are there any minimums or any caps to be applied on royalties? Will there be any advances required from the licensee?*
Term	*How long will the agreement last? Will the duration of the agreement depend on any events?*
Future versions	*Will there be an agreement on any license rights to future versions of the technology?*
Obligations	*What other obligations should either party have beyond the license (e.g. testing, marketing, clinical trials, meeting standards, etc.)?*
Disputes	*Where will legal disputes be settled?*
Important dates and deadlines	

**Source: World Intellectual Property Organisation (WIPO)*[6]

[6] WIPO (2015), "Successful Technology Licensing", IP Assets Management Series, available at: www.wipo.int/edocs/pubdocs/en/licensing/903/wipo_pub_903.pdf

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« VIDAVO,
Matching financing modes with business development stages »

Case study in the framework of the Health-2-Market project seminar
"Identifying entrepreneurial opportunities and understanding modes of financing"

Author: Q-Plan NG

"Health-2-Market is supported by the European Commission under the FP7-HEALTH programme"

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Tables and figures

1. Key questions addressed by the case

The financing needs of a company may vary greatly throughout its life cycle. It is imperative for entrepreneurs to carefully assess their capital needs, time horizon and motives before deciding which financing tools to utilize and when. This case presents an example of financing choices that were made depending on the stage of the business life cycle. For this purpose it follows the development course of Vidavo S.A., a small research oriented start-up that managed to evolve into a sustainable business by matching emerging business opportunities with the proper financing solutions.

The case addresses the participants of seminar 8: Identifying entrepreneurial opportunities and modes of financing.

Participants are expected to learn how to:

- Recognise what might constitute an opportunity for entrepreneurship.
- Analyze an opportunity and its constitutive parts, as well as evaluate its attractiveness.
- Understand different modes of financing and their advantages/disadvantages for entrepreneurial ventures.
- Determine where and what kind of financing to seek depending on the stage of their business life cycle.

2. Vidavo S.A. company

2.1. Profile of the company

Vidavo S.A. is a high tech company that operates in the field of eHealth and specializes in health telematics. The company was established in 2002 in Greece by a group of experienced scientists aiming at the:

- Development of novel integrated telematics solutions in the health care sector.
- Provision of continuous technical support of the health telematics applications.
- Provision of consulting services necessary for the effective integration of medical informatics in the health sector and for the optimization of the quality of the health care services.

The initial focus of the company was mainly in research and development. However, in 2005 the management team of Vidavo decided it was time to emphasize on the commercial exploitation of their developed and certified products. Critical to this endeavour was the help of business incubator THERMI S.A. which participated in the company's share capital and financed its commercial ventures. In 2010 the company was listed in the public Alternative Market of the Athens Stock Exchange market. During its 10 and more years of operation, Vidavo has won several awards and distinctions for its innovative action. Moreover, it has participated in several projects under EU funded Framework Programmes for Research and Development accumulating extensive experience in the implementation of both national and European research and deployment projects and has developed close collaboration links with health care authorities, key market players, technology brokers, telecommunication actors and academic / research institutes.

Currently Vidavo S.A. is the leader of the Greek health telematics market employing 16 highly efficient and experienced professionals (engineers, computer scientists and economists) out of which 12 are located in its headquarters in Thessaloniki, two in Athens and two in Cyprus. The company maintains affiliate cooperation with experts in Brussels, Barcelona and Boston.

Vidavo envisages the adoption and local commercial deployment of international eHealth trends and practices in an attempt to bridge the gap between health care centres and patients while striving for wellness and prevention, instead of disease management and treatment plans.

2.2. Vidavo's Solutions

Vidavo offers a unique combination of innovative health telematics solutions assisting citizens on the move and medical professionals to manage health and wellness by utilizing the latest developments in wireless communication and telemedicine. Specifically, the company offers a wide array of products and services that may be classified into two general categories, namely **innovative technology integration** and **guidance**.

Innovative technology integration regards the technical aspect of telematics and encompasses the following:

- **Provision of comprehensive eHealth solutions** consisting of telematics equipment and software applications for health care providers, developed by the company's department of research and development.
- **Development and customization of software** in accordance with European and international standards addressing the particular needs of individual customers and aiming at the optimization of the quality of the health care services.
- **Development of advanced telematics applications**, addressing all aspects of the health care provision ranging from prevention to remote diagnosis and remote monitoring.
- **Integration and interoperability** of the new products/services with existing systems and services.
- **Technical support and continuous development** of aforementioned products and systems.

The main systems and services of this category are:

- **Vida24 (telemetry)**: an innovative patient telemonitoring service, which enables ubiquitous communication and interaction between patient and doctor.
- **Vidahome (homecare)**: an advanced personal emergency response service ideal for supporting the independent living of seniors.
- **VidaΨ (telepsychiatry)**: an innovative web based psychiatry system that focuses on the psychological/mental state of the patient and supports teleconference and teleconsulting.
- **Vidatrack (tracking and safety)**: a personal tracking service for emergency situations concerning children, elderly people and patients with chronic diseases.

Apart from software developed by the company's R&D department, **Vidavo also uses standardized commercial applications for the deployment of integrated health telematics solutions**. The applications are purchased along with the medical equipment necessary for the specific service.

The **guidance service category** regards the consulting aspect of telematics and incorporates:

- **Guidance and consulting services to healthcare providers** for the effective exploitation of novel technologies and the identification of opportunities in the field of health telematics, specializing in interoperability and integrated large scale applications in eHealth.
- **Support of health actors on the strategic level,** aiming at improved processes, better management of medical information, improved health care provision and cost reduction.

- **Conduction of viability and feasibility studies and cost effectiveness analyses** in order to explore the effectiveness of a new application prior to market launch and integration in everyday activities.
- **Project management of privately or publicly funded Health related research projects**, aiming at the development of new products and systems.

2.3. Vidavo's Market

According to the World Health Organization (WHO) the term **eHealth** refers to the "transfer of health resources and health care by electronic means". It encompasses **three main areas**: (i) The **delivery of health related information** for health professionals and health consumers via the internet and telecommunications, (ii) **employing the potential of Information and Communication Technologies (ICT) and e-commerce** in order to improve public health services (e.g. through the education and training of the workforce), and (iii) the **adoption of e-commerce and e-business practices** in health management systems.

Health telematics applications utilize information and communication technologies for the delivery of health related information enabling the near instantaneous transmission of information over vast physical distances. As such, health care can become accessible in places and situations where none or very little was available before. Moreover, the remote monitoring of vital signs enables the monitoring of chronic patients without requiring the physical presence of the patient in a medical centre. Considering the fast paced life style of contemporary times, remote monitoring can be translated into saving time and money. The many benefits of telematics applications in health care make the respective market a rapidly growing segment of the broader eHealth market.

Demand for health telematics in Greece, stems mainly from patients suffering from chronic conditions (e.g. cardiac, lung diseases and diabetes). Vidavo's market research (2007) revealed that the prevalence of chronic cardiac diseases, obstructive pulmonary diseases, asthma and diabetes, among the Greek population is reaching 20%, 8.4%, 2-3% and 3-4% respectively. Patients suffering from the aforementioned diseases are advised to periodically monitor their vital signs. However, for more severe cases patients are required to follow a more rigorous regime, monitoring their vital signs at least 2 times a day. Vidavo has estimated the demand for health telematics coming from chronic patients:

Chronic Disease	Severe cases (%)	Patient Population
Cardiac	11%	1,100,000
Pulmonary	7%	700,000
Diabetes	1%	100,000
Total		**1,900,000**

Table 1: Demand estimates for health telematics

However, health telematics applications are not limited to chronic patients. Vidavo's health telematics solutions can be applied to a variety of scenarios and situations addressing the needs of a broad spectrum of the population:

- Post-surgery patients, while recovering at home, following hospitalization.
- People with disabilities.
- Older people who must often monitor their health status.
- Athletes (and sports teams) monitoring their health status and keeping records of their vital data, before and after practise in the sports field.
- All citizens who wish to monitor their health status and maintain their wellness.

Vidavo targets both end users and health care providers (private and public), facilitating the seamless flow of information between doctors and patients by offering innovative applications for the remote monitoring of patients' vital signs as well as the remote monitoring of chronic diseases. Specifically, **prospective customer groups** for Vidavo's service include **private health care providers that purchase the service as to enrich their own service portfolio**. They do not directly sell the service but employ it as complementary to their own. There are also **private health care providers that obtain the service in order to provide it directly to the end user**. This category encompasses mostly private diagnostic centres and ICT companies. An additional customer group regards **public health care providers** that buy the service in order to upgrade the quality of the services they provide to the general public. Finally, **end users** can also serve as potential customers as they are able to purchase the service from the company either directly or through an intermediary (e.g. technology broker). Specifically, end users are required to purchase a fixed-term subscription along with the specific medical device, designed for their particular condition.

Vidavo operates in close collaboration with several **intermediaries and partners** that support the company and contribute to its development. In particular, ICT companies support Vidavo by developing the informatics applications and the respective software that is necessary for the deployment of health telematics solutions. Additionally, manufacturing firms supply the company with the necessary telematics medical devices while consultancy firms provide assistance for the introduction of new business units.

In contrast, Vidavo faces **competition** in the health telematics market mainly from specialized ICT companies that focus on the development of systems and applications in the health care sector (e.g. Computer Team, Datamed and Apollo) and large ICT companies with departments that specialize in the development of telemedicine applications (e.g. Intracom and Altec Group).

2.4. Profile of the management team and current associates

The business development of Vidavo is inextricably connected with its management executives.

Founder and CEO

Dr. Angelides is the CEO and main shareholder of Vidavo. He has contributed vigorously to the creation and development of Vidavo S.A. and is a vital executive of the company. He is an Associate Professor at the department of Informatics and Telecommunications Engineering, University of Western Macedonia, Greece. He received his diploma and his Ph.D. from the School of Electrical Engineering, Aristotle University of Thessaloniki, Greece. He was a visiting scholar of MIT Media Lab 2009-10 and a lecturer at the University of Barcelona, Medical School. He has patented two telemedicine devices. He has worked as a technology expert in the areas of Telecommunications and eHealth for the past 20 years and has served as a project manager in over twenty international eHealth projects. He has presented more than 50 papers in international scientific conferences and published more than 30 original articles in international research journals. He serves as an evaluator of ICT projects for the European Commission in the areas of eHealth and Digital Inclusion. He was the leader of the CEN eEHIC PT and a member of the EC M/403 eHealth-INTEROP PT His research focuses on the accumulation, processing, transmission and representation of quality of life related information.

General Management

Ms. Psymarnou is the general manager of Vidavo. She has a B.Sc. in Business Management. She has many years of experience in designing and deploying health telematics projects and is an expert in the development of commercialization plans for research outcomes. She has served as coordinator of several research projects in the healthcare sector and has conducted numerous sustainability studies

of eHealth services. She has been part of Vidavo since the establishment of the company and has participated in various health telematics applications projects co-funded by the EU.

R&D and Co-funded projects
Ms. Vellidou is an Electrical Engineer (NTUA, GR), and holds a M.Sc. in Digital Signal Processing (UMIST, UK) and a M.Sc. in Management of Business Innovation and Technology (AIT, GR). She has spent more than 15 years in the telecom industry and her professional experience ranges from product research and development to management of large scale telecom projects implementation. She has participated in numerous European and national research projects mainly of the eHealth and biotechnology domains. Her current research interests include medical informatics, telemedicine, vital signal processing and diagnostic support systems. She leads the company's European collaboration activities and is a member of the Technical Chamber of Greece.

THERMI S.A.
THERMI S.A. consists of a group of companies that support the development of technologically innovative companies in all the stages of their business life cycle. THERMI Business Incubator nurtured the commercial growth of Vidavo and provided financial support during the company's early stages of development by participating in its share capital. THERMI S.A. still holds a company share of about 24% of Vidavo.

3. Company Development and Financial Choices

3.1. Concept Stage (2000 – 2001)

The concept of Vidavo was born from the entrepreneurial idea of Dr. Angelides and his fellow researchers. The vision was to match emerging information and communication technologies with the needs of the health care field. The entrepreneur recognized an emerging opportunity in the health telematics field and as a result the development of a prototype system began in the medical informatics lab of Aristotle University of Thessaloniki.

This **prototype system** (now called Vida24) was a comprehensive telematics application that enabled the remote provision of health care services away from the typical points of delivery (e.g. medical centres). Even though the product was originally designed to address the needs of patients suffering from chronic cardiac diseases, it **held the potential to revolutionize the Greek health care sector**, by introducing a novel type of remote health care service delivery, namely home care.

The **potential for an entrepreneurial venture** was very promising at the time. Vidavo would address a **very young and untapped market** in Greece with **great potential for growth**. The competition was still very low and **no company was offering integrated solutions** combining the deployment of health telematics applications along with supplementary consulting services. In addition, the **geographical landscape of Greece** includes numerous remote areas (islands and mountain regions) that do not have direct or easy access to health care services and where the health telematics applications of Vidavo could have an immense impact. Furthermore, **support from the national government** concerning the development of novel ICT solutions for the innovation of health and social care infrastructure was steadily increasing. Consequently, many **early adopters within the private health care sector** were beginning to search for innovative technology solutions to adopt. In fact, a well established diagnostic centre had already shown strong interest for the novel system of Vidavo. Finally, the synergies that could arise during the upcoming **Olympic Games (Athens 2004)** were very promising as well.

The financial resources for the development of the prototype were co-funded by the EU within the framework of the **"Distance Information Technologies for Home Care (CHS)" research project** under the **"Fifth Framework Programme - Information Society Technologies (FP5-IST)" programme**. Other costs involved in this concept stage, such as market research, product design, networking etc. were covered by the entrepreneur.

3.2. Start-up Stage (2002 – 2004)

The establishment of a start-up company requires the deployment of a variety of financial resources that have to be properly secured. The **initial costs** that Vidavo had to face involved mainly the expenditure for the procurement of the **medical equipment** that was required for the deployment of its solutions and the salaries of its **personnel**. Additional initial expenses included the conduction of a **market research study**, **promotion and advertising**, **overhead** costs (e.g. office rent and utilities bills) and **outsourcing** fees (e.g. accounting).

The personal funds of the entrepreneur were not sufficient to cover the start-up capital needs of the company and as a result, external sources had to be found. Available external modes of finance for Vidavo at this starting phase of the business life cycle were grants and other funding programmes (local or international) that aimed to boost technology transfer from academic and research organizations to the market.

The supplementary funds for the establishment of Vidavo were secured within the framework of **"Youth Entrepreneurship", a publicly funded Structural Funds programme** for the support of young entrepreneurs. In order to secure funding, the entrepreneur had to prove the feasibility of the venture, the credibility of the business model and the fact that the product or service will address an attractive market segment. The early composition of an effective business plan along with the attainment of the Innotender Innovation Competition Award (Innovation EC programme) were proved essential for Vidavo's approval, securing a funding rate of 50% for the company's start-up costs (the rest were covered by the entrepreneur).

With its initial capital needs covered, Vidavo focused its operations, during the first few years, on research and development by gaining several **national and EU research grants**. Furthermore, by participating in publicly funded R&D projects and by running pilot projects and applications Vidavo was able to fine tune its developed products and services and lay the groundwork for the commercial deployment of its solutions. Last but not least, the company was able to complement the funding of its operational costs with an additional **Structural Funds grant** that was released under the **Greek operational programme "Competitiveness"**.

3.3. Growth Stage (2005 – 2009)

In 2005 the management team of Vidavo decided that they were ready to focus their efforts on the commercial exploitation of their research outcomes. A critical task for any company at this phase is to secure the capital that is required to back the commercial ventures as equity from operational profits is still low. Options for alternative funding sources for Vidavo included business angels, venture capitals and business assistance programs such as business incubators. Ultimately, the commercial exploitation of Vidavo's novel solutions was supported by **business incubator "THERMI S.A."**.

Business incubators are designed to support the business development of entrepreneurial companies. Although most incubators differ in the way they provide their services and the type of clients they serve, the core of business incubation remains the same and consists of the **value-added**

services provided to their tenants. Such services include shared office services, administrative assistance, access to finance and business networks.

The main reasons that led Vidavo to become an incubatee in THERMI S.A. were to **access the valuable networking services** of the incubator and **secure the necessary capital** to focus on the commercial exploitation of its solutions while **enhancing the company's reputation and social standing**.

Vidavo was able to become a tenant of THERMI S.A. by following a specific procedure which began with the submission of the company's business plan. The business plan of Vidavo was initially screened by THERMI S.A. officials and was subsequently forwarded to the admission committee who made the final decision.

The **main admission criteria** upon which Vidavo was judged regarded the **existence of an effective business plan** and the **abilities of the management team**. The admission committee of THERMI S.A. also thoroughly assessed **the technology** that Vidavo employed and consequently **the level of the innovation**. The **magnitude of the targeted market** and the **development prospect** played an important role in the approval of Vidavo as well.

In addition to accessing the value added services (office space and networking) of THERMI S.A., Vidavo also received **Venture Capital** funding from the incubator aimed at the support of its commercial endeavours. The venture capital was offered via a **share capital increase**. The financial structure of Vidavo's share capital before and after the funding was as follows:

Shareholder	Share Price	Before			After		
		Shares	*Percentage*	*Capital*	*Shares*	*Percentage*	*Capital*
Dr. Angelides	0.6	99,990	99.99%	€59,994	99,990	54.73%	€59,994
Ms. Maglavera	0.6	10	0.01%	€6	10	0.01%	€6
THERMI S.A.	0.6	-	-	-	82,693	45.26%	€49,615.8
Total	**0.6**	**100,000**	**100%**	**€60,000**	**182,693**	**100%**	**€109615.8**

Table 2: Share capital structure before and after the venture capital

Vidavo issued a total of 82,693 additional shares. THERMI S.A. acquired these shares at the **premium price** of €9.07 each (€8.47 premium) resulting in roughly **€750,000 venture capital**. A written agreement was signed between THERMI S.A. and Vidavo setting specific milestones and goals for the company, ensuring the efficient use of the received funds.

Apart from funds provided by business incubator THERMI S.A., Vidavo was able to bolster its growth by securing additional financing via the participation in several **publicly funded research projects** (Appendix). However, national and EU funded research projects did not serve as a short term capital source for the operational needs of the company. The **funds acquired this way were utilized in the R&D department as a long term investment**. The experience and knowledge through the deployment of such projects contributed to the future development and improvement of products and services (Vidatrack, VidaHome and VidaΨ), nurturing new lucrative operations. Furthermore, Vidavo executives participated (and still do) in several national and European Standardization and Strategy groups. By participating in these groups, the company had the opportunity to exchange knowledge and opinions with distinguished scientists and industrial actors of the field while contributing to the development of a legislative framework on matters concerning eHealth. This way the company was able to follow closely the advances in related technology and standards as well as

have access to vital information on regulatory aspects and trends in them. Consequently, Vidavo was able to develop communication channels with potential suppliers and learn about new business models and value added services that could later be transferred over to the Greek market.

3.4. Expansion Stage (2010 – 2011)

After 8 years of operation, Vidavo had established a firm position in the Greek eHealth sector and was entering a new stage of its life cycle, ready to explore **new possibilities for business expansion**. Specifically, the company was searching for an external financing source in order to **introduce a new business unit** (eWellness) as well as **upgrade** its **existing telematics products and services**. Additional funding would also be required to cover the **marketing and promotional activities** of the company, **establish new strategic partnerships with doctors** and **explore entry possibilities in new foreign markets**.

Before seeking finance from external investors, however, Vidavo developed a detailed **investment plan** that the company would have to implement in the next 2 years in order to achieve its strategic goals and expand its business operations.

Category	Value (€)			Total Contribution (%)
	2010	*2011*	*Total*	
Office Space	20,000.00	9,925.00	29,925.00	2.99%
Hardware Equipment	87,743.10	-	87,743.10	8.77%
Software	300,000.00	284,706.00	584,706.00	58.47%
Special Installations	15,000.00	7,500.00	22,500.00	2.25%
Medical Devices	10,000.00	9,391.90	19,391.90	1.94%
Studies	-	52,000.00	52,000.00	5.20%
Equipment and Studies Subtotal	**432,743.10**	**363,522.90**	**796,266.00**	**79.63%**
Promotion in Scientific journals	22,268.50	22,268.50	44,537.00	4.45%
Promotion in Mass Media	27,993.50	27,993.50	55,987.00	5.60%
Promotional Material	12,260.00	-	12,260.00	1.23%
Online promotion	4,950.00	10,000.00	14,950.00	1.50%
Participation in conferences and exhibitions	-	24,000.00	24,000.00	2.40%
Conference sponsorships	-	52,000.00	52,000.00	5.20%
Promotion Subtotal	**67,472.00**	**136,262.00**	**203,734.00**	**20.37%**
TOTAL	**500,215.10**	**499,784.90**	**1,000,000.00**	**100.00%**

Table 3: Investment plan (2010 – 2011)

Vidavo decided that the best way to secure the necessary capital to materialize its goals at this stage of its development was to join a **public market**. The admittance to a public market would not only ensure access to an additional financing source but also greatly improve the company's business image. The enhanced credibility and reliability that a company listed in a public market enjoys would give Vidavo the additional momentum it needed to enter foreign markets.

The most suitable national public market for the needs of Vidavo was the **Alternative Market (EN.A.) of the Athens Stock Exchange Market (ATHEX)**. The EN.A. is a relatively flexible public market more suitable for fast growing SMEs such as Vidavo, as it enjoys less strict admission and ongoing requirements than those of the main market (ATHEX). While the admission process is simple and suitable for smaller companies, it is still subject to certain requirements and regulations. A company seeking to join a public market should be properly informed about the legal and regulatory

framework governing the overall operation of the market and have a clear view of the goals it is trying to achieve by entering.

In this case, as a prerequisite for admittance into the E.NA., Vidavo had to designate a **Nominated Adviser (NOMAD)**. The NOMAD provided assistance and consulting services to the company making sure that the company met all the legal requirements and followed all the procedures required for the listing. In cooperation with the NOMAD the company decided the method (**private placement**) that was to be followed for the listing as well.

Vidavo joined the EN.A. through a **private placement** that was realised via a **10% share capital increase.** The company listed a total of 857,210 shares in the market out of which 85,758 were sold to private investors. The initial negotiation price was set at €3.14 per share resulting to a total of about **€269,280** accumulated capital. The following table indicates the structure of the company's share capital before and after the private placement.

Shareholder	Before		After	
	Shares	*Percent*	*Shares*	*Percent*
Dr. Angelides	558,223	72.36%	558,223	65.12%
Ms. Maglavera	77	0.01%	77	0.01%
THERMI S.A.	213,152	27.63%	213,152	24.87%
Private investors	-	-	85,758	10%
Total	**771,452**	**100%**	**857,210**	**100%**

Table 4: Share capital structure before and after the private placement

The **€269,280** that Vidavo secured from private investors by joining the public market in combination with the company's equity stemming from forecasted operational profits of the next 2 years (**€412,216**) were not sufficient to cover the capital needs of the investment plan, while additional funds acquired via participation in **publicly funded research projects** (Appendix) would be directed to the R&D department of the company. Therefore, Vidavo had to find an additional external source of funding to complement the **€1,000,000** that was required in order to implement the investment plan. The supplementary financial resources (**€318,504**) were ultimately secured in the form of a grant that was released under the **national investment law** in 2011:

Financing Source	Year		Total
	2010	*2011*	
Investment grant	-	€318,504	€318,504
Public market funding	€269,280	-	€269,280
Equity from operational profits	€210,720	€201,496	€412,216
Total	**€480,000**	**€520,000**	**€1,000,000**

Table 5: Financing Plan (2010 – 2011)

4. Lessons learnt and thinking further

Vidavo is a pioneer among the companies that operate exclusively in the field of health telematics in Greece. The entrepreneur realized that this emerging market segment within the Greek eHealth sector posed a very promising entrepreneurial opportunity and acted promptly. The fact that the company was one of the first to enter this attractive young market provided a substantial competitive advantage that was enhanced by the innovative nature of the services and factors of the national socioeconomic environment. To sustain its competitive edge the company needed to grow and further develop its business operations. The careful planning and selection of the most appropriate external source of funding to match the capital needs of the company throughout each stage of the business life cycle have been essential antecedents of Vidavo's success and long term sustainability.

	Vidavo's business life cycle stages			
External Modes of Finance	*Concept*	*Start-up*	*Growth*	*Expansion*
	• Research grant	• Structural Funds grants • Research grants	• Business Incubation • Venture Capital • Publicly funded research projects	• Public market • Investment grant • Publicly funded research projects

Table 6: Business life cycle stages and modes of finance

Vidavo is now in the midst of its expansion stage. After the successful implementation of the investment plan that was prepared for the private placement, Dr. Angelides faces a new challenge: **What should be the next step in Vidavo's expansion?** The entrepreneur along with the rest of the company's management team is examining **two distinct scenarios** that will allow Vidavo **to further develop its business operations:**

Scenario 1: Development of own manufacturing department

A prospective next step for Vidavo could be the development of a manufacturing department within the company in order to produce its own medical devices (**vertical integration**). The company has already developed 2 telemedicine devices which are nearly ready for commercialization. The in-house production of these devices along with the development of specialized software will enable the company to attract additional customer groups and expand its operations. Vidavo will need to carefully plan and assess the capital needs and time horizon of the investment in order to identify the appropriate financing tool for the endeavour.

Scenario 2: International Expansion

Another very interesting option for the future expansion of Vidavo involves the penetration of foreign markets such as the lucrative markets of North and Western Europe countries. **Direct foreign investments** require significant financial resources and involve substantial risk. A relatively safer method that the company could employ is entering the targeted foreign markets through the

formation of **strategic alliances** with key market players (e.g. medical device suppliers, technology brokers, medical centers etc.), even though selecting the most suitable strategic partner for such an endeavor can sometimes prove to be challenging task. The proper strategic partner, however, can help Vidavo lower the financial requirements of the venture and ensure faster and more effective commercial development in the new targeted market.

Questions and ideas for further thinking

- *What modes of finance are available for the further expansion of Vidavo? Discuss the advantages and disadvantages of the alternative options. What other issues should Vidavo examine before selecting the proper financing tool for its future endeavors?*
- *Identify the modes of finance that best fit the specific requirements of each expansion opportunity. What are their implications for the successful implementation of the different strategic scenarios?*
- *Evaluate the potential of the two scenarios under consideration. Which one do you think constitutes the most promising opportunity and therefore should be the next step in the development of Vidavo?*

APPENDIX

Publicly Funded Research Projects

(2007- 2010)

Project	Call / Programme	Start Date	Duration	Total Budget	Vidavo Funding
Broadband	Information Society Operational Programme, Measure 4.3	1/2/2007	12 Months	€682,123.00	€303,100.77
EGNATIA-Information Science	Egnatia Information Science Programme, Measure 1.4	11/4/2008	24 months	€113,309.52	€51,339.71
Coolness	Industry-Academia Partnerships and Pathways (IAPP)	4/6/2008	36 Months	€411,954.00	€196,363.85
e-Services	Information Society Operational Programme, Measure 3.2	11/12/2008	3 months	€26,890.00	€16,134.00
CLAP—Cross Layer Algorithms for Phealth	Marie Curie Actions—International Outgoing Fellowships (IOF)	15/5/2009	30 months	€265,301.00	€265,301.00
Independent	FP7-ICT Policy Support Programme	10/1/2010	36 months	€5,250,000.00	€133,152.00
Exalted	FP7-ICT 5th Call	1/9/2010	30 months	€10,980,000.00	€268,665.00

« UTILIZING EARLY STAGE RESEARCH RESULTS THROUGH INTELLECTUAL ASSET PORTFOLIO MANAGEMENT »

Prepared for Health-2-Market, supported by the European Commission under the FP7-HEALTH programme

Author: University of Gothenburg

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1. Giving the benefit of the doubt

It was a snowy December 10, 2010, and it was not without a sense of hesitation that Prof. Mats Kaj swiped the card and opened to door to the institute for Environment and Respiratory Medicine at Lund University, and let innovation manager Julie Lee in to present her results. This was his second attempt at developing his project together with the "innovation system", and up until now, the supposed support had only created more problems than solutions. The advice that had been given only seemed to confirm all his preconceptions about "business people", and did not fit with his own visions and ambitions with the research project. The previous innovation system coach had recommended that he should assign the invention to a limited company, and run the development as an entrepreneur. Flowcharts, spreadsheets and checklists were presented to show what it would take to commercialize the research, what was expected of him, and the different organizations that could be contact for taking the project forward. It was clear that commercializing the research would be a full-time job involving business plan writing, raising venture capital and negotiating deals. Not only did he find this uninteresting, but the academia was his home, and he could not see himself going anywhere else. There was also unease that an aggressive commercial agenda would potentially compromise the research group's future work. The results had been very well received in the academic community, and there were certainly many interesting directions that the group could take the project going forward.

Mats had started his research career as a doctoral student focusing on the evaluation of exhaled nitric oxide (eNO) as a biomarker in risk occupations (e.g. pulpmill workers). He had investigated whether measurement of NO in exhaled air could be a useful biomarker for monitoring the effects of ozone at ambient levels on the respiratory tract. By exposing healthy volunteers to ozone, it was then possible to measure the response by measuring the amount of Nitric Oxide (NO) in their exhaled breath. Exhaled NO appeared to be a marker for airway inflammation after repeated occupational exposure to ozone, but not after experimental exposure to ozone in ambient concentrations. In the thesis, he further concluded that gassing from ozone seemed to be associated with increased prevalence of adult onset of asthma, current asthma symptoms and rhinitis. Another finding was that sensitization to perennial allergens and reported symptoms of asthma or rhinitis were found to be associated with higher levels of eNO. Clearly, there was an interesting correlation between exhaled gas and airway inflammation that could be further investigated. Mats was however not the first within the research area. NO levels in exhaled air had been proposed as a biomarker of airway inflammation already in 1996 and it had long been known that NO-production in vascular endothelium was intimately linked to inflammation. The biological understanding of its function was that the endothelium of blood vessels uses NO to signal the surrounding smooth muscle to relax, thus resulting in vasodilation (widening of blood vessels) and increasing blood flow. NO is highly reactive, yet diffuses freely across membranes. These attributes made compound ideal as transient paracrine (between adjacent cells) and autocrine (within a single cell) signaling molecule. The presence of excessive levels of cytokines (signaling molecules), as part of the inflammatory process, stimulated the production of NO in the tissues. While a small amount of NO in vascular endothelium (part of the blood vessel wall) was beneficial and could even be considered anti-inflammatory, the large amounts of NO released in response to cytokines could destroy host tissues.

Before Mats started his research, important contributions had been made by Professor Lars Gustafsson at the Karolinska Insitute (KI) in Stockholm, who in 1991 led the first group to report the presence of NO in exhaled air. A parallel group led by Kjell Alving, also at KI, was stimulated by Gustafsson's findings to investigate the possibility that NO was elevated in patients with

inflammatory airways disease. Their research group had assembled a device that could be used to measure the exhalations of the colleagues themselves, some of whom were allergic. The research had produced striking results and showed that the allergy sufferers in the group had significantly higher levels of NO in their exhaled air. Further studies were done and Gustafsson and Alving joined forces to develop a device that could be routinely used to measure exhaled NO in clinical settings. In 1997, Aerco AB was founded, and while Mats was working on his doctoral thesis, the company had received CE certification and begun selling their NIOX® product.

After his dissertation, Mats set up the new research project together with some of the key people within the area, including Göran Holmgren, postdoc, Sofia Blomquist, postdoc and Gustav Edlund, a very promising PhD student. A year passed and one of the early outcomes of the project was a novel method for capturing exhaled breath, which involved inhale-exhale schedules to produce different forms of samples for different purposes. In a next step, the group wanted to develop a physical apparatus to collect samples based on the novel method. The purpose of the apparatus was to speed up the process and enable a more efficient research process. Prof. Bengt Skogman, researcher in the area of chemistry and molecular biology at the University of Gothenburg, was added to the team and contributed with his expertise on how breath collection could be accomplished and thus facilitate chemical analysis. One of the outcomes of Bengt's involvement was the realization that the group needed a method for collecting solid particles, not gas. In 2005, a first working prototype was built by Bengt using cardboard along with various bits and pieces from the technician's shop at Chalmers University of Technology. Much of the technology was readily available and could be assembled for the specific purpose without having to be modified, while some parts needed to be customized. To determine airflow and monitoring particle distributions, a particular algorithm was developed. The research group then used the apparatus in several studies to collect and determine the content of not only NO, but also ammonium and potassium. The algorithm was then further developed and optimized for the analysis of different compounds and for different analysis purposes.

The research was funded by governmental organizations and part of the financial resources had been specifically earmarked for securing intellectual property rights on the research results. A patent was filed in late 2007 based on the method and apparatus for studying airway inflammation through the collection of particles in exhaled air. Only a month or two before the meeting with Julie, the patent application had moved into the expensive national phase, and it had become necessary to attract additional funds to pay for the prosecution in each of the desired designated countries. The feeling of the group was that filing the patent application was more an obligation than anything else. Mats to some extent agreed, but also knew that if the research were to be used in the industry, investors would put a lot of emphasis on the patent situation. Increasingly, Mats felt pressured to either exploit the commercial opportunity through a new venture, or simply drop the patent application and thus potentially miss the opportunity to commercially develop the research. He was hesitantly leaning towards the later, but decided to give this second try the benefit of the doubt, and let Julie in.

2. Opportunities and complexity in equal measures

Having worked with the development and utilization of early-stage university research for many years, Julie was no stranger to complexity. But the findings from the first meeting with Mats had made her somewhat stumped, and the task proved to be more challenging than usual.

The first observation had been that the research portfolio was certainly much more expansive than Julie's pre-meeting research had indicated. In an E-mail before the meeting, Mats had explained that the primary commercial value was in a "useful prototype that they were in the process of patenting". The prototype had then been used to generate some very interesting research results, that they now wanted to publish. After the meeting, it had been clear that more of value had been created. Several methods in relation to the gathering and analysis of exhaled breath particles, as well as minor tweaks and improvements to the device, were interesting. The application of the methods on humans had created large datasets, from which correlations and patterns could be extracted and analyzed. In addition, algorithms implemented in software for analyzing the gathered particles had been developed, as well as specific reference profiles associated with different medical conditions. In short, there were many different research results in the project, which could certainly have varying value in relation to different utilization options. Finally, it was clear that the patent application was not going to cover everything, and other control mechanisms were relevant, including trade secrets and copyright.

The second key observations had been that there seemed to be significant interest in the research, not only within the academic community, but also from various companies who, at different occasions, had visited the research group and expressed interest in their results. On the academic side, researchers at the University of Michigan had stumbled upon Mats and his research group's publications, and believed their results were quite useful in their work on developing improved training methods for racing greyhounds. They seemed particularly interested in accessing the device to use in their research, but as far as Julie knew, nothing more than a couple of phone conferences had materialized. Various companies had also expressed interest in the research, and Aerco, already selling products within the area, had approached Mats group and asked if they could access some of the underlying technology. Aerco was mainly interested if they could receive the research reference profiles, as well as the compiled research databases. So far, Mats had decided to not send over the material since he was afraid of leakage and possible competition, especially if he was to start his own start-up company in the future. If a start-up company would be created, the initial innovation coach had been fairly clear on that "all intellectual property" had to be transferred to the firm. This would include the patented invention and related designs, databases, algorithms as well as the reference profiles. Mats was particularly worried about the future of the research in such a scenario. Especially since furthering the academic agenda was dependent on the right to use the prototype device, as well as accessing and developing the databases and reference profiles.

It had been clear to Julie that the research portfolio was significantly more substantial than her initial impression, and at the same time there were multiple, and potentially conflicting, ways in which the research could be utilized. The complexity was certainly weighty, and Julie now had to put together a plan for how to first clarify, and secondly evaluate, the different options going forward.

3. After the meeting

After the first meeting with Mats, Julie had decided to do additional interviews with the other key researchers within the group[1]. There were certainly differences of opinion on how to take the project forward. Even the question of commercial exploitation of research raised a heated debate, and there was little consensus. In the next step, Julie had decided to go forward with a joint "intellectual asset workshop", with the purpose of creating a shared understanding and overview of the research results. From the initial impression of a fairly limited portfolio of research results, the workshop had resulted in over 20 intellectual assets; that included software as well as databases and inventions. In addition to defining the intellectual assets, the current control situation was also discussed, and several potential patent applications were identified. Finally, the identified intellectual assets were combined with the understanding of their respective relevance for the different utilization options (1. Research, 2. Start-up, 3. Univ. of Michigan and 4. Aerco), focusing on the importance of control. What emerged was still a complex image, but it had now become significantly more manageable. A week from now Julie were having a workshop together with Mats and the other researchers, the key item on the agenda would be to discuss the different options for taking the project forward. The goal was not to design a complete solution, but rather to present a set of overall alternatives, and highlight the existing trade-offs between them. Julie certainly had a couple of intense days ahead of her, December 10 was approaching quickly.

[1] Appendix A. Excerpts from researcher interviews

"Health-2-Market is supported by the European Commission under the FP7-HEALTH programme"

4. Appendix:

4.1. Appendix A. Excerpts from researcher interviews

"Well, if someone else than us would want to use it – that person would need some training or some detailed instructions. We have started to write a manual, but it's not finished yet."

f"I believe Aerco was not only interested in the reference profiles and the databases, but also possibly in the patent application. They expressed some interest in a first option to license the patent when it was granted in the US."

"There are certainly some ideological differences within the research group. Some of us are quite supportive of not only allowing for commercial development of our results, but even driving them, while others are adamantly against it in the name of academic freedom."

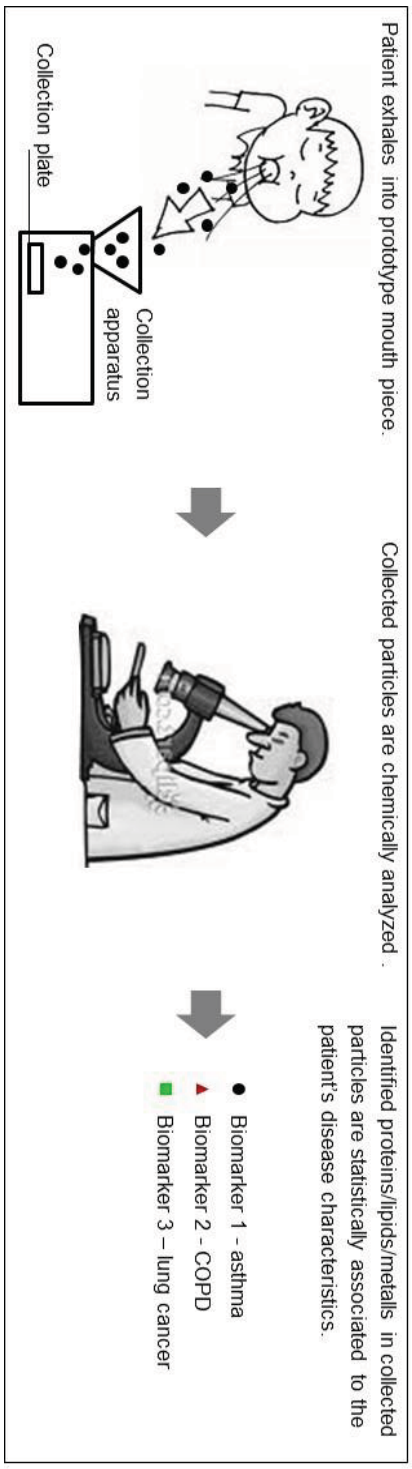
"Aerco has managed to build up a portfolio of several complementary technologies. Integrating them with our prototype would enable even cleaner results, something of great value to our future research."

"I believe we have enough ideas and results to support interesting research for another ten years."

"I have been thinking that we might propose a researcher exchange program together with the University of Michigan. There are certainly overlapping research interest, and I believe both research group could benefit from sharing ideas."

"We have kept the non-published material fairly secret, and been careful in always signing NDA's when we have had to shared ideas with external parties."

4.2. Appendix B. Illustration of biomarker analysis process and utilization opportunities



4.3. Appendix C. Intellectual asset list (1/3)

IA #	Type	Description	Comment	Control
IA001	Method	A method of colleting, sorting and analyzing exhaled particles to determine medical condition		Patent application, published after filing
IA002	Method	A method for collecting non-volatile particles using SCP	Enables particle and sample collection	Patent application, published after filing
IA003	Method	A method of adopting IA002 to enhance speed and throughput	Enables quicker start-up and increases quality	Secret, shared under NDA
IA004	Design	A technical improvement to IA001 to increase the collection of smaller particles ..., for particles down to 0,3 micrometer	Enables collection of smaller particles	Secret
IA005	Method	A method to reduce contamination by ambient particles using a specific mouthpiece	Reduces background noise in data collection	Secret, shared under NDA
IA006	Method	A method of sorting compounds using SNK process	Adapted sorting process to IA001. Reduces background noise in data collection	Public
IA007	Method	A method modification to IA006 specifically focused on NO particles	Increasing sorting capabilities for NOx compounds	Secret
IA008	Method	A method modification to IA008 wherein particles are sorted according to their mass using an inertial impactor		Patent application
IA009	Method	A method of determining medical condition by comparing particle		Secret

		distribution profiles with medical condition profiles		
IA010	Algorithm	An algorithm for removing unwanted noise in the creation of particle distribution profiles		Secret
IA011	Design	A design implementation of IA001 including a reservoir, mouthpiece, inertial impactor and more	Component breakdown of an actual prototype/design	Patent application
IA012	Instruction	A method on how to breath to increase particle formation, (airway closure)		Public

4.4. Appendix C. Intellectual asset list (2/3)

IA #	Type	Description	Comment	Control
IA013	Prototype	Prototype: Mark I - thermostat bath and cooler	No longer in use	Physical ownership
IA014	Prototype	Prototype: Mark II - pipe design eliminating thermostat bath and cooler	Current working prototype	Physical ownership
IA015	Prototype	Prototype: Mark III - A vision for a smaller, user friendly, high throughput prototype without a particle counter where unsolved problems include weighing the particles and fixing the flow through the apparatus	Not yet developed, vision state	Physical ownership

IA016	Software	A software solution for analyzing particle distribution profiles and determining medical condition.	C++ for windows source code	Copyright
IA017	Software	A software for visual feedback of exhalation flow and volume	C++ for windows source code	Copyright
IA018	Database	A database of asthma severity and exhale reference profiles of ~ 300 test subjects (including non-asthma individuals)	Used to create medical conditions profiles, work in progress.	Copyright, summary published
IA019	Database	A database with reference profiles information before and after treatment of asthma ~150 test subjects	Used to create medical conditions profiles, work in progress.	Copyright, summary published

4.5. Appendix C. Intellectual asset list (3/3)

IA #	Type	Description	Comment	Control
IA020	Database	A database of esophageal cancer severity and exhale reference profiles of ~50 test subjects (including non-cancer individuals)	Used to create medical conditions profiles, work in progress	Copyright, summary published
IA021	Data	Reference profile for determining asthma medical condition	Needs further verification	Secret
IA022	Data	Reference profile for determining asophageal cancer medical condition	Needs further verification	Secret

5. Tasks

1. What were the key difficulties in utilizing the project? Why was Mats not pleased with the advice of the first innovation coach?

2. Julie created an inventory of the "intellectual assets", what are the key advantages of this approach? What are the risks if you had tried to advise the research group without such a list?

3. What are the different options for utilizing the research, and what would you advise Mats and the research group to do? What are important control aspects to consider in relation to the different utilization options (e.g. exclusive/non-exclusive, access/ownership, rights to improvements)?

« NAVIGATING OWNERSHIP AND RIGHTS CLAIMS IN EARLY STAGE RESEARCH UTILIZATION, THE CASE OF PROSOUND »

Prepared for Health-2-Market, supported by the European Commission under the FP7-HEALTH programme

Author: University of Gothenburg

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1. Background to Prosound

"Prosound aspire to be the world leader in hearing aid instruments. We offer state-of-the art solutions to our customers through innovative hearing aid products, world class services and legendary commitment to improving the life for everyone who wears Prosound instruments"

Prosound was incorporated in 1984 as a subsidiary of the at the time public Swedish company Sonitus Group AB, a holding company owning a number of companies in the audio processing industry. Prosound was to expand into the high-end hearing aid market by utilizing market knowledge, technology know-how and distribution channels already established by other companies owned by Sonitus. The venture proved to be very successful and Prosound subsequently broadened their product line to include a number of different hearing aid offerings, all marketed under the "Auris" brand. Different product versions such as "Caseus", "Pius", "Blandior" were successively launched over a couple of years, and Prosound started to cover most relevant hearing aid market segments. The Auris product line brand was quickly recognized for quality and reliability as well as an advanced signal processing technology inherited from the Sonitus Group legacy. In 1997 Prosound launched their second product line "Vita", targeting customers with even more serious hearing disorders. The two products Vita Green and Vita Blue were successful and managed to establish a solid market share in a growing and profitable segment.

In 1999 Sonitus was forced to sell Prosound due to liquidity problems and a decision was made to take Prosound 100% public on the Stockholm exchange in November 16, 1999. During the first few years the company experienced continuous growth and expansion, primarily in Western Europe. But in 2002 the first signs of a more challenging future emerged. Even though the global market continued to steadily grow, now primarily in emerging markets, Prosound started to see its profits stagnate due to shrinking margins and market shares. The decreased profitability was primarily caused by increases in the R&D and marketing costs, driven by the need to keep up with the gradually more aggressive competition. As shareholder became progressively more impatient with Prosound's performance, the company initiated a major re-organization of the research and development department, as well as the complete product development function. To speed up the development, lower the development costs and increase Prosound's innovation agility, it was decided to start sourcing technology externally from universities, research institutes and other firms. The "Externalization Task Force" (ETF) was created to scout, evaluate and source external technology projects to drive Prosound's competitiveness. Prosound management and researchers had always prided themselves with the industry's strongest and most innovative engineering team; the new initiative was therefore very hesitantly received, especially among the researchers. There was a widespread opinion at the company that ETF's credibility was very much dependent on the success or failure of their initial projects, both from a commercial, but not least from a technical perspective.

2. The Externalization Task Force

Ofelia Stark, the CEO of Prosound since 1999, had, to CFO Anathema Jones slight irritation, personally hand-picked Staffan Sindhav to head the Externalization Task Force at Prosound. At the time he was approached by Ofelia, he was working as a consultant with technology transactions and had advised Prosound on some minor issues. Before his work as a consultant, he had a long experience from working with evaluation and licensing of technology at Swedish universities and research institutes. Because of his background, he did not only have a long experience from deal making, but also a deep understanding of, and network within, the public sphere. The name Externalization Task Force was perhaps misleading, Staffan was the only person fully staffed in "the group". He did however have at his disposal the legal team, as well as access to researchers and market staff for weekly review meetings and expert opinions. One of the first things Staffan, together with Anathema, initiated was the development of a framework for guiding ETF's deal making prioritizations. The framework was summarized in four bullets:

1. Prioritize technology that strengthen miniaturization and/or sound clarity for the Vita product line
2. Ready for market within 2-3 years
3. Proprietary control position, with exclusive license or ownership of key technology
4. High access to key researchers, to accelerate technology verification and integration

The bullet framework would ensure that EFT's deals were aligned with identified customer needs (1), synchronized with Prosound's internal innovation cycle (2), support competitive advantage (3) and ensure efficiency, and reduce risks in the transaction (4).

Staffan's strategy for launching the externalization initiative was to build relationships with a number of high profile research groups around Sweden, starting with some of his already established connections. One group that had produced solid quality research for many years was Prof. Linus Berglund's team at the Institute of Communication and Signal Processing at Chalmers University of Technology. The research group had generated several high impact publications as well as spun out a few start-ups who had received noteworthy investments from the VC industry. After some discussions with Linus, it was quite clear that one project seemed particularly well aligned with Prosound's interests. Since a few years back, Linus together with his two colleagues Neda and Bo had been working within the area of signal separation, with the goal of converting raw sensor inputs to useful information. Linus was confident that the technology was particularly well suited for improving hearing aid sound clarity. In addition, the suggested signal separation technology (SST) could also find applications within telecommunications, satellite communications, image processing, heart monitoring and more. Staffan thus initiative a due diligence process of the project to determine the fit with Prosound's objectives, and at the same time identify potential risks with licensing in the technology. Early on, the ownership and rights situation was determined to be of particular risk to the evaluated deal, where several people and organizations in different ways could potentially claim ownership and rights on the developed technology. Not only could this result in unexpected and unpleasant surprises, but the actual design of the licensing transaction was to a large extent dependent on the clarification of these claims.

3. The signal separation technology

The key element of SST consisted of a class of methods for separating two or more signals which are mixed in an unknown way by signal separation. The common theme of the methods was the modelling of the mixture by means of filter delays[1]. Linus was generally seen as the primary inventor of the foundational methods sometimes between 2001 and 2002. Neda and Bo had later contributed with the refinement, implementation and testing; including the creation of crude prototype, that produced surprisingly good results. In 2002, an international patent application on the methods was filed[2]. Some of the important additions to the project include initial test results where the prototype was tested together with a heart monitoring device. The device was borrowed from a research group at Sahlgrenska at the University of Gothenburg. While the initial tests indicated some interesting results, the project was postponed for future investigations. Neda, together with a master student, had been the primary investigators. After the heart monitoring related research, Neda had moved on and focused her efforts on the development of a software solution that further enhanced the signal separation process. At the core, she had developed several new algorithms, specifically adapted for enhancing the output of the separation methods, and implemented them in a software. The implementation of the algorithms in the software was fairly work intensive, and require some significant investments in time (estimated 5-6 months for one full time skilled programmer). The research group had then, through Chalmers University of Technology, hired a sub-contractor (Syncode) to perform some of the "bulk work"[3]. Neda was estimated to have written about one third of the code. In addition to working on the software and algorithms, Neda had recently initiated a project together with a research group at Lund University. The goal of the collaboration was to combine SST with complementary research at Lund University to miniaturize the system even further. The work was still in a very early stage but at least one potential patent application had already been discussed. No agreements was signed with the researchers at Lund University. Bo Holgersson, with a background in telecommunications, focused some of his research on the implementation of SST in mobile phone base stations. Through previous connections at Ericsson, a partnership was established where Ericsson would fund some testing and modification of SST for telecommunication applications. In addition to the funding, Ericsson also provided some testing equipment to be used by the research group. The testing equipment has primarily been useful for analysis of SST in relation to telecommunication applications, but Linus could already see great advantages in using the testing equipment in the development of other applications as well. An agreement regulating the collaboration was signed by Linus Berglund[4].

Staffan knew he had a complex task at hand, with several ownership related risks and potential conflicts. At the same time, initial indications of the technology performance were very positive, and the pressure was high to deliver a successful deal; not least to justify ETF and his own position within the firm. His next step would be to clarify the situation even further, and determine if a viable deal was really possible. Maybe fortunes could be better found elsewhere, he thought.

[1] Appendix D. Patent application WO 04/16170 for a detailed description of the methods
[2] Ibid.
[3] Appendix B. Excerpts from the agreement between Syncode AB and Chalmers University of Technology
[4] Appendix C. Excerpts from the agreement between Ericsson AB and Linus Berglund

4. Appendix

4.1. Appendix A. Researcher profiles

Linus Berglund		
Research interest	- Signals modeling and filtering - Modulation and coding - Signal processing applications - Spread spectrum	
Positions	2002 -	Professor Communication and Signal Processing, Chalmers University of Technology
	1998 - 2001	Senior research expert Saab Space
	1994 - 1998	Associate Professor The Adaptive Communications and Signal Processing, Cornell University
	1996 - 1998	Post-doc Signal and Image Processing Laboratory, University of Rochester
Education	1992 - 1996	PhD. Chalmers University of Technology
	1988 - 1992	MSc. Electrical Engineering

Neda Goli		
Research interest	- Statistical signal processing - Functional programming and signal manipulation - Nonlinear signal processing	
Positions	2001 -	Post-Doc Communication and Signal Processing, Chalmers University of Technology
Education	1996 - 2001	PhD Computer Science Lund University
	1988-1992	MSc. Computer Science and engineering Lund University

Bo Holgersson		
Research interest	- Signal separation in telecommunications - Blind source separation algorithms - Scheduling of wireless transmissions	
Positions	1995 - 2001	Researcher Ericsson AB
	1993 - 1995	LVCom AB Testing center
Education	2001 -	PhD. Chalmers University of Technology In progress
	1988 - 1993	MSc. Electrical Engineering

4.2. Appendix B. Excerpts from the agreement between Syncode AB and Chalmers University of Technology

"Syncode AB (SUBCONTRACTOR) has been hired by Chalmers University of Technology (CONTRACTEE) to develop a set of software components (SOFTWARE) as specified in Exhibit A: Software development specification, for the purpose of furthering the CONTRACTEE's research programs…"

"The SUBCONTRACTOR agrees to provide the CONTRACTEE with the following services (SERVICES):

- *design, develop and program the software components (SOFTWARE), including source code, object code, libraries, interfaces, graphical symbols and concepts allowing one to use, create, handle, access or otherwise effect the SOFTWARE's content*
- *design elementary software documentation (SOFTWARE DOCUMENTATION), to make sure further developments to the SOFTARE are possible*
- *…"*

"…The CONTRACTEE will be granted a free, non-exclusive license to the SOFTWARE copyright by the SUBCONTRACTOR…"

"…The SOFTWARE, as well as the SOFTWARE DOCUMENTATION will be provided to the CONTRACTEE after the payment in full of all amounts according to the agreement…"

"…alpha and beta testing will be conducted jointly with the CONTRACTEE, and is thus subject to the availability of the CONTRACTEE…"

4.3. Appendix C. Excerpts from the agreement between Ericsson AB and Linus Berglund

"Ericsson (PROVIDER) is making testing rig GK8929 (DEVICE) available to Prof. Linus Berglund (RECIPIENT) and the Institute of Communication and Signal Processing at Chalmers University of Technology, as described in schedule 1, as part of developing the SST technology for telecommunication applications."

"The DEVICE is wholly owned by PROVIDER, and Linus Berglund has no claims to the ownership of the DEVICE, nor any of the technology encompassing its physical implementation, including technical inventions, designs or arrangements."

"The DEVICE is held in trust under the terms of the agreement, and the RECIPIENT has no rights to obtain Intellectual Property Rights (IPRs) on any of the outcomes of the usage of the DEVICE. The RECIPIENT, therefore, hereby agrees not to claim ownership on any IPRs resulting from the usage of the DEVICE. "

"Any IPRs created through the usage of the DEVICE will wholly and fully be owned by the PROVIDER. The PROVIDER will grant the RECIPIENT a full non-exclusive free license, to any IPRs resulting from the usage of the DEVICE, for non-commercial, and not-for-profit, research purposes only."

"The RECIPIENT agrees that a notification on any public disclosure of any research results from the usage of the DEVICE, including conference presentations, research papers, web-page announcements, or in any other public form, must be made to the PROVIDER at least 120 days before publication, to allow for the PROVIDER to make decisions on possible IPR applications."

4.4. Appendix D. Patent application WO 04/16170

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : **H03H 21/00**	**A2**	**(11) International Publication Number:** **WO 04/16170** **(43) International Publication Date:** 1 April 2004 (01.04.04)

(21) International Application Number: PCT/SE03/01590

(22) International Filing Date: 7 September 2003 (07.09.03)

(30) Priority Data:
0203212-2 5 September (05.09.02) SE

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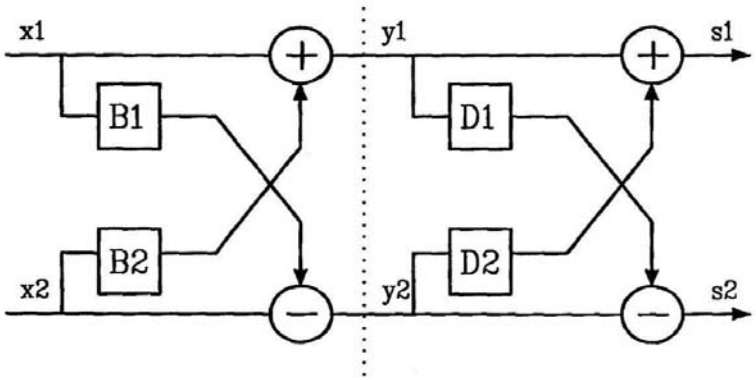
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
In English translation (filed in Swedish).
Without international search report and to be republished upon receipt of that report.

(54) Title: DEVICE FOR SEPARATION OF SIGNALS



(57) Abstract

Method for separating at least two signals from a mixture of signals, in which method the number of different mixtures is at least as great as the number of signals to be separated, the method comprising a modified criterion based on a criterion, which is to be minimised for estimating parameters in a separation structure and a regularising amendment, characterised in that the amendment comprises a first vector with the parameters to be estimated, a second vector with possible information concerning real parameters and a weight matrix, and a product of a difference between said first and second vector, the weight matrix and a conjugated and transposed difference between said first and second vector.

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Device for separation of signals

Technical field

Background of invention

Algorithms for signal separation are well known. Many of the described methods deal with mixtures without memories (so called 'instantaneous mixtures'). These are mixtures with constants, i.e. without delays. The signals are assumed to be mixed without having been delayed in time between the sensors.

A scenario more appropriate for regularising in the criterion is for mixtures with delays (so called 'dynamic mixtures'). One of the first methods for attacking this problem was presented by Widrow et al ("Adaptive noise cancelling: Principles and applications", IEEE Proceedings, December 1975). This method is based on two measurable signals, of which one only contains the disturbance and no contribution from the desired signal. According to the present invention both disturbances and the desired signal can be present in all measurable signals. This problem is unavoidable when the sensors are located near to each other, for instance in a cellular phone or a hearing aid.

An often used criterion is based on a contrast function suggested by Comon ("Independent component analysis, a new concept?", Signal Processing, 1994). A contrast function must be scaling invariant and assume its maximum value for statistically independent signals. A variety of different contrast functions has been suggested.

Criteria which are based on cross correlations between out signals from the separation structure have been suggested. Lindgren et al have described a criterion for two observable signals (Lindgren, Broman, "Source separation: Using a criterion based on second order statistics", Technical Report CTH-TE-36, Chalmers, Sweden, 1996, forthcoming in IEEE Trans. on Signal

Processing):

$$V = \sum_{m=-L}^{L} (R_{s_1 s_2}(m))^2$$

where L is a positive integer and $R_{s_1 s_2}(m)$ denotes the cross correlation between s_1 and s_2 for a delay of one of the signals with m samples. This criterion describes how much the signals s_1 and s_2 are correlated for delays between -L and L.

The signals that you want to separate do not have to be acoustic. Sahlin describes (Sahlin and Broman, "Blind separation of images", Proceedings of 30th Asilomar Conference on Signals, Systems and Computers, 1996) how signal separation can be applied on images (two dimensional signals).

Regularising can be found at system identification. The method is then used e.g. to avoid problem with inverting poorly conditioned matrices (e.g. Ljung, "System Identification, Theory for the user, Prentice-Hall, Englewood Cliffs, NJ, 1987) or to reduce the variance of parameter estimates to a cost of increased systematic error (Ljung, Sjöberg, "A comment on 'leakage' in adaptive algorithms", Technical Report LiTH-I-ISY-1304, Linköping University, Sweden, 1992). The choice of the magnitude of δ has been dealt with in the latter reference in the case of linear regression models and a criterion based on the square of the prediction error.

The European patent application No. 565 479 discloses a method based on the cross poly spectrum. The procedure according to this patent application is based on higher order statistics (HOS). It is publicly known that methods based on higher order statistics require a large number of samples in order to achieve good estimates. This results in that algorithms based on HOS converge

slowly and performs worse compared to methods based on second order statistics.

The patent US-4, 208, 786 discloses a signal separation algorithm based on second order statistics, but which does not work in a general case. The suggested algorithm only works if both channel filters have the same value of the direct term, i.e. $a_0 = b_0$ with references according to equation (14) and (15) in the description. That the method does not work for different direct terms is clear from equations (49) and (50). These equations describe how coefficients are estimated. The updating equations for the filter coefficients are the following when only dealing with the direct terms.

$$A_0(n) = a_0(n-1) + Y_1V_2(n)V_1(n)$$

and

$$B_0(n) = b_0(n-1) + Y_2V_1(n)V_2(n).$$

It is clear that the updating terms for the direct terms are identical. Also, others have presented similar algorithms but under the assumption that both direct terms are zero (Van Gerven, Van Compernolle; "Signal separation by symmetric adaptive decorrelation: Stability, Convergence and Uniqueness", IEEE Trans. Signal Processing, July, 1995).

The invention

The invention relates to a class of methods for separating two or more signals which are mixed in an unknown way by signal separation. The present invention relates to a way of improving the performance of the methods by means of regularising of the criterion. Regularising means that the parameters are 'drawn' to specific values. Thereby, regularising decreases the problem which may occur due to over parameterisation.

Short description of the drawings

In the following preferred embodiments of the invention will be described giving reference to the appended drawings, in which:

Figure 1 shows a cellular phone with the invention implemented therein;

Figure 2 shows a scheme according to the invention;

Figure 3a-3f shows graphs of systematic error, standard deviation och means square error.

Figure 4 shows the increase of SNB as a function of the regularising according to the present invention.

Detailed description of preferred embodiments

Signal separation can be applied when you want to separate a number of signals from each other. The method is based on access to at least as many different mixtures as you want to separate. For instance, the method can be used if two persons are talking to each other at the same time in a room, and you are having problem hearing what one of the persons is saying due to the other voice. Signal separation is a method based on signals from e.g. two microphones to determine filters in a separation structure and therefrom filter out each voice.

The method is based on modelling the mixture by means of filters comprising delays. Figure 2a shows an example where a model of a mixture of two signals is presented. Here x_1 and x_2 denote the desired but unknown and unmeasurable signals. The only signals which are measurable are y_1 and y_2. y_1 is modelled as x_1 plus a filtered version of x_2, i.e.

$$Y_1 = X_1 + B_2X_2$$

In the same way the following is modelled

$$Y_2 = X_2 + B_1X_1$$

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The model of the mixture includes the filters B_1 and B_2. The signals Y_1 and Y_2 are measurable and based on them a filter in a separation structure will be estimated. The output signals from the separation structure is

$$S_1 = Y_1 - D_2Y_2 = (1-D_2B_1)X_1 + (B_2-D_2)X_2$$

and

$$S_2 = Y_2 - D_1Y_1 = (1-D_1B_2)x_2 + (B_1-D_1)X_1$$

According to the above it is clear if $B_1 = D_1$ and $B_2 = D_2$ the signals are being separated, i.e. the out signals S_1 and S_2 are only dependent on X_1 and X_2, respectively. A common way of performing the determination of the estimates of the filters in the separation structure is to search for the filter parameters which give minimum or maximum value of a criterion V. A plurality of different criteria have been suggested, e.g. based on cross correlations, contrast functions and cross poly spectrum, as described above.

Performance of signal separation can be defined in many ways. Mean square deviation between estimated and true parameters is one of these measures. A measure closer to application is how well the method can suppress interfering signals, i.e. the signal to noise ratio, SNR). Above all the measured value of the increase of SNR between measured signals and separated signals is of interest.

The effect of regularising

Estimates of the channel is by nature afflicted with deviations from the truth. A measure of the mean deviation from the true value is the "systematic error". The systematic error for a parameter is the average of the deviations of the estimated parameter from the truth. "The variance" of the parameter

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estimates is a measure of variations of the mean deviation from the mean value of the estimate, i.e. how much the parameter estimate varies between each estimate. The variance is the mean value of the difference between estimate and squared mean value. "Standard deviation" is the square root of the variance. Finally the "mean square deviation" is the mean value of the difference between estimate and true value of the square of the parameter.

Regularising can be introduced in the signal separation algorithm as a means to reduce the variance of the parameters to be estimated. These parameters are usually the coefficients of the filters in a separation structure. Another name for regularising is leakage. The need arises primarily when the problem is heavily over parameterised. This can occur when only a few filter parameters not will be zero, but you do not know which ones. A method to solve this problem is to try to estimate by means of some method what parameters are necessary, and then only determine the values of these. If the system varies with time also this model structure must be varying with time. An alternative way of performing this method of obtaining model estimates is to introduce regularising.

Regularising can be introduced as a modified criterion, V':

$$V' = V + \delta|\theta-\theta^*|$$

Here V denotes the criterion to be minimised in order to estimate the parameters of a separation structure, δ is a design variable determining the degree of which the criterion should be regularised, θ is a column vector comprising the parameters to be estimated and θ^* is a column vector with possible knowledge of the real parameters. The regularising is thus introduced by adding a so called regularising term to the original criterion.

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A more general formulation is

$$V' = V + (\theta-\theta^{i})C(\theta-\theta^{i})^{H},$$

where C is a weight matrix and H denotes the Hermitian operator (conjugating and transposing operator). This latter formulation gives e.g. a possibility to a varying regularising of the parameters.

Thus, a possibility which is given when using regularising in the algorithm is to control the parameters towards specific values by a suitable choice of θ^{i}. These specific of the parameters can be obtained from physical modelling (e.g sound propagation in a room) or measurements under controlled circumstances. In the case of over parameterisation it is possible to choose θ^{i} to a vector of zeros, which means that all parameters are drawn towards zero.

An illustration is shown in figure 3. There it can be seen how systematic error, standard deviation and mean square error vary with different values of the regularising parameter δ. In the figure it can be seen how mean square error is greatly reduced in an interval of δ and then it increases outside the interval. In figure 4 the result of the method is presented as the quality improvement of one of the signals expressed as signal to noise ratio (SNR). A great increase in SNR for s_1 is presented in an interval compared to a non regularised criterion (small δ values). The signals used in figures 1 and 2 are computer generated sequences.

Regularising decreases the variance of the parameters on behalf of an increased systematic error. The parameter δ should thus be selected so that the gain accomplished in the performance of the method due to decreased variance does not exceed the loss in performance due to increased systematic error. Ideally δ should

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be chosen so that these two effects balance each other in the point which results in a maximisation of the performance of the algorithm.

An application is signals from microphones which are located at an approximate distance of 10 cm from each other. Figure 1 shows application of the method according to the invention in a cell phone 10 provided with two microphones, 11 and 12 as the first and second signal sources. The transport of sound in the room can be described with a few parameters but knowledge of which ones these are is not normally at hand. In order not to introduce limitations of from where the signals come filters with up to 20 coefficients each are required. The introduction of regularising in the criterion results in that the algorithm becomes practically applicable.

In the following a synopsis of some possible fields of application for signal separation using regularising is presented. Use of the method is when there are two or more signals which are mixed in an unknown way och there is a desire to filter out one or more of these. The method requires as many sensors as (or differently put, as many different versions of the mixes) as the number of signals to be filtered out. The strength of introducing regularising is that the sensitivity for over parameterisation decreases.

Signal separation with regularising is well suited for noise suppression in telephony. A receiver of the signals without any noise reducing method will perceive noise and other disturbances in the surroundings to the speaker as very disturbing. This is especially the case with cellular phones which are used in the most varying surroundings. Also the coding methods for the cellular phones of today adapted for human speech why acoustic disturbances can be even more disturbing for the receiver. Therefore it is important to achieve a higher signal quality

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before the transmission to the receiver. A requirement for the method to work is that the phone comprises at least two microphones. These are to be mounted at such a distance from each other so that the signals from them are essentially different. At the same time a long distance between the microphones creates the need of a filter with many coefficients in the modelling of the channel between the microphones. This strengthens the need of regularising when the introduction allows introduction of many filter coefficients without any greater decrease in performance.

People with hearing aids often have the problem that all sounds in the surroundings are equally amplified. Several persons talking simultaneously, music, machines etc creates surroundings where the person with a hearing aid cannot have a normal conversation due to the limited perception of others speaking. By mounting more than one microphone on the hearing aid and introducing a signal separation algorithm med regularising the level of perception can be greatly increased.

Signal separation is to filter ECG (Electrocardiogram) of fetus as described in an article by Zarzoso et al (Bacharis, A.K. Nandi and V. Zarzoso, "Foetal ECG Extraction using Blind Source Separation Methods", Proceedings of EUSIPCO '96). When measuring ECG of fetus also the mother's ECG is included. There is a desire to diminish this by means of filtering by using several sensors and a signal separation algorithm. Zarzoso only used channel models without delays which is considered insufficient at a high sampling rate and with sensors well distributed on the mother. Also methods based on higher order statics were often used which as opposed to methods based on higher order statistics requires a great number of samples (long measuring time) in order to work well. The introduction of the regularised criterion probably improves performance and also gives a more robust algorithm. Signal separation with regularising can also be used within fields close at hand such as EEG (Electroence-phalogram) and ENG

(Electroneurogram).

In an article by Sahlin (H. Sahlin and H. Broman, "Blind Separation of Images", Proceedings of 30th Asilomar Conference on Signals, Systems, and Computers) use of signal separation in image processing is suggested. The method is based on a criterion of squared cross correlations and access to more than one image of mixtures. The method is suggested to be used in e.g. medical image processing (X ray, ultra sound, magnetic resonance, etc.) where representations of inner organs and the like often are disturbed by over- and underlying structures. The signal separation algorithm would then estimate the differences between the registered images and use this information to generate clearer images of desired structures. The differences between the registered images can e.g. be the sharpness at different levels, the natural movements of the organs or a minor movement of the camera. In the two latter cases the introduction of regularising would probably imply a great improvement in performance when movement can be modelled by a filter a few coefficients not being zero but with a great number of coefficient with zero value. When modelling of these filters there is normally no knowledge available of which coefficients to be estimated and which are zero which results in a heavily over parameterised problem. The introduction of a regularised criterion would result in a better result.

Other possible application are hydro phone technology, measurement of vibration, radio communication with broad band signals, or when ever there is access to two or more measurements of unknown mixtures of signals.

The invention is not limited to the described preferred embodiments. Variations and modifications within the scope of the appended patent claims can naturally be found.

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CLAIMS

1. Method for separating at least two signals from a mixture of signals, in which method the number of different mixtures is at least as great as the number of signals to be separated, the method comprising a modified criterion based on a criterion, which is to be minimised for estimating parameters in a separation structure and a regularising amendment,
c h a r a c t e r i s e d i n,
that the amendment comprises a first vector with the parameters to be estimated, a second vector with possible information concerning real parameters and a weight matrix, and a product of a difference between said first and second vector, the weight matrix and a conjugated and transposed difference between said first and second vector.

2. Method for separating at least two signals from a mixture of signals, in which method the number of different mixtures is at least as great as the number of signals to be separated, the method comprising a modified criterion based on a criterion, which is to be minimised for estimating parameters in a separation structure and a regularising amendment,
c h a r a c t e r i s e d i n,
that the amendment comprises a first vector with the parameters to be estimated, a second vector with possible information concerning real parameters and a design variable, and a product of the design variable and a modulus of a difference between said first and second vector.

3. Method according claims 1 or 2,
c h a r a c t e r i s e d i n,
that the second vector with possible information concerning the real parameters is decided by means of physical modelling, such as sound propagation in a room.

4. Communication device comprising at least two microphones (11, 12), which device is arranged for separating at least two signals from a mixture of signals, where the number of different mixtures is at least as great as the number of signals to be separated, the device being arranged to comprise a modified criterion based on a criterion, which is to be minimised for estimating parameters in a separation structure and a regularising amendment,
characterised in,
that the amendment is arranged to comprise a first vector with the parameters to be estimated, a second vector with possible information concerning real parameters and a weight matrix, and a product of a difference between said first and second vector, the weight matrix and a conjugated and transposed difference between said first and second vector.

5. Method according claim 4,
characterised in,
that it is a telephone (10) or a hearing aid.

6. Device comprising at least two sensors for medical diagnosing, such as ECG, which device is arranged for separating at least two signals from a mixture of signals, in which device the number of mixtures is at least as great as the number of signals to be separated, the device being arranged to comprise a modified criterion based on a criterion, which is to be minimised for estimating parameters in a separation structure and a regularising amendment,
characterised in,
that the amendment is arranged to comprise a first vector with the parameters to be estimated, a second vector with possible information concerning real parameters and a weight matrix, and a product of a difference between said first and second vector, the weight matrix and a conjugated and transposed difference between said first and second vector.

7. Device at image processing for providing clearer images of desired structures, which device is arranged for separating at least two signals from a mixture of signals, where the number of mixtures is at least as great as the number of signals to be separated, the device being arranged to comprise a modified criterion based on a criterion, which is to be minimised for estimating parameters in a separation structure and a regularising amendment,

characterised in,

that the amendment is arranged to comprise a first vector with the parameters to be estimated, a second vector with possible information concerning real parameters and a weight matrix, and a product of a difference between said first and second vector, the weight matrix and a conjugated and transposed difference between said first and second vector.

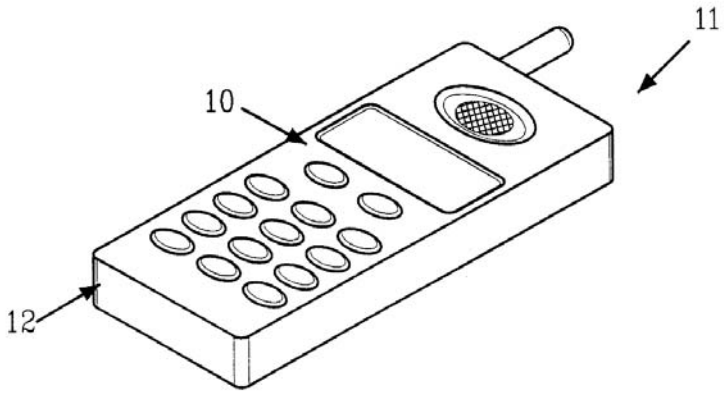

FIG.1

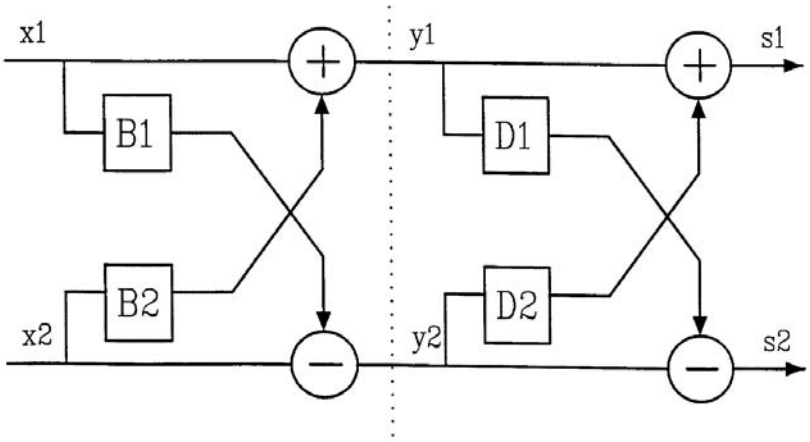

FIG.2

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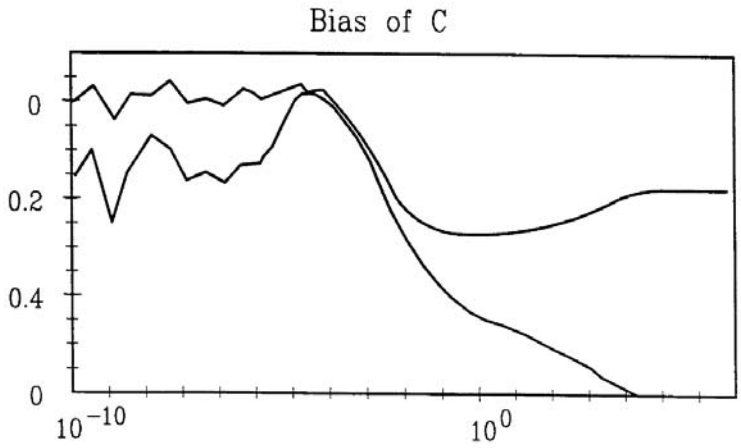

FIG.3a

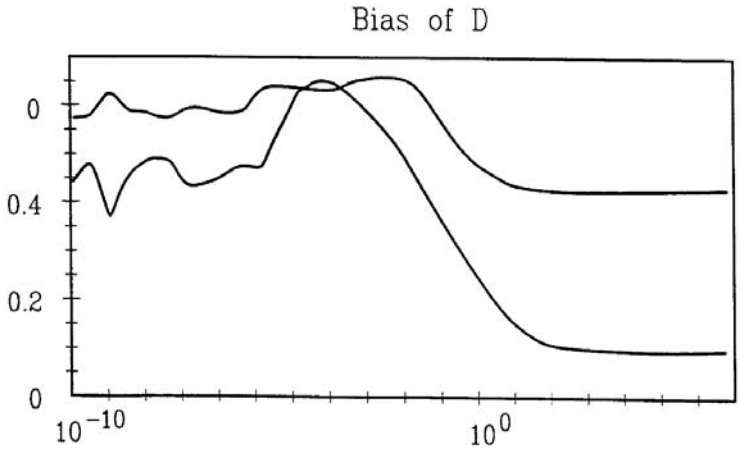

FIG.3b

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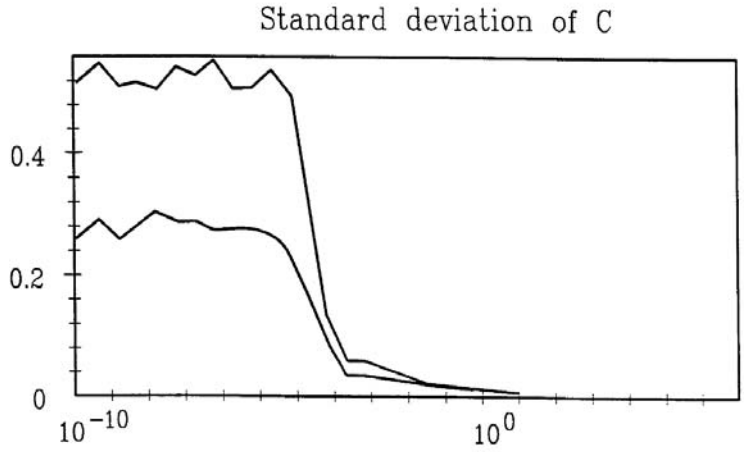


FIG.3c

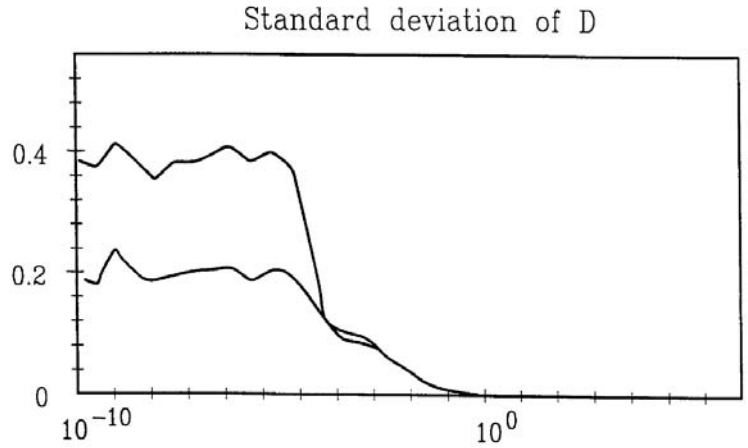


FIG.3d

"Health-2-Market is supported by the European Commission under the FP7-HEALTH programme"

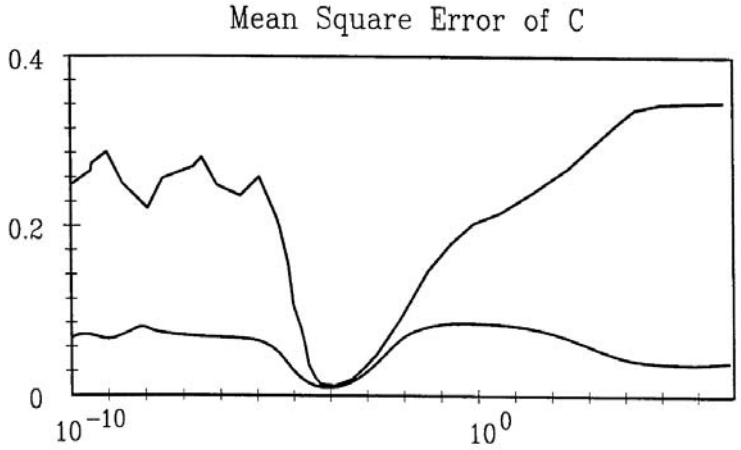

Mean Square Error of C
0.4
0.2
0
10^{-10}
10^{0}

FIG.3e

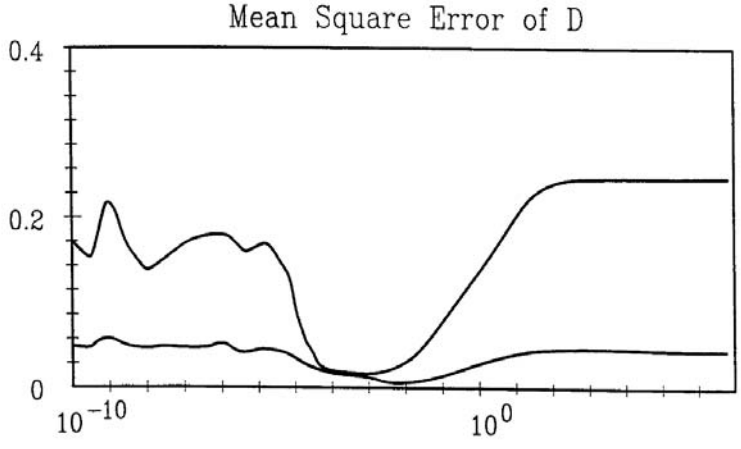

Mean Square Error of D
0.4
0.2
0
10^{-10}
10^{0}

FIG.3f

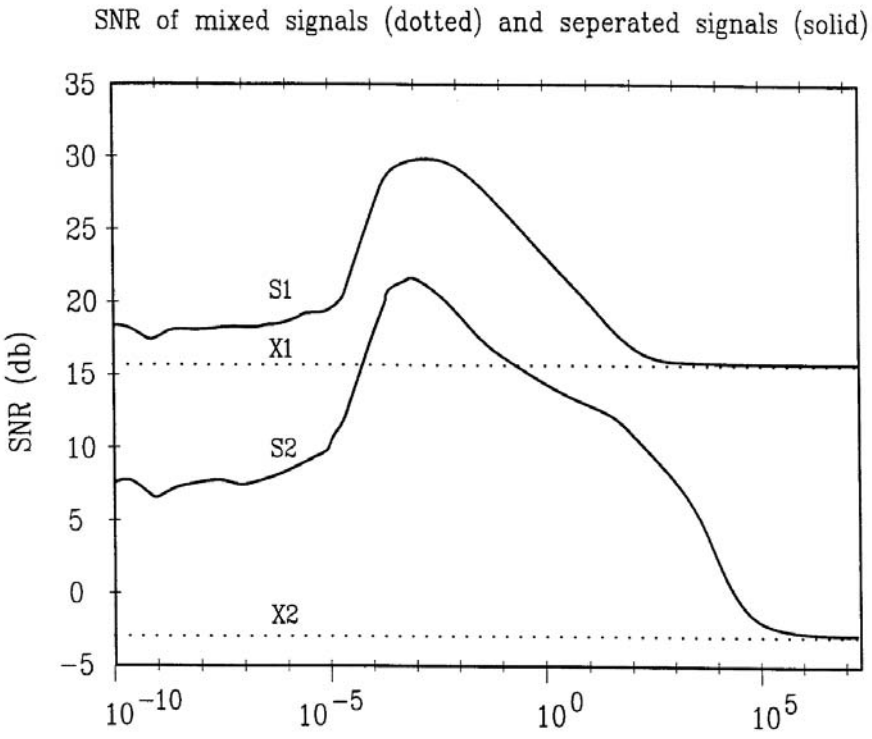


FIG.4

"Health-2-Market is supported by the European Commission under the FP7-HEALTH programme"

5. Tasks

1. What were the key difficulties in utilizing the project? Why was Mats not pleased with the advice of the first innovation coach?

2. Julie created an inventory of the "intellectual assets", what are the key advantages of this approach? What are the risks if you had tried to advise the research group without such a list?

3. What are the different options for utilizing the research, and what would you advise Mats and the research group to do? What are important control aspects to consider in relation to the different utilization options (e.g. exclusive/non-exclusive, access/ownership, rights to improvements)?

« EVALUATING AND DRAFTING TERM SHEETS FOR BIOTECHNOLOGY PLATFORM TECHNOLOGIES, THE CASE OF NEMTOX »

Prepared for Health-2-Market, supported by the European Commission under the FP7-HEALTH programme

Author: University of Gothenburg

Table of content

1. Background to Nemtox

"To be the apparent choice for sourcing innovative biotechnology solutions in agricultural development."

- Vision Nemtox

"Nemtox's mission is to globally improve the quality of life through the development of seed technology"

- Mission Nemtox

Nemtox had from the outset prided itself as a company with an "open" and "scientific" approach to decision making, both in conducting ground break research but also in business development. As the company grew, it had however become painfully obvious that the approach was certainly easier to adhere to with few employees and research projects. As the company branched out from the initial focus on technologies for drought resistant corn growth, and built a portfolio of over six key research streams, the conflicts within the firm had increased. A number of research units had been formed within the company, where each was fighting for their share of the budget. At the same time, it became clear that it would not be possible to follow through with all the projects, and prioritizations had to be made. John Langston had joined the company as a new CEO in early 2010 at the wish of the lead investor HA Ventures. John's key priority had been to position the company for an exit in 2013-2014, most probably through an IPO. To maximize the investment value of the exit, Nemtox technology portfolio was reviewed and a "package of clear and attractive growth opportunities" created. One of the outcomes of the review, except for internal friction, was a strategy for how to take each of the six projects forward. It had been decided that the original Anti Drought (AD) project, which represented over 65% of the Nemtox revenue in 2010, would be kept as is. While AD did not represent any significant growth opportunities it was seen as a stable and reliable income, and would serve to finance investment opportunities for several years to come. A second project, and about 20% of the revenue in 2010, relating to salt resistance (SR) was also kept. With one license deal signed and opportunities for several more, the project was the typical pipeline project that John wanted in the portfolio. The remaining four projects had been more difficult to plan. A pet project of Göran Spove, one of Nemtox founders, had shown great promise where the patented recombinant DNA sequence for Nitrogen Use Efficiency (NUE), originally developed for wheat, was to be adopted to rice and corn. Due to technical challenges, and consequential delays, the project was finally spun out, and the net proceeds were distributed on the remaining three projects, all kept in-house. The most interesting such project related to gene silencing, and the development of the project was seen as a key component in "the sell" to future investors and the success of the exit.

2. The gene silencing portfolio

In 2009, Nemtox had initiated a collaboration together with the Australian national science agency –the Commonwealth Scientific and Industrial Research Organization (CSIRO) – with the objective to turn off gene expression using gene-silencing RNA technology (GSRNAT), sometimes called antisense RNA. CSIRO had done significant work in the area and represented an ideal target for Nemtox strategy. Gene silencing had for many years been a heavily researched area, with the purpose of switching off genes that would have been turned on under normal circumstances. The technology was from the start used as a quicker alternative to "gene knockout", which has primarily been used to turn off genes to determine its function in an organism. Gene silencing could thus be used to identify genes with a particular function in for example a plant. The identified gene could then be introduced in a new and genetically modified crop, to enhance its properties. Gene-silencing could furthermore target particular parts of the organism, and thus function as a potential "gene silencing drug" to treat various forms of diseases[1]. A slightly different technology using double-stranded RNA (dsRNA) had been shown to be a more efficient solution compared to more conventional antisense RNA mediated methods. dsRNA had however been less practical to produce and therefore too expensive for most applications. For this reason, researchers at CSIRO focused on improving the conventional antisense RNA methods, and after a few years claimed to have reach the same efficieny levels as dsRNA, while still keeping the production costs low. A patent had been filed in 2002[2], and the assignment later transferred to Nemtox as part of the collaboration agreement. The patent covered methods for efficient down-regulation of the expression of any gene of interest in eukaryotic cells (cells with a distinct membrane-bound nucleus) and organisms, thus providing a powerful way to study gene function in a rapid timeframe[3]. In addition, Nemtox received a non-exclusive license to other relevant patents in CSIRO's portfolio. Jointly with CSIRO, Nemtox later developed methods for constructing chimeric RNA molecules, and built up a general experience how to implement the technology in plants. In the agreement between CSIRO and Nemtox, it was specificed that Nemtox would hold ownership to the developed foreground (IP coming out of the collaboration), to which CSIRO would receive a non-exclusive free license for research purposes. CSIRO would also receive 30% in royalty of net licensing fees (including both royalties and up-fronts) that Nemtox might receive from licensing out the "GSRNAT patent family relating to US 7 576 262 B2". It was Nemtox belief that the commercial potential for the technology was extremely promising, as it not only served as an internal research platform that could be used as a foundation for creating new add-on projects, but it would also be possible to license out the method to other organizations. An example of such add-on project that Nemtox initiated was the use of GSRNAT to counter the threat of nematodes (NS), a worm-like organism that plague crops by root pruning and root lesions. In Europe, a fear has been spreading that the notorious nematode species - the sting nematode (Belonolaimus spp.) – through spontaneous mutations would adapt to the European climate and threaten wheat production. Nemtox decided to use the GSRNAT to analyze a number of plants that were known to be resistant to nematodes, and identify genes that could be introduced in wheat. The NS project was just one example of how the GSRNAT could be used as a platform for identifying genes and developing modified plants. Nemtox envisioned a whole host of other comparable projects in different plants, where the technology could be used in a similar fashion. The work had not only resulted in useful chimeric RNA and DNA molecules, but also a novel method based on the GSRNAT, that allowed for high-throughput screening for creating optimized, target specific inhibitors (Nemtox

[1] Appendix A. Illustration of gene silencing technology
[2] Appendix B. Excerpt pages from US 7 576 262 B2
[3] Appendix C. Term sheet proposed by RAML Pharmaceuticals

has a patent pending). It was thus possible for Nemtox to use the technology to build up a large proprietary database of chiral compounds, possible over 200 per year, where many of them could be patented. Working with the GSRNAT had in addition generated a skillset among Nemtox staff on how to successfully operate the technology, which was quite troublesome if you had little experience with the procedures. Another possible business model that had been discussed was the exploitation of the GSRNAT through partnerships with agricultural biotechnology companies, and use the technology to validate and prioritize potential gene targets through customized services. The GSRNAT could also be licensed out to other firms for them to use in their R&D processes.

3. The license opportunity

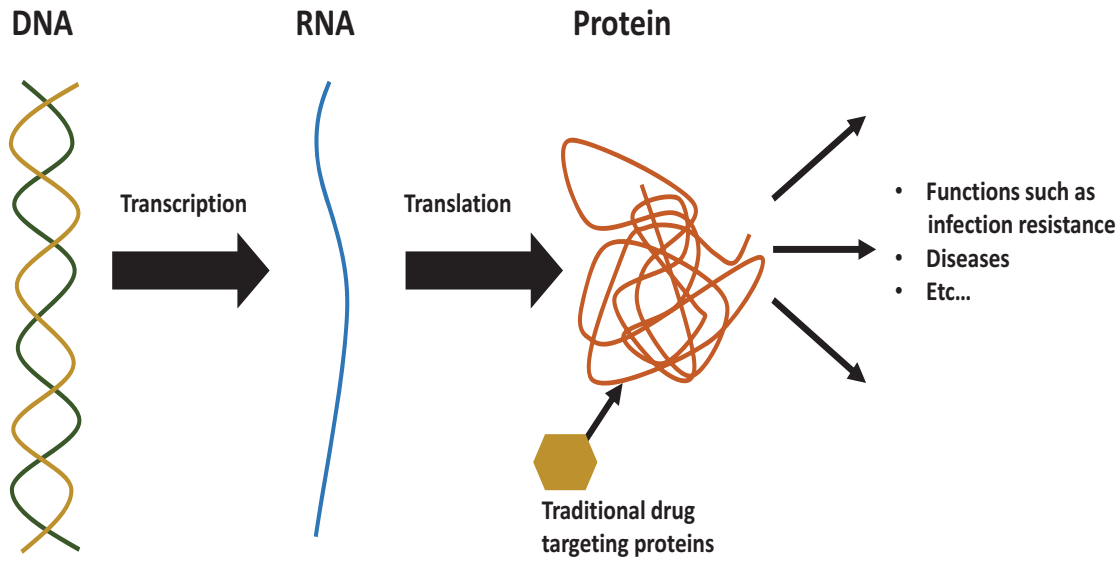
Shortly after Nemtox had officially announced the CSIRO deal they had been contacted by RAML Pharmaceuticals (RAML), a mid-size drug development company based in Geneva, Switzerland. RAML had been one of the pioneers in double stranded antisense technology, which was based on in-licensed patents from Brandeis University in the US. For a couple of years RAML had tried to use their antisense RNA technology in the development of an Ebola treatment. Their initial studies had provided very promising results, with a 75% recovery rate on tests performed on rhesus monkeys. By increasing the efficiency of the treatment using the GSRNAT the researchers at RAML now believed it could be possible to raise the recovery rate up to 90 – 100 %. RAML was therefore interested in performing another round of pre-clinical studies on monkeys, using the GSRNAT, before moving into clinical trials about 1.5 years into the future.

John had begun initial discussions with RAML about the possibility to license in the technology Nemtox. Since Nemtox was a committed developer of seed and agriculture, John did not see the opportunity as core business. At the same time, the technology did obviously have broad applications, and if the up-side was good enough it would certainly be of interest to the company. Initial discussions had fairly rapidly moved into a proposed term-sheet, prepared by RAML. It was clear that RAML wanted to move forward quickly. John pondered the pros and cons back and forth and a number of questions seemed especially significant. What would the implications of the deal be on Nemtox core business, and in particular the other business models identified for the exploitation of GSRNAT? Secondly, was the deal even attractive to Nemtox, or would it only drain large resources from the company and cause significant risks? Thirdly, what were key considerations in the design of the deal? How would Nemtox respond to RAML's proposed term sheet? And finally, what would the reactions from potential investors be, would they see it as adding to the attractiveness of the investment prospect, or as a distraction from the core business? The questions were many, and John more than a little bewildered. It was time to reply to RAML, either with a decline or with a revised term-sheet.

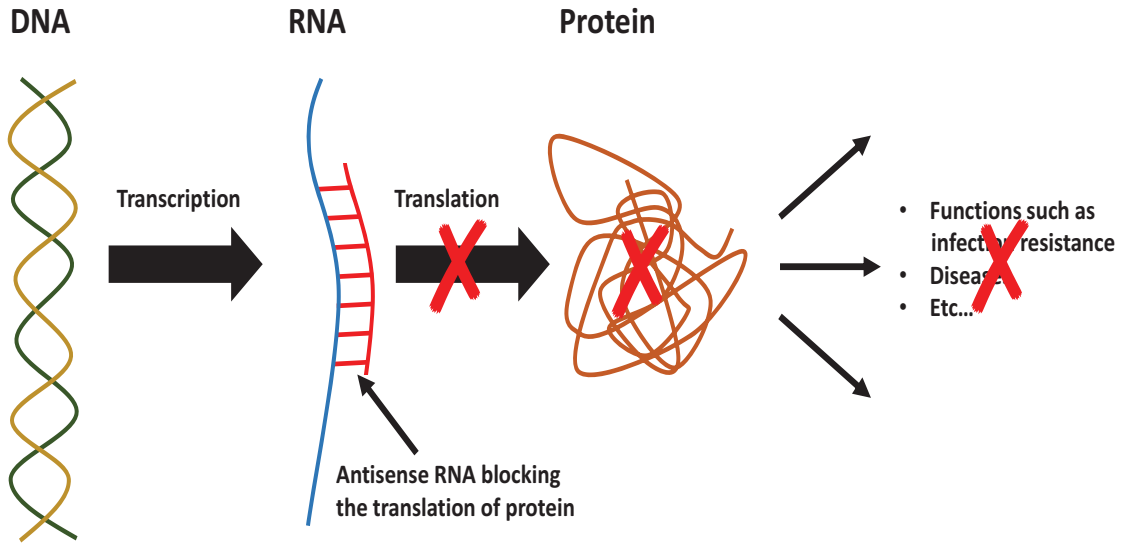
4. Appendix

4.1. Appendix A. Illustration of gene-silencing technology

The "central dogma" of molecular biology, where DNA makes RNA that makes Proteins which perform a vast array of functions within living organisms. The functions can be both harmful and beneficial, and traditional drugs typically target proteins to treat diseases.



Antisense RNA attaches to RNA strands and thus hinder the translation of proteins. By blocking specific RNA strands, and thus the expression of associated DNA genes, it is possible to understand the effect of a gene in an organism. Using antisense RNA technology allows for the screening of genes, to identify genes with beneficial or disease causing functions. It is furthermore possible to create antisense RNA that block translation of proteins and hinder disease development.



4.2. Appendix B. Excerpt pages from US 7 576 262 B2

The following pages include some excerpts from the patent application that in total is 32 pages. Filings have been made in the following countries United States, Germany, France, Spain, Portugal, Brazil, Australia, Canada, China, Japan, and United Kingdom.


US007576262B2

(12) **United States Patent**
Wang et al.

(10) **Patent No.: US 7,576,262 B2**
(45) **Date of Patent: Aug. 18, 2009**

(54) **MODIFIED GENE-SILENCING RNA AND USES THEREOF**

(75) Inventors: **Ming-Bo Wang**, Kaleen (AU); **Peter Waterhouse**, Canberra (AU)

(73) Assignee: **Commonwealth Scientific and Industrial Research Organization**, Campbell (AU)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 860 days.

(21) Appl. No.: **10/385,521**

(22) Filed: **Mar. 12, 2003**

(65) **Prior Publication Data**

US 2003/0180945 A1 Sep. 25, 2003

Related U.S. Application Data

(60) Provisional application No. 60/363,851, filed on Mar. 14, 2002.

(51) **Int. Cl.**
C12N 15/82 (2006.01)
C12N 5/10 (2006.01)
A01H 5/00 (2006.01)

(52) **U.S. Cl.** **800/286**; 435/419; 435/468; 435/320.1

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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(Continued)

Primary Examiner—Ashwin Mehta
(74) *Attorney, Agent, or Firm*—Buchanan Ingersoll & Rooney, PC

(57) **ABSTRACT**

Methods and means for efficiently downregulating the expression of any gene of interest in eukaryotic cells and organisms are provided. To this end, the invention provides modified antisense and sense RNA molecules, chimeric genes encoding such modified antisense or sense RNA molecules and eukaryotic organisms such as plants, animals or fungi, yeast or molds, comprising the modified antisense and/or sense RNA molecules or the encoding chimeric genes.

35 Claims, 5 Drawing Sheets

MODIFIED GENE-SILENCING RNA AND USES THEREOF

This application claims priority under 35 U.S.C. § 119 to U.S. Provisional Application No. 60/363,851 entitled MODIFIED GENE-SILENCING RNA AND USES THEREOF and filed on Mar. 14, 2002.

FIELD OF THE INVENTION

The present invention relates to methods for efficiently downregulating the expression of any gene of interest in eukaryotic cells and organisms. To this end, the invention provides modified antisense and sense RNA molecules, chimeric genes encoding such modified antisense or sense RNA molecules, and eukaryotic organisms such as plants, animals or fungi, yeasts or molds, comprising the modified antisense and/or sense RNA molecules and/or the chimeric genes encoding those RNA molecules.

BACKGROUND ART

Recently, it has been shown that introduction of double-stranded RNA (dsRNA) also called interfering RNA (RNAi), or hairpin RNA is an effective trigger for the induction of gene silencing in a large number of eukaryotic organisms, including animals, fungi, and plants.

Both the qualitative level of dsRNA-mediated gene silencing (i.e., the level of gene silencing within an organism) and the quantitative level (i.e., the number of organisms showing a significant level of gene silencing within a population) have proven superior to the more conventional antisense RNA or sense RNA mediated gene silencing methods.

For practical purposes, the production of antisense RNA molecules and chimeric genes encoding such antisense RNA is more straightforward than the production of dsRNA molecules or the genes encoding those RNA molecules. Indeed, the chimeric nucleic dsRNA molecules or the genes encoding those RNA molecules contain large, more or less perfect inverted repeat structures, and such structures tend to hamper the intact maintenance of these nucleic acids in intermediate prokaryotic cloning hosts. The methods and means to increase the efficiency of antisense-RNA mediated gene silencing as hereinafter described provide a solution to this problem as described in the different embodiments and claims.

U.S. Pat. No. 5,190,131 and EP 0 467 349 A1 describe methods and means to regulate or inhibit gene expression in a cell by incorporating into or associating with the genetic material of the cell a non-native nucleic acid sequence. The sequence is transcribed to produce an mRNA that is complementary to and capable of binding to the mRNA produced by the genetic material of that cell.

EP 0 223 399 A1 describes methods to effect useful somatic changes in plants by causing the transcription in the plant cells of negative RNA strands which are substantially complementary to a target RNA strand. The target RNA strand can be an mRNA transcript created in gene expression, a viral RNA, or other RNA present in the plant cells. The negative RNA strand is complementary to at least a portion of the target RNA strand to inhibit its activity in vivo.

EP 0 240 208 describes a method to regulate expression of genes encoded in plant cell genomes, achieved by integration of a gene under the transcriptional control of a promoter which is functional in the host. In this method, the transcribed strand of DNA is complementary to the strand of DNA that is transcribed from the endogenous gene(s) one wishes to regulate.

WO95/15394 and U.S. Pat. No. 5,908,779 describe a method and construct for regulating gene expression through inhibition by nuclear antisense RNA in mouse cells. The construct comprises a promoter, antisense sequences, and a cis-or trans-ribozyme that generates 3'-ends independently of the polyadenylation machinery and thereby inhibits the transport of the RNA molecule to the cytoplasm.

WO98/05770 discloses antisense RNA with special secondary structures such as $(GC)_n$-palindrome-$(GC)_n$, or $(AT)_n$- palindrome-$(AT)_n$, or $(CG)_n$-palindrome-$(CG)_n$, and the like.

WO 01/12824 discloses methods and means for reducing the phenotypic expression of a nucleic acid of interest in eukaryotic cells, particularly in plant cells, by providing aberrant, possibly unpolyadenylated, target-specific RNA to the nucleus of the host cell. Unpolyadenylated target-specific RNA may be provided by transcription of a chimeric gene comprising a promoter, a DNA region encoding the target-specific RNA, a self-splicing ribozyme and a DNA region involved in 3' end formation and polyadenylation.

WO 02/10365 provides a method for gene suppression in eukaryotes by transformation with a recombinant construct containing a promoter, at least one antisense and/or sense nucleotide sequence for the gene(s) to be suppressed, wherein the nucleus-to-cytoplasm transport of the transcription products of the construct is inhibited. In one embodiment, nucleus-to-cytoplasm transport is inhibited by the absence of a normal 3' UTR. The construct can optionally include at least one self-cleaving ribozyme. The construct can also optionally include sense and/or antisense sequences to multiple genes that are to be simultaneously downregulated using a single promoter. Also disclosed are vectors, plants, animals, seeds, gametes, and embryos containing the recombinant constructs.

Zhao et al., J. Gen. Virology, 82, 1491-1497 (2001) described the use of a vector based on Potato Virus X in a whole plant assay to demonstrate nuclear targeting of Potato spindle tuber viroid (PSTVd).

WO 02/00894 relates to gene silencing methods wherein the nucleic acid constructs comprise within the transcribed region a DNA sequence that consists of a stretch of T bases in the transcribed strand.

WO 02/00904 relates to gene silencing methods wherein nucleic acid constructs comprise (or encode) homology to at least one target mRNA expressed by a host, and in the proximity thereto, two complementary RNA regions which are unrelated to any endogenous RNA in the host.

SUMMARY OF THE INVENTION

In one embodiment of the present invention a method for downregulating the expression of a target gene in cells of a eukaryotic organisms is provided, comprising the steps of:

- providing the cells of the eukaryotic organism with a chimeric RNA molecule comprising:
  - one or more target gene-specific regions comprising a nucleotide sequence of at least about 19 consecutive nucleotides, which has at least about 94% sequence identity with the complement of about 19 consecutive nucleotides from the nucleotide sequence of the target gene, operably linked to
  - a largely double-stranded RNA region comprising a nuclear localization signal from a viroid of the Potato spindle tuber viroid (PSTVd)-type such as Potato Spindle tuber viroid, Citrus viroid species III, Citrus viroid species IV, Hop latent viroid, Australian grapevine viroid, Tomato planta macho viroid, Coconut

tinangaja viroid, Tomato apical stunt viroid, Coconut cadang-cadang viroid, *Citrus exocortis* viroid, Columnea latent viroid, Hop stunt viroid and Citrus bent leaf viroid or the largely double-stranded RNA region or a largely double-stranded RNA region comprising at least about 35 repeats of the trinucleotides CUG, CAG, GAC or GUC, such as between about 44 and about 2000 repeats of these trinucleotides; and

identifying those eukaryotic organisms wherein the expression of the target gene is downregulated.

The chimeric RNA molecule may comprise an intron sequence. The viroids may have a genomic nucleotide sequence selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7 and SEQ ID NO: 8. The eukaryotic organism may be a plant. Suitable plants include *Arabidopsis*, alfalfa, barley, bean, corn, cotton, flax, pea, rape, rice, rye, safflower, sorghum, soybean, sunflower, tobacco, wheat, asparagus, beet, broccoli, cabbage, carrot, cauliflower, celery, cucumber, eggplant, lettuce, onion, oilseed rape, pepper, potato, pumpkin, radish, spinach, squash, tomato, zucchini, almond, apple, apricot, banana, blackberry, blueberry, cacao, cherry, coconut, cranberry, date, grape, grapefruit, guava, kiwi, lemon, lime, mango, melon, nectarine, orange, papaya, passion fruit, peach, peanut, pear, pineapple, pistachio, plum, raspberry, strawberry, tangerine, walnut and watermelon. The eukaryotic organism may also be a fungus, yeast or mold, or an animal such as a human, mammal, bird, fish, cattle, goat, pig, sheep, rodent, hamster, mouse, rat, guinea pig, rabbit, primate, nematode, shellfish, prawn, crab, lobster, insect, fruit fly, Coleopteran insect, Dipteran insect, Lepidopteran insect, or Homeopteran insect.

It is an object of the present invention to provide a chimeric RNA molecule for downregulating the expression of a target gene in a cell of a eukaryotic organism, comprising one target gene-specific region or multiple target gene-specific regions. A target gene-specific RNA region may comprise a nucleotide sequence of at least about 19 consecutive nucleotides having at least about 94% sequence identity with the complement of about 19 consecutive nucleotides from the nucleotide sequence of the target gene. The target gene-specific region may be operably linked to a largely double-stranded RNA region comprising a nuclear localization signal from a viroid of the Potato spindle tuber viroid (PSTVd)-type. Exemplary PSTVd-type viroids include Potato Spindle tuber viroid, Citrus viroid species III, Citrus viroid species IV, Hop latent viroid, Australian grapevine viroid, Tomato planta macho viroid, Coconut tinangaja viroid, Tomato apical stunt viroid, Coconut cadang-cadang viroid, *Citrus exocortis* viroid, Columnea latent viroid, Hop stunt viroid and Citrus bent leaf viroid. Alternatively, the target-gene-specific region may be operably linked to a largely double-stranded RNA region comprising at least about 35 repeats of the trinucleotide CUG, CAG, GAC, or GUC, such as between about 44 and about 2000 repeats of the trinucleotide CUG, CAG, GAC or GUC, wherein the chimeric RNA molecule, when provided to cells of the eukaryotic organism, downregulates the expression of the target gene.

It is another object of the invention to provide a chimeric DNA molecule for reduction of the expression of a target gene in a cell of a eukaryotic organism, comprising

a promoter or promoter region capable of being recognized by RNA polymerases in the cells of the eukaryotic organism; operably linked to

a DNA region, which when transcribed yields an RNA molecule, the RNA molecule comprising

at least one target gene-specific region comprising a nucleotide sequence of at least about 19 consecutive nucleotides having at least about 94% sequence identity with the complement of about 19 consecutive nucleotides from the nucleotide sequence of the target gene; operably linked to

a largely double-stranded RNA region comprising

a nuclear localization signal from a viroid of the Potato spindle tuber viroid (PSTVd)-type such as Potato Spindle tuber viroid, Citrus viroid species III, Citrus viroid species IV, Hop latent viroid, Australian grapevine viroid, Tomato planta macho viroid, Coconut tinangaja viroid, Tomato apical stunt viroid, Coconut cadang-cadang viroid, *Citrus exocortis* viroid, Columnea latent viroid, Hop stunt viroid and Citrus bent leaf viroid, or

at least about 35 repeats of the trinucleotide CUG, CAG, GAC or GUC, such as between about 44 and about 2000 repeats of the trinucleotide CUG, CAG, GAC or GUC; and optionally

further comprising a transcription termination and polyadenylation signal operably linked to the DNA region encoding the RNA molecule,

wherein the chimeric DNA molecule, when provided to cells of the eukaryotic organism, reduces the expression of the target gene.

Depending on the eukaryotic host organism, the promoter or promoter region may be a promoter or promoter region that functions in animals, a promoter or promoter region that functions in yeast, fungi or molds, or a plant-expressible promoter or promoter region. The promoter may also be a promoter or promoter region recognized by a single subunit bacteriophage RNA polymerase.

The invention also provides cells from a eukaryotic organism comprising chimeric DNA or RNA molecules according to the invention, as well as eukaryotic organisms comprising in their cells a chimeric DNA or RNA molecule according to the invention.

It is yet another object of the invention to provide the use of a chimeric RNA or DNA molecule according to the invention for reduction of the expression of a target gene in a cell of a eukaryotic organism.

The invention also provides a method for making a transgenic eukaryotic organism wherein expression of a target gene in cells of the organism is reduced, the method comprising the steps of:

providing a chimeric DNA molecule according to the invention to a cell or cells of the organism to make a transgenic cell or cells; and

growing or regenerating a transgenic eukaryotic organism from the transgenic cell or cells.

The invention also provides a method for downregulating the expression of a target gene in cells of a eukaryotic organism, comprising the steps of

providing the cells of the eukaryotic organism with a first and second chimeric RNA molecule, wherein

the first chimeric RNA molecule comprises an antisense target gene-specific RNA region comprising a nucleotide sequence of at least about 19 consecutive nucleotides having at least about 94% sequence identity with the complement of about 19 consecutive nucleotides from the nucleotide sequence of the target gene;

the second chimeric RNA molecule comprises a sense target gene-specific RNA region comprising a nucleotide sequence of at least about 19 consecutive nucle-

otides having at least about 94% sequence identity to the complement of the first chimeric RNA molecule;

the first and second chimeric RNA are capable of base-pairing at least between the about 19 consecutive nucleotides of the first chimeric RNA and the about 19 consecutive nucleotides of the second chimeric RNA; and

wherein either the first or the second chimeric RNA molecule comprises a largely double stranded RNA region operably linked to the antisense target-specific RNA region or to the sense target-specific RNA region; and

identifying those eukaryotic organisms wherein the expression of the target gene is down regulated.

Both the first and second chimeric RNA molecule may comprise a largely double-stranded region.

It is another object of the invention to provide a cell from a eukaryotic organism (and eukaryotic organisms comprising such cells), comprising a first and second chimeric RNA molecule, wherein

the first chimeric RNA molecule comprises an antisense target gene-specific RNA region comprising a nucleotide sequence of at least about 19 consecutive nucleotides having at least about 94% sequence identity with the complement of about 19 consecutive nucleotides from the nucleotide sequence of the target gene;

the second chimeric RNA molecule comprises a sense target gene-specific RNA region comprising a nucleotide sequence of at least about 19 consecutive nucleotides having at least about 94% sequence identity to the complement of the first chimeric RNA molecule;

the first and second chimeric RNA are capable of basepairing at least between the about 19 consecutive nucleotides of the first chimeric RNA and the about 19 consecutive nucleotides of the second chimeric RNA; and

further wherein either the first or the second chimeric RNA molecule comprises a largely double-stranded RNA region operably linked to the antisense target-specific RNA region or to the sense target-specific RNA region.

The invention further provides chimeric sense RNA molecules or chimeric DNA molecules encoding such chimeric sense RNA molecules for reduction of expression of a target gene in a cell of a eukaryotic organism in cooperation with a chimeric antisense RNA molecule. In this embodiment of the invention, the chimeric sense RNA molecule comprises a sense target gene-specific RNA region comprising a nucleotide sequence of at least about 19 consecutive nucleotides having at least about 94% sequence identity to the nucleotide of the target gene, operably linked to a largely double-stranded RNA region.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1**. Schematic representation of the secondary structure predicted using MFOLD software for different viroids of the PSTVd-type. A. Potato spindle tuber viroid; B. Australian grapevine viroid; C. Coconut tinangaja viroid; D. Tomato planta macho viroid; E. Hop latent viroid of thermomutant T229; F. Tomato apical stunt viroid.

FIG. **2**: schematic representation of the various chimeric gene constructs used in Examples 1 to 3, below. 35S-P: CaMV 35S promoter; Pdk intron: *Flaveria trinervia* pyruvate orthophosphate dikinase 2 intron 2; cEIN2: cDNA copy of the EIN2 gene from *Arabidopsis* (gene required for sensitivity to ethylene; Alonso et al. 1999 Science 284, 2148-2152) the orientation of this region with respect to the promoter is indicated by the arrow; gEIN2: genomic copy of the EIN2 gene from *Arabidopsis*; PSTVd: cDNA copy of the genome of potato spindle tuber viroid; PSTVd*: partial sequence from PSTVd from nucleotide 16 to nucleotide 355, cloned in inverse orientation with regard to the intact copy of PSTVd; OCS 3': 3' region of the octopine synthase gene from *Agrobacterium tumefaciens*.

FIG. **3**: Phenotype of EIN2-silenced plants when germinating on 1-aminocyclopropane-1-carboxylic acid (ACC). A. In the dark; B. under light conditions. Wt: wild-type plants.

FIG. **4**: schematic representation of the various chimeric gene constructs used in Example 4. CMV promoter: cytomegalovirus promoter; SV40 poly(A): transcription termination and polyadenylation region from SV40; PSTVd: potato spindle tuber viroid sequence; CUGrep: sequence comprising 60 repeats of the CUG sequence; humGFP: humanized green fluorescent protein coding region (adapted to the codon usage of human genes; the orientation of this region with respect to the promoter is indicated by the arrow).

FIG. **5**: Schematic representation of the predicted secondary structure of pSTVd in pMBW491 (A; adopting almost the wild-type configuration) and in pMBW489, where a 10 nucleotide deletion results in a structure different from the wild-type configuration.

DETAILED DESCRIPTION OF THE DIFFERENT EMBODIMENTS

Method and means are described herein for obtaining enhanced antisense RNA-mediated downregulation of gene expression. These methods and means are based upon the unexpected observation that operably linking the target gene-specific RNA sequence to a largely double-stranded RNA region, such as an RNA region comprising the nucleotide sequence of a Potato spindle tuber viroid genome, which in turn comprises a nuclear localization signal for the RNA in which it is embedded, when introduced into cells of a host organism, such as a plant cell, increased both the number of lines wherein gene expression of the target gene was down-regulated, as well as the number of lines wherein gene expression of the target gene was significantly downregulated or even abolished.

Thus, in one embodiment of the invention, a method is provided for downregulating the expression of a target gene in cells of a eukaryotic organisms, comprising the steps of:

providing the cells of the eukaryotic organism with a chimeric RNA molecule wherein the RNA molecule comprises

a target-gene specific RNA region comprising a nucleotide sequence of at least about 19 consecutive nucleotides having at least about 94% sequence identity with the complement of about 19 consecutive nucleotides from the nucleotide sequence of the target gene (the "antisense RNA"); operably linked to

a largely double-stranded RNA region; and

identifying those eukaryotic organisms wherein the expression of the target gene is downregulated.

"Chimeric gene" or "chimeric nucleic acid," as used herein, refers to any gene or any nucleic acid that is not normally found in a particular eukaryotic species or, alternatively, any gene in which the promoter is not associated in nature with part or all of the transcribed DNA region or with at least one other regulatory region of the gene.

As used herein, "antisense RNA" refers to RNA molecules that comprise a nucleotide sequence that is largely complementary to part of the nucleotide sequence of the biologically

-continued

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ggcaaaaaag gacggtgggg agtgcccagc ggccgacagg agtaattccc gccaaacagg 180

gttttcacct ttcctttctt cgggtgtcct tcctcgcgcc cgcaggacca cccctggacc 240

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We claim:

1. A method for downregulating the expression of a target gene in cells of a plant, comprising the steps of:

providing the cells of the plant with a chimeric RNA molecule, wherein the chimeric RNA molecule comprises

a target gene-specific RNA region comprising a nucleotide sequence of at least about 50 consecutive nucleotides, which has at least about 94% sequence identity with the complement of about 50 consecutive nucleotides from the nucleotide sequence of the target gene, operably linked to

a largely double-stranded RNA region that folds into a rod-like structure by internal base-pairing, said rod-like structure comprising non-matching nucleotides which bulge out from within said structure, and wherein said RNA molecule does not comprise any double stranded RNA region of at least 19 consecutive matching base-pairs or any double stranded region of 19 consecutive basepairs having only one mismatch, wherein the largely double-stranded RNA region localizes the chimeric RNA to the nucleus of said cells; and

wherein said cells have an increased concentration of said chimeric RNA molecule in the nucleus relative to cytoplasm of said cells compared to cells of a plant provided with an RNA molecule having said target gene specific RNA region but lacking said largely double stranded RNA region, and wherein the expression of the target gene is downregulated,

wherein the largely double-stranded RNA region comprises the viroid genome nucleotide sequence selected from the group consisting of the genome nucleotide sequence of Potato Spindle tuber viroid, the genome nucleotide sequence of Citrus viroid species III, the genome nucleotide sequence of Citrus viroid species IV,

the genome nucleotide sequence of Hop latent viroid, the genome nucleotide sequence of Australian grapevine viroid, the genome nucleotide sequence of Tomato planta macho viroid, the genome nucleotide sequence of Coconut tinangaja viroid, the genome nucleotide sequence of Tomato apical stunt viroid, the genome nucleotide sequence of Coconut cadang-cadang viroid, the genome nucleotide sequence of *Citrus exocortis* viroid, the genome nucleotide sequence of Columnea latent viroid, the genome nucleotide sequence of Hop stunt viroid and the genome nucleotide sequence of Citrus bent leaf viroid.

2. The method according to claim **1**, wherein the largely double-stranded RNA region comprises the nucleotide sequence of SEQ ID NO: 3.

3. The method according to claim **1**, wherein the viroid genome nucleotide sequence is selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO:6, SEQ ID NO:7 and SEQ ID NO:8.

4. The method according to claim **1**, wherein the viroid genome nucleotide sequence is the genome nucleotide sequence of Potato spindle tuber viroid strain RG1.

5. The method of claim **4**, wherein the genome nucleotide sequence has the nucleotide sequence of SEQ ID NO:3.

6. The method according to claim **1**, wherein the RNA molecule comprises multiple target gene-specific regions.

7. The method according to claim **1**, wherein the plant is selected from the group of *Arabidopsis*, alfalfa, barley, bean, corn, cotton, flax, pea, rape, rice, rye, safflower, sorghum, soybean, sunflower, tobacco, wheat, asparagus, beet, broccoli, cabbage, carrot, cauliflower, celery, cucumber, eggplant, lettuce, onion, oilseed rape, pepper, potato, pumpkin, radish, spinach, squash, tomato, zucchini, almond, apple, apricot, banana, blackberry, blueberry, cacao, cherry, coconut, cranberry, date, grape, grapefruit, guava, kiwi, lemon, lime, mango, melon, nectarine, orange, papaya, passion fruit, peach, peanut, pear, pineapple, pistachio, plum, raspberry, strawberry, tangerine, walnut and watermelon.

8. The method according to claim **1**, wherein the chimeric RNA is produced by transcription from a chimeric DNA molecule.

9. A chimeric RNA molecule for downregulating the expression of a target gene in a cell of a plant, comprising

a target-gene specific RNA region comprising a nucleotide sequence of at least about 50 consecutive nucleotides, which has at least about 94% sequence identity with the complement of about 50 consecutive nucleotides from the nucleotide sequence of the target gene in the cells of the plant; operably linked to

a largely double stranded RNA region that folds into a rod-like structure by internal base-pairing, said rod-like structure comprising non-matching nucleotides which bulge out from within said structure, and wherein said RNA molecule does not comprise any double stranded RNA region of at least 19 consecutive matching base-pairs or any double stranded region of 19 consecutive basepairs having only one mismatch, wherein the largely double-stranded RNA region localizes the chimeric RNA to the nucleus of said cells;

wherein the chimeric RNA molecule, when provided to cells of the plant, has an increased concentration in the nucleus relative to cytoplasm of said cells compared to cells of a plant provided with an RNA molecule having said target gene specific RNA region but lacking said largely double stranded RNA region and wherein said chimeric RNA molecule, when provided to cells of the plant, downregulates the expression of the target gene,

and wherein the largely double-stranded RNA region comprises the viroid genome nucleotide sequence selected from the group consisting of the genome nucleotide sequence of Potato Spindle tuber viroid, the genome nucleotide sequence of Citrus viroid species III, the genome nucleotide sequence of Citrus viroid species IV, the genome nucleotide sequence of Hop latent viroid, the genome nucleotide sequence of Australian grapevine viroid, the genome nucleotide sequence of Tomato planta macho viroid, the genome nucleotide sequence of Coconut tinangaja viroid, the genome nucleotide sequence of Tomato apical stunt viroid, the genome nucleotide sequence of Coconut cadang-cadang viroid, the genome nucleotide sequence of *Citrus exocortis* viroid, the genome nucleotide sequence of Columnea latent viroid, the genome nucleotide sequence of Hop stunt viroid and the genome nucleotide sequence of Citrus bent leaf viroid.

10. The chimeric RNA molecule according to claim **9**, wherein the largely double stranded RNA region comprises the nucleotide sequence of SEQ ID NO: 3.

11. The chimeric RNA molecule according to claim **9**, wherein the viroid genome nucleotide sequence is selected from group consisting of SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7 and SEQ ID NO:8.

12. The chimeric RNA molecule according to claim **9**, wherein the viroid genome nucleotide sequence is the genome nucleotide sequence of Potato spindle tuber viroid strain RG1.

13. The chimeric RNA molecule of claim **12**, wherein the genome nucleotide sequence has the nucleotide sequence of SEQ ID NO:3.

14. The chimeric RNA molecule according to claim **9**, wherein the RNA molecule comprises multiple target gene-specific regions.

15. A chimeric DNA molecule for reduction of the expression of a target gene in a cell of a plant, comprising

a promoter or promoter region capable of being recognized by RNA polymerases in the cells of the plant, operably linked to

a DNA region that, when transcribed, yields a chimeric RNA molecule comprising

a target gene-specific RNA region comprising a nucleotide sequence of at least about 50 consecutive nucleotides having at least about 94% sequence identity with the complement of 50 consecutive nucleotides from the nucleotide sequence of the target gene in the cells of the plant, operably linked to

a largely double-stranded RNA region that folds into a rod-like structure by internal base-pairing, said rod-like structure comprising non-matching nucleotides which bulge out from within said structure, and wherein said RNA molecule does not comprise any double stranded RNA region of at least 19 consecutive matching base-pairs or any double stranded region of 19 consecutive basepairs having only one mismatch, wherein the largely double-stranded RNA region localizes the chimeric RNA to the nucleus of said cells;

wherein the chimeric DNA molecule, when provided to cells of the plant, yields an increased concentration of the chimeric RNA molecule in the nucleus relative to cytoplasm of said cell compared to cells of a plant provided with an RNA molecule having said target gene specific RNA region but lacking said largely double stranded RNA region and wherein said chimeric RNA molecule, when provided to cells of the plant, reduces the expression of the target gene,

and wherein the largely double-stranded RNA region comprises the viroid genome nucleotide sequence selected from the group consisting of the genome nucleotide sequence of Potato Spindle tuber viroid, the genome nucleotide sequence of Citrus viroid species III, the genome nucleotide sequence of Citrus viroid species IV, the genome nucleotide sequence of Hop latent viroid, the genome nucleotide sequence of Australian grapevine viroid, the genome nucleotide sequence of Tomato planta macho viroid, the genome nucleotide sequence of Coconut tinangaja viroid, the genome nucleotide sequence of Tomato apical stunt viroid, the genome nucleotide sequence of Coconut cadang-cadang viroid, the genome nucleotide sequence of *Citrus exocortis* viroid, the genome nucleotide sequence of Columnea latent viroid, the genome nucleotide sequence of Hop stunt viroid and the genome nucleotide sequence of Citrus bent leaf viroid.

16. The chimeric DNA molecule according to claim **15**, wherein the largely double stranded RNA region comprises the nucleotide sequence of SEQ ID NO: 3.

17. The chimeric DNA molecule according to claim **15**, wherein the viroid genome nucleotide sequence is selected from group consisting of SEQ ID NO: 3, SEQ ID NO:4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7 and SEQ ID NO: 8.

18. The chimeric DNA molecule according to claim **15**, wherein the viroid genome nucleotide sequence is the genome nucleotide sequence of Potato spindle tuber viroid strain RG1.

19. The chimeric DNA molecule of claim **18**, wherein the genome nucleotide sequence has the nucleotide sequence of SEQ ID NO: 3.

20. The chimeric DNA molecule according to claim **15**, wherein the RNA molecule comprises multiple target gene-specific regions.

21. The chimeric DNA molecule according to claim **15**, further comprising a transcription termination and polyadenylation signal operably linked to the DNA region encoding the RNA molecule.

22. The chimeric DNA molecule according to claim **15**, wherein the promoter or promoter region is recognized by a single subunit bacteriophage RNA polymerase.

23. A cell from a plant comprising a chimeric DNA molecule according to claim **15**.

24. A plant cell comprising a chimeric RNA molecule according to claim **9**.

25. The cell according to **23**, wherein the plant is selected from the group of *Arabidopsis*, alfalfa, barley, bean, corn, cotton, flax, pea, rape, rice, rye, safflower, sorghum, soybean, sunflower, tobacco, wheat, asparagus, beet, broccoli, cabbage, carrot, cauliflower, celery, cucumber, eggplant, lettuce, onion, oilseed rape, pepper, potato, pumpkin, radish, spinach, squash, tomato, zucchini, almond, apple, apricot, banana, blackberry, blueberry, cacao, cherry, coconut, cranberry, date, grape, grapefruit, guava, kiwi, lemon, lime, mango, melon, nectarine, orange, papaya, passion fruit, peach, peanut, pear, pineapple, pistachio, plum, raspberry, strawberry, tangerine, walnut and watermelon.

26. A plant comprising in its cells a chimeric DNA molecule according to claim **15**.

27. A plant, comprising in its cells a chimeric RNA molecule according to claim **9**.

28. The plant according to **26**, wherein the plant is selected from the group of *Arabidopsis*, alfalfa, barley, bean, corn, cotton, flax, pea, rape, rice, rye, safflower, sorghum, soybean, sunflower, tobacco, wheat, asparagus, beet, broccoli, cabbage, carrot, cauliflower, celery, cucumber, eggplant, lettuce, onion, oilseed rape, pepper, potato, pumpkin, radish, spinach, squash, tomato, zucchini, almond, apple, apricot, banana, blackberry, blueberry, cacao, cherry, coconut, cranberry, date, grape, grapefruit, guava, kiwi, lemon, lime, mango, melon, nectarine, orange, papaya, passion fruit, peach, peanut, pear, pineapple, pistachio, plum, raspberry, strawberry, tangerine, walnut and watermelon.

29. A method for making a transgenic plant in which expression of a target gene in cells of the plant is reduced, the method comprising the steps of:

providing a chimeric DNA molecule according to claim **15** to cells of the plant to make transgenic cells; and

growing or regenerating a transgenic plant from the transgenic cells.

30. The method according to claim **1**, wherein said rod-like structure is the structure of the largely double stranded RNA region in its energetically most favorable conformation.

31. The method according to claim **1**, wherein said rod-like structure comprises stretches of double stranded RNA and wherein the longest stretch of perfectly basepaired RNA is 11 contiguous basepairs in size.

32. The chimeric RNA molecule according to claim **9**, wherein said rod-like structure is the structure of the largely double stranded RNA region in its energetically most favorable conformation.

33. The chimeric RNA molecule according to claim **9**, wherein said rod-like structure comprises stretches of double stranded RNA and wherein the longest stretch of perfectly basepaired RNA is 11 contiguous basepairs in size.

34. A cell from a plant comprising the chimeric RNA molecule of claim **32**.

35. A cell from a plant comprising the chimeric RNA molecule of claim **33**.

* * * * *

4.3. Appendix C. Term sheet proposed by RAML Pharmaceuticals

NON-BINDING TERM SHEET FOR A FUTURE LICENSE AGREEMENT

Clause title	Proposed terms
Background	Nemtox AB has licensed in technology relating to gene silencing through RNA interference from the Commonwealth Scientific and Industrial Research Organization (CSIRO), including the patent family to which Patent No. US7576262B2 is part. The technology licensed in from CSIRO, as well improvements made to it by Nemtox, have been deemed to be of interest to RAML Pharmaceuticals for treating various forms of virus infections in humans. RAML Pharmaceuticals will license in technology from Nemtox AB relating to gene silencing through RNA interference to research, develop, manufacture and commercialize treatments of virus infections in humans.
Licensor	Nemtox AB (LICENSOR)
Licensee	RAML Pharmaceuticals (LICENSEE)
Licensed technology	The LICENSED TECHNOLOGY includes all technology described in PATENT RIGHTS, NON-PATENT INTELLECTUAL PROPERTY RIGHTS, and KNOW-HOW. The LICENSOR warrants that it has the right to grant the LICENSEE such rights as described.
Patent rights	PATENT RIGHTS are defined as all matter claimed in U.S. Patent Applications Serial No. US7576262B2 and any other patents belonging to the same patent family, as well as divisions, continuations, continuations-in-part or reissues arising therefrom or issued thereon from such patent family. LICENSOR shall prosecute, finance, and maintain the PATENT RIGHTS.
Non-patent intellectual property rights	NON-PATENT INTELLECTUAL PROPERTY RIGHTS are defined as all intellectual property excluding PATENT RIGHTS and including copyrights, trademarks, industrial design rights and trade-secrets, owned, developed, and registered or in any other way claimed by the LICENSOR relating to the technology described in PATENT RIGHTS.
Know how	KNOW-HOW is defined as the necessary knowledge and human competence to allow the LICENSEE to implement the LICENSED TECHNOLOGY according to the FIELD OF USE, including methods, processes, designs, formulas, expert opinion and all other information and data of relevance. To enable such transfer of knowledge, the LICENSOR is to spend a sum of no less than 5 work weeks of staff at the location of the LICENSEE's research facilities. The LICENSEE

	does also have the right to spend at least 2 weeks at the research site of the LICENSOR.
Scope of license	Exclusive right to use, develop, manufacture, make, have made, sell, license out and in any other ways commercialize the LICENSED TECHNOLOGY within the defined FIELD OF USE and LICENSED TERRITORIES
Field of use	The FIELD OF USE shall mean the field of human therapy and treatment of virus infections.
Licensed territories	The LICENSED TERRITORIES shall mean a worldwide license
Financial terms	**License fee** The LICENSEE shall pay the LICENSOR a non-refundable licensing fee of € 200 000 within sixty days of the effective date of the agreement **Royalties** 5% royalty payable on net sales received by the LICENSEE to the LICENSOR from the selling or licensing of technology as covered by the claims of the intellectual property in PATENT RIGHTS
Term duration	The agreement shall be in place from the day of signing and terminated at the time of the expiration of the PATENT RIGHTS
Governing law	Swiss law shall apply

5. Tasks

1. Define the business models that Nemtox envision for the GSRNAT. What do you consider to be pros and cons, as well as key assets, for each of them?

2. Analyzing RAML Pharmaceuticals term sheet:
    a. What are the primary risks with the deal?
    b. What is the primary upside and Nemtox most important priorities in signing the deal?
    c. How could the term sheet be modified to better suit Nemtox situation?

« PATENT PROSECUTION AND CLAIM COVERAGE, ALIGNING PATENT STRATEGY WITH CORPORATE GOALS »

Prepared for Health-2-Market, supported by the European Commission under the FP7-HEALTH programme

Author: University of Gothenburg

Table of content

1. The history of C-Sensus

C-Sensus AB was founded in 2000 in Gothenburg Sweden, with the goal of developing and selling innovative measurement solutions for the automotive industry. Through the exploitation of a novel "Fibre-Optical Measuring System" (titled FOMS), originally developed at Viktoria Swedish ICT (VSICT), the company aimed to improved pressure measurement in "extreme environments", more specifically cylinders of combustion engines for cars and trucks. The automotive industry was decided to be an attractive market for the technology since it represented significant size, there was a clear and growing demand for measurement solutions for "green engines", and Volvo AB, a local truck company, had expressed interest in solutions such as FOMS. The inventor of the measuring system, Dr. Gnaeus Naevius, had joined C-Sensus as Chief Technology Officer, and Tove Lauritzen, with experience from several start-ups, headed the company as a CEO. Early on, the team managed to attract finance through governmental seed funding as well as business angels. The pursued business model was to develop FOMS into a product that would be marketed by C-Sensus, but outsourced for large scale production. During the following years, the development of the technology went more or less according to plan, but the hopes of commercial success did not materialize. It had proved to be much more difficult to become a supplier in the automotive value chain than what Tove and Gnaeus had initially believed. In 2003, the company decided to take their technology in a completely different direction. One of the key advantages of FOMS was its resistance to radio magnetic interference. The ability to resist magnetic interference, along with the other advantages of the technology, was especially suitable for the application of measuring intracranial pressure, often caused by head trauma. In 2004, C-Sensus initiated a collaboration with the engineering service company Acra Devices, to develop FOMS for the new application. One of the advantages of the new taget market was the ability to increase the volume of sold sensors, as they would not be re-used due to the inherent infection risks. In early 2008, the company had to yet again face the fact that the market was more difficult to enter than they had initially believed. The treatment of head trauma at hospitals followed a number of very standardized processes, and changing them would require significant resources in education and persuasion. Dejected and close to the point of giving up, Tove had approached Geven, a medical device company based in Spain, with a suggestion to initiate a collaboration. Geven was a company of significant size (1 725 MEURO) with long standing relationships with the hospitals and potential users of C-Sensus technology. More specifically, Geven already sold products relating to head trauma treatments and FOMS could now be integrated and added to their next product version. The collaboration could provide C-Sensus with a new distribution channel and a better route to market. Geven was willing to include the prospect in their product development cycle for evaluation, but only under a number of conditions.

1. C-Sensus would have to sign a deal with at least two sub-contractors for producing the sensors. Having at least two suppliers would increase the competition and thus keep the costs down. In addition, the supply service level would be higher due to the reduced dependency on the operations of only one company.
2. Geven wanted to use their interface technology for connecting C-Sensus sensors to their devices.
3. Geven would receive a license to C-Sensus technology for the control and measurement unit. For this, C-Sensus would be payed a yearly fee for maintaining and upgrading the software, as well as adapting it to changes in Geven's medical device platform.

As Tove pondered the business proposition[1], it became evident that one of the key issues for its success would be C-Sensus control position. What bargaining position, and hence ability to generate good margins, would C-Sensus have? What were the risks of technology leakage and could other companies come in and reap the rewards of C-Sensus work? To analyze the situation she decided to review the technology portfolio, including the patent family. A central question was the claim coverage of the patent application; how did it apply to the business model? Could C-Sensus develop a control position around their other assets? To complete the analysis she also needed to analyze the other involved stakeholders control positions. She decided to start with a complete review of C-Sensus technology portfolio, and then the US patent, which covered what would certainly be the most important market for the company going forward.

2. The Fibre-Optical Measuring System

The Fibre-Optical Measuring system had initially been developed with the purpose of measuring pressure in car engines. Previous fibre-optical sensors were known to have problems with interference in the signal transmission path, for example caused by fibre couplings or through sensor bending. By adding a reference signal, FOMS solved this problem and at the same time kept the benefits of an optical solution. As C-Sensus developed its business further, it became gradually more apparent that the car engine market was not only difficult to enter, but the unique qualities of the measurement solution were even more valued in other applications. The real advantage of FOMS was its ability to measure pressure without being affected by external interference (such as electro-magnetic radiation or radio frequency fields). In addition, the sensors could be implemented in very small sizes and therefore used in many unique environments, such as intracranial pressure measurements.

The implementation of FOMS includes a combination of hardware and software, covering both the actual sensor elements, as well as the measurement and control unit that analyses the sensor generated data. Through the development of the technology, C-Sensus had furthermore created an enhanced cavity design, which not only simplified the production of the sensor, but also improved the accuracy and sensitivity of the measurements. The thickness of the sensor membrane was another area that had an important effect on the accuracy and sensitivity. After significant testing, a relationship between the membrane thickness, the size of the sensor, and the sensor performance had been identified. The research on the membrane had created some really unexpected results and advanced the ability to make the components smaller. The research had also resulted in a database of values that, in combination with the measured relationship between the measuring signal and reference signal, generated the final and correct pressure measurement figure. The database would be stored in the “measuring and control unit connected to the sensor. Finally, a graphical user interface that presented the measurement results, as well as allowed the user to program the device, had been created. No additional patents had been filed on any of these assets, but they had been kept secret, and when shared, always under a non-disclosure agreement.

[1] Appendix A. Discussed collaboration and business model between C-Sensus and Geven

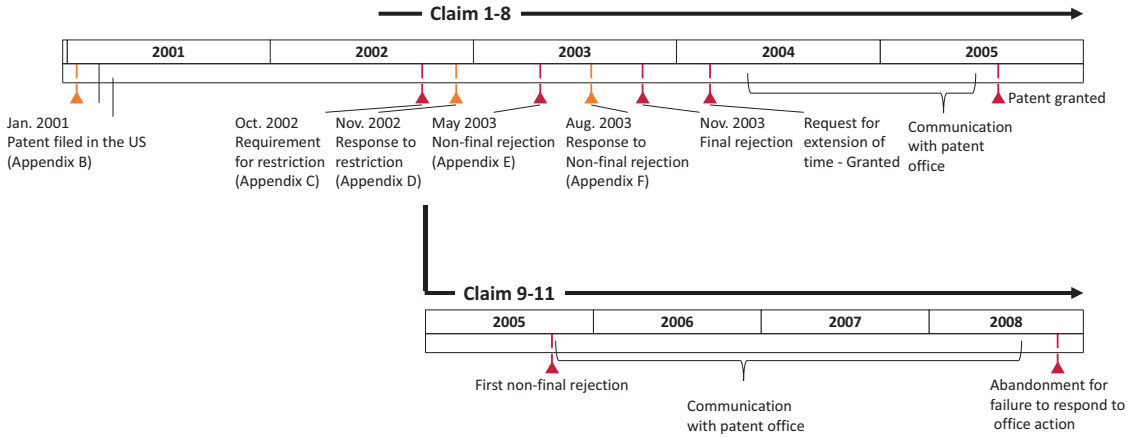
3. The FOMS patent prosecution process (US Patent)

The patent relating to FOMS was filed by VSICT on the 18th of June, 1999. VSCIT decided to first file a patent at the Swedish Patent and Registration Office, and later, through an international PCT application, designate Japan, the United States, and various European states. In January 2001 the patent was officially filed in the United States based on the claims in the PCT application2. The United States Patent and Trademark Office replied in October 2002, with a rejection based on the opinion that the application contained two separate inventions. The filed patent thus lacked "unity of invention" which is a requirement where a granted patent has to relate to only one invention, or a group of closely related inventions3. Later in 2002, C-Sensus acknowledged the opinion of the patent office, and decided to remove the claims relating to "the measuring system with a record carrier" (claims 9-11), while keeping claims 1-8, that covered the "technical features to correct a measurement signal due to bending". C-Sensus did however reserve the right to file for a divisional patent application, and thus splitting the application in two4. The focus was on the application relating to claim 1-8 and in May 2003, the first non-final rejection was submitted by the patent office examiner5. The claims were rejected because they, together with the specification, were "failing to particularly point out and distinctly claim the subject matter" (35 USC § 112) and were "obvious" in relation to the state of the art (35 USC § 103). C-Sensus replied with some amendments to the claims, together with a number of arguments describing why they considered the claims to be valid6. After a couple of additional rounds of communication and amendments the patent was finally granted in August 20057.

C-Sensus had also decided to file a divisional patent application on claim 9-11 from the initial application, the claims relating to the connection between the sensor and the measuring and control unit. The international search report, that was performed when the PCT application was filed, had already rejected these claims due to "lacking novelty". C-Sensus thus knew that the divisional patent could be difficult to get, but decided to go ahead anyways8. After additional communication with the patent office it did however become obvious that C-Sensus would not receive any meaningful claim coverage in the patent. The patent was finally abandoned in 20089.

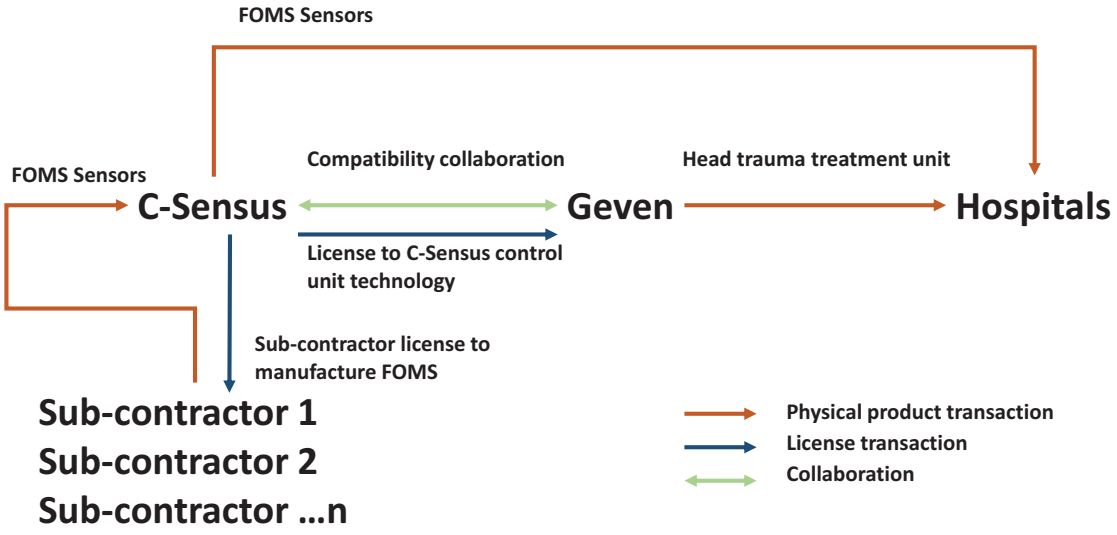
The patent prosecution in the US was now complete, and the final claim scope was certainly different from what was initially filed. Not only had the language in the claims changed10, but the measurement and control unit integration had been completely removed. It was clear to Tove that the patent application had served several purposes from its inception, but was it now aligned with the strategy they wanted to pursue? Could they have written the patent differently, and how important was it that they lost the integration coverage with the measurement system?

[2] Appendix B. Claims filed through application number 10/018220
[3] Appendix C. Requirement for restriction
[4] Appendix D. Response to restriction
[5] Appendix E. Examiners search strategy and non-final rejection
[6] Appendix F. Applicant response to non-final rejection with claim amendments
[7] Appendix G. Granted patent US6934015B1
[8] Appendix H. Excerpt from the international search report
[9] Appendix I. Rejected and abandoned patent US2009/0027659A1
[10] Appendix J. Claim 1 comparison between filed (10/018220) and granted (US6934015B1) application


Claim 1-8
2001
2002
2003
2004
2005
Jan. 2001
Patent filed in the US
(Appendix B)
Oct. 2002
Requirement
for restriction
(Appendix C)
Nov. 2002
Response to
restriction
(Appendix D)
May 2003
Non-final rejection
(Appendix E)
Aug. 2003
Response to
Non-final rejection
(Appendix F)
Nov. 2003
Final rejection
Request for
extension of
time - Granted
Communication
with patent
office
Patent granted
Claim 9-11
2005
2006
2007
2008
First non-final rejection
Communication
with patent office
Abandonment for
failure to respond to
office action

4. Appendix

4.1. Appendix A. Discussed collaboration and business model between C-Sensus and Geven



4.2. Appendix B. Claims filed through application number 10/018220

CLAIMS

1. A method for bending compensation in intensity-based optical measuring systems, comprising a sensor element (8) connected to a measuring and control unit (16) via an optical connection (4) and being adapted for providing a signal corresponding to a measurement of a physical parameter in connection with the sensor element (8), said method comprising

generation of a measuring signal (λ_1) that is brought to come in towards the sensor element (8),

generation of a reference signal (λ_2) that is transmitted through the optical connection (4) without being influenced in the sensor element (8), said measuring signal and said reference signal having different wavelengths,

detection of said measuring signal (λ_1) and

detection of said reference signal (λ_2),

characterised by comprising bending compensation through correction data based upon pre-stored data concerning the relationship between the measured reference signal (λ_2) and the measured measuring signal (λ_1) as a function of the bending influence upon said optical connection (4).

2. The method according to claim 1, characterised by the feeding of said measuring signal (λ_1) to the sensor element (8) causing optical interference in a cavity (8a) associated with the sensor element (8).

3. The method according to claim 1, characterised by said correction data consisting of a stored table or function, describing a relationship measured beforehand, between the reference signal (λ_2) and the measuring signal (λ_1), as a function of the bending influence.

4. A method according to any one of the preceding claims, characterised by being utilised for pressure (p) measurements, said sensor element (8) defining a membrane (8b) being affected by the pressure (p) surrounding the sensor element (8).

5. A device for measurements in optical measuring systems comprising; an optical connection (4) connected to a sensor element (8) adapted for providing a signal corresponding to a measurement of a physical parameter in connection with the sensor element (8); a first light source (2) and a second light source (3) arranged at the opposite end of the optical connection (4) and functioning to emit a first light signal (λ_1) and a second light signal (λ_2), respectively, at different wavelengths, the first light signal (λ_1) defining a measuring signal, brought to come in towards the sensor element (8), and the second light signal (λ_2) defining a reference signal, conveyed through the optical connection (4) without being influenced in the sensor element (8); a first detector (12) intended for the detection of a light signal modulated by the sensor element (8); a second detector (13) intended for the detection of a light signal reflected by the sensor element; and a computerised measuring and control unit (14), to which said detectors (12, 13) are connected, characterised by said unit (14) comprising means for processing the values detected by said detectors (12, 13), means for storing data concerning the relationship between the measured reference signal (λ_2) and the measured measuring signal (λ_1) as a function of the bending influence upon said optical connection (4), and means for correcting the value detected by the first detector (12) in dependence of said correction data.

6. The device according to claim 5, characterised by said sensor element (8) comprising a cavity (8a), shaped so as to create optical interference when feeding said measuring signal (λ_1) into the cavity (8a).

7. The device according to claim 6, characterised by said cavity (8a) being obtained through building up molecular silicone and/or silicone dioxide layers, and an etching procedure.

8. The device according to claim 7, characterised by said cavity (8a) being obtained through utilising a bonding procedure.

9. A measuring system for measuring a physical parameter (p) influencing a sensor element (8) adapted to be connected to a measuring and control unit (16), characterised by comprising a separate information-carrying unit (18) comprising a memory and being adapted for connection to said measuring and control unit (16), said information-carrying unit (18) being co-ordinated with the sensor element (8) by containing stored information regarding the properties of the measuring system and the sensor element (8) during measurements.

10. The measuring system according to claim 9, wherein said sensor element (8) is connected to said measuring and control unit (16) via an optical connection (4), characterised by said stored information including pre-defined correction data concerning the relationship between the measured reference signal and the measured measuring signal as a function of the bending influence upon said optical connection (4).

11. The measuring system according to claim 9 or 10, characterised by said reference signal and said measuring signal are of the same wavelength.

4.3. Appendix C. Requirement for restriction

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/018,220	04/26/2002		000515-281	3449

21839 7590 10/30/2002

BURNS DOANE SWECKER & MATHIS L L P
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

EXAMINER	
NGUYEN, TU T	

ART UNIT	PAPER NUMBER
2877	

DATE MAILED: 10/30/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 07-01)

AK

Office Action Summary	Application No. 10/018,220	
	Examiner: Tu T Nguyen	Art Unit: 2877

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-11 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) 1-11 are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

U.S. Patent and Trademark Office
PTO-326 (Rev. 04-01) **Office Action Summary** Part of Paper No. 7

DETAILED ACTION

Election/Restrictions

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1-8, drawn to an optical measuring system involving technical features to correct a measurement signal due to bending.

Group II, claim(s) 9-11, drawn to a measuring system with a record carrier with stored information about a sensor and the measuring system.

The inventions listed as Groups I do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special

technical features for the following reasons: group I relates to correct a measurement signal due to bending and group II relates to storing information.

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(I).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tu T Nguyen whose telephone number is (703) 306-9185. The examiner can normally be reached on M-T 7:30-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frank G Font can be reached on (703) 308-4881. The fax phone numbers for the organization where

this application or proceeding is assigned are (703) 872-9318 for regular communications and (703) 872-9319 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0956.

Tu Tuan Nguyen

Patent Examiner TC 2877

10/25/02

4.4. Appendix D. Response to restriction

Patent
Attorney's Docket No. 000515-281

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#8
12/12/02

In re Patent Application of)
)
) Group Art Unit: 2877
)
Application No.: 10/018,220) Examiner: T. Nguyen
)
Filed: April 26, 2002)
)
For: A METHOD AND A DEVICE FOR)
BENDING COMPENSATION IN)
INTENSITY-BASED FIBRE-OPTICAL)
MEASURING SYSTEMS)

RESPONSE TO RESTRICTION REQUIREMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In response to the Restriction Requirement set forth in the Office Action dated October 30, 2002, Applicants hereby elect, for prosecution in connection with the above-identified application, Group I - including claims 1-8, which the Office described as being drawn to an optical measuring system involving technical features to correct a measurement signal due to bending.

Applicants reserve the right to file divisional applications covering the subject matter of the non-elected claims.

Should the Examiner have any questions regarding this response, he is urged to contact the undersigned at 703.838.6540.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: _____
Kenneth B. Leffler
Registration No. 36,075

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620

Date: November 25, 2002

(10/01)

4.5. Appendix E. Examiners search strategy and non-final rejection

	Type	L #	Hits	Search Text	DBs	Time Stamp
1	BRS	L1	187	(((first and second) near3 signal$2) or ((measur$5 and referenc$5) near3 signal$2)) with (differen$5 near2 wavelength)	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM_TDB	2003/01/30 09:56
2	BRS	L8	129	1 and @ad<=19990618	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM_TDB	2003/01/30 12:31
3	BRS	L15	33686	(compensat$5 or correct$5 or adjust$5) near4 (bend$5 or noise)	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM_TDB	2003/01/30 12:21
4	BRS	L22	5	8 and 15	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM_TDB	2003/01/30 10:01
5	BRS	L29	14550	(compensat$5 or correct$5 or adjust$5) near4 bend$5	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM_TDB	2003/01/30 12:26
6	BRS	L36	318893	optical and (sensor or detector)	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM_TDB	2003/01/30 12:28
7	BRS	L43	18927	(determin$5 or detect$5 or calculat$5 or measur$5) near4 (bend$5)	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM_TDB	2003/01/30 12:31
8	BRS	L50	1466	36 and 43 and @ad<=19990618	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM_TDB	2003/01/30 12:54
9	BRS	L57	168	50 and 29	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM_TDB	2003/01/30 12:55

01/30/2003, EAST Version: 1.03.0002

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United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/018,220	04/26/2002		000515-281	3449

21839 7590 02/05/2003

BURNS DOANE SWECKER & MATHIS L L P
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

EXAMINER	
NGUYEN, TU T	

ART UNIT	PAPER NUMBER
2877	

DATE MAILED: 02/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 07-01)

Office Action Summary	Application No. 10/018,220	
	Examiner Tu T Nguyen	Art Unit 2877

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

U.S. Patent and Trademark Office
PTO-326 (Rev. 04-01) Office Action Summary Part of Paper No. 9

Serial Number: 10/018,220
Filing Date: 04/26/02

Paper No: 9

Detailed Office Action

Election/Restriction

Applicant's election without traverse of group I, claims 1-8 in Paper No. 8 is acknowledged.

Specification

The disclosure is objected to because of the following informalities:

In the specification, pages 1-2, the terms "claim 1", "claim 5", "claims 1 and 5" should be deleted.

Claim Objections

Claims 1,5 are objected to because of the following informalities:

Claim 1 is a method claim. It should contain all the steps to perform the measurement. In claim 1, line 6, 8, 11, 12, the phrases "generation", "generation", "detection", detection" should be changed to " generating", "generating", "detecting", "detecting", respectively.

Claim 5, line 13, the term "said unit" should be changed to "said computerized measuring unit".

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1,5,7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, lines 2-4, the phrase " a sensor element connected ... in connection with the sensor element" is not clear. It is not clear how the sensor element connected to the measuring and control unit. The claim does not provide a connection between the components in order for an ordinary skill in the art to understand the invention.

In claim 1, lines 11-12, the phrase " detection of said measuring signal and detection of said reference signal" is not clear. It is not clear how to detect the signals. Does Applicant mean detecting the reflected signals? Or where are the detectors located?

In claim 1, line 9; claim 5, lines 8-9, the phrase "without being influenced in the sensor element" is not clear. It is not clear how the reference signal is transmitted without being influenced in the sensor element.

In claim 1, lines 13-16, the phrase "characterized by comprising ... pre-stored data concerning the relationship between the measured reference signal and the measured measuring signal" is not clear. It is not clear how to perform the correction. What does applicant mean by "compensation through correction data"?

In claim 5, lines 2-4, the phrase "for providing signal corresponding ... the sensor element" is not clear. It is not clear which element " optical connection" or "the sensor element" providing the measurement signal.

In claim 7, line 2, the term "and/or" is indefinited.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hall et al (6,210,346).

With respect to claims 1,5, Hall discloses a system for measuring a pressure. The system comprises: a sensor 21 (fig 3) connected to an optical connection 14 (fig 3), a light source 10 (fig 3) for generating a measurement signal, a detector 30 (fig 3) for detecting the reflected signal.

Hall does not disclose a second light source for generating a reference signal without being influenced in the sensor element. Hall's prior art discloses an additional light source for generating a reference signal without being influenced with the sensor to compensate for the variations in transmittance caused by bending of the optical connector (column 2, lines 51-60). It would have been obvious to modify Hall with the compensating element as taught in the prior art to make the system more accurate.

Hall does not disclose compensating the measured data through the pre-stored data. However, compensating the measured data to the pre-stored data for determining characteristic

of a test device would have been known. It would have been obvious to modify Hall with the known compensating method to make the system to process the bending function faster.

With respect to claims 2,6, since Hall feeds the measuring signal 10 (fig 3) to a sensor 21 (fig 3), Hall would have been inherently disclosed an optical interference in a cavity associated with the sensor element.

With respect to claims 3-4, the claimed stored table and the pressure measurement would have been known. It would have been obvious to modify Hall's system with the known stored table and the pressure measurement to measure the pressure of the test system.

With respect to claims 7-8, it would have been obvious a design choice to modify the cavity with different bonding procedure or different layers for different environment. The modification involves only routine skill in the art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tu T Nguyen whose telephone number is (703) 306-9185. The examiner can normally be reached on M-T 7:30-5:30.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frank G Font can be reached on (703) 308-4881. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9318 for regular

communications and (703) 872-9319 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0956.

Tu Tuan Nguyen

Patent Examiner TC 2877

1/31/03

4.6. Appendix F. Applicant response to non-final rejection with claim amendments

Attorney's Docket No. 10\018,220
Application No. 000515-281
Page 8

REMARKS

Claims 1-8 are currently pending. Non-elected claims 9, 10 and 11 have been canceled without prejudice or disclaimer to facilitate allowance of the present application. Two new claims have been added to round out the scope of protection being sought.

The Office Action includes an objection to the written description noting references to claims 1 and 5. These passages on pages 1 and 2 have been changed to avoid mention of specific claims.

The Office Action also includes claim objections. The claims have been extensively revised to place them in more conventional U.S. claim format and, as a result of these other changes, it is believed that each of the concerns underlying these objections raised by the Office have been avoided.

The Office Action also includes a rejection of claims 1, 5 and 7 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. The claims, again for purposes of bringing them into conformance with typical U.S. claim format, have been revised and as amended avoid each of the issues raised in the rejection. Accordingly, it is respectfully submitted that this rejection has been rendered moot and its withdrawal is respectfully requested.

The Office Action also includes a rejection of claims 1-8 under 35 U.S.C. §103 as allegedly being unpatentable over the *Hall et al.* patent (U.S. Patent 6,210,346) this rejection is respectfully traversed.

produces a correction signal that compensates for variations in transmittance caused by bending of the catheter.

Hence, even assuming *arguendo* that one would be motivated by the passage at column 2 lines 52-59 to modify the main embodiment of the *Hall et al.* patent to include a second set of optical fibers, the resulting hypothetical device would not meet the recitations of the pending claims as explained in detail below.

The Present Invention

The present invention relates to a method for compensation for bending of an optical fibre in light intensity-based optical measurement systems. As disclosed, the invention can include a sensor element 8 with a cavity 8a and that a first light signal λ1 is guided into the cavity 8a where a second light signal λ2 is guided into the sensor element but is reflected without entering the cavity, such as shown in Figure 1a, without being influenced by the cavity and the measurements taken thereby. Further, both of the first light signal λ1 and a second light signal λ2 are guided through a single optical fiber 4 and are detected by means of two detectors 13 and 14, for example.

As reflected in pending claim 1, the present invention is distinct from the *Hall et al.* apparatus and recite the first light signal λ1 (the "measurement signal") and the second light signal λ2 (the "reference signal") according to the invention are guided to the same optical fiber this has the advantage that the same optical path is being measured. This is in contrast to a system, such as the prior art system as described in the *Hall et al.* patent that

required two sets of optical paths, one of which might be damaged or bent more than the other, resulting in a mis-calibration.

For this reason, it is respectfully submitted that claims 1 and 5, and therefore the claims dependant therefrom, are allowable and Applicants respectfully request withdrawal of this rejection.

Another distinguishing aspect of the invention, as reflected in independent claims 1 and 5, is that the sensor is manufactured in such a manner that the measurement light will be separated from the reference light, e.g., the first light signal will be selected to exceed its limit for threshold of the sensor whereas the second light signal will be lower than its limit, for example.

Finally, dependent claim 12 has been added to clearly recite that the present invention comprises a cavity (e.g., cavity 8a) into which a first signal is guided, whereas the second signal is reflected by a sensor element (such as sensor element 8) and guided back into the optical fiber as shown in Figure 1a, but without entering the cavity. This is a further distinction from the applied prior art.

In light of the foregoing, Applicants respectfully request reconsideration and allowance of the above-captioned application. If any residual issues exist, the Examiner is invited to contact the undersigned at the number listed below.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

Date: August 5, 2003

By: _____
Charles F. Wieland III
Registration No. 33,096

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620

AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in the application:

LISTING OF CLAIMS:

1. (Currently Amended) A method of compensating for bending of an optical fibre ~~compensation~~ in light intensity-based optical measuring systems, said light intensity-based optical measuring systems comprising a sensor element connected to a measuring and control unit via ~~an optical connection~~ optical fibre and being adapted for providing a signal corresponding to a measurement of a physical parameter ~~in connection with the sensor element~~, said method comprising

generating ~~generation of~~ a measuring light signal ~~that;~~

transmitting the measuring light signal through ~~is brought to come in~~ the optical fibre towards the sensor element,

generating ~~generation of~~ a reference light signal ~~that is transmitted~~;

transmitting the reference light signal through the same optical ~~connection~~ fibre without being ~~influenced in~~ affected by the sensor element due to the measuring light being separated from the reference light, wherein said measuring signal and said reference signal ~~having~~ have different wavelengths,

detecting ~~detection of~~ said measuring signal after being influenced by the sensor element; ~~and~~

detecting ~~detection of~~ said reference signal after being transmitted through the optical fibre;~~,~~

compensating for bending of the optical fibre by reference to ~~characterized by comprising bending compensation through~~ correction data based upon pre-stored data concerning ~~the~~ a relationship between the measured reference signal and the measured measuring signal as a function of the bending influence upon said optical connection.

2. (Currently Amended) The method according to claim 1, ~~characterized by the feeding of~~ wherein said measuring signal causes ~~to the sensor element causing~~ optical interference in a cavity associated with the sensor element.

3. (Currently Amended) The method according to claim 1, ~~characterized by~~ wherein said correction data ~~consisting of~~ includes a stored table or function, describing a relationship measured beforehand, between the reference signal and the measuring signal, as a function of the bending influence.

4. (Currently Amended) A method according to claim 1, ~~characterized by being~~ wherein said sensor is utilized for pressure measurements, said sensor element ~~defining~~ including a membrane being affected by the pressure surrounding the sensor element.

5. (Currently Amended) A device for measurements in optical measuring systems comprising:

a sensor element adapted for providing a signal corresponding to a measurement of a physical parameter in connection with the sensor element;

an optical ~~connection~~ fibre connected to ~~a~~ the sensor element ~~adapted for providing a signal corresponding to a measurement of a physical parameter in connection with the sensor element~~;

a first light source and a second light source arranged at the opposite end of the optical ~~connection~~ fibre and functioning to emit a first light signal and a second light signal, respectively, at different wavelengths, the first light signal defining a measuring signal, ~~brought to come in~~ transmitted towards the sensor element through the optical fibre, and the second light signal defining a reference signal, ~~conveyed~~ transmitted through the optical ~~connection~~ fibre without being ~~influenced in~~ affected by the sensor element due to the measuring light being separated from the reference light;

a first detector intended ~~for the detection of~~ to detect a light signal modulated by the sensor element;

a second detector intended ~~for the detection of~~ to detect a light signal reflected by the sensor element; and

a ~~computerized~~ measuring and control unit, to which said detectors are connected, whereby ~~characterized by~~ said measuring and control unit comprising means for processing the values detected by said detectors, means for storing data concerning the relationship

between the measured reference signal and the measured measuring signal as a function of the bending influence upon said optical connection, and means for correcting the value detected by the first detector in dependence of said correction data.

6. (Currently Amended) The device according to claim 5, ~~characterized by~~ wherein said sensor element comprising a cavity, shaped so as to create optical interference when feeding said measuring signal into the cavity.

7. (Currently Amended) The device according to claim 6, ~~characterized by~~ wherein said cavity ~~being obtained through building up~~ includes a plurality of molecular silicone and/or silicone dioxide layers~~, and an etching procedure~~ which have been etched.

8. (Currently Amended) The device according to claim 7, ~~characterized by~~ whereby said cavity ~~being obtained through utilizing a bonding procedure~~ includes bonding layers.

9. (Canceled)

10. (Canceled)

11. (Canceled)

12. (New) The method according to claim 1, further comprising guiding the first measuring signal into a cavity of the sensor element; and reflecting the reference signal from the sensor element without entry into the cavity.

13. (New) The device of claim 5, wherein the sensor element comprises a cavity into which the measurement signal is guided, whereas the reference signal is reflected by sensor element without entering the cavity.

4.7. Appendix G. Granted patent US6934015B1

US006934015B1

(12) **United States Patent**
Naevius

(10) **Patent No.: US 6,934,015 B1**
(45) **Date of Patent: Aug. 23, 2005**

(54) **METHOD AND A DEVICE FOR BENDING COMPENSATION IN INTENSITY-BASED FIBRE-OPTICAL MEASURING SYSTEMS**

(75) Inventors: **Gnaeus Naevius**, Kållered (SE);

(73) Assignee: **C-Sensus AB**, Gothenburg (SE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/018,220**

(22) PCT Filed: **Jun. 16, 2000**

(86) PCT No.: **PCT/SE00/01296**

§ 371 (c)(1),
(2), (4) Date: **Apr. 26, 2002**

(87) PCT Pub. No.: **WO00/79233**

PCT Pub. Date: **Dec. 28, 2000**

(30) **Foreign Application Priority Data**

Jun. 18, 1999 (SE) 9902320

(51) **Int. Cl.**[7] **G01N 21/00**
(52) **U.S. Cl.** **356/73.1**
(58) **Field of Search** 356/73.1; 250/227.14–227.23; 385/11–13, 115–119

(56) **References Cited**

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FOREIGN PATENT DOCUMENTS

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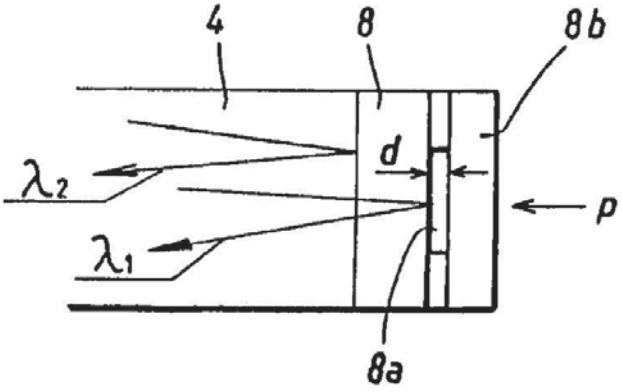
* cited by examiner

Primary Examiner—Tu T. Nguyen
(74) *Attorney, Agent, or Firm*—Burns, Doane, Swecker & Mathis, L.L.P.

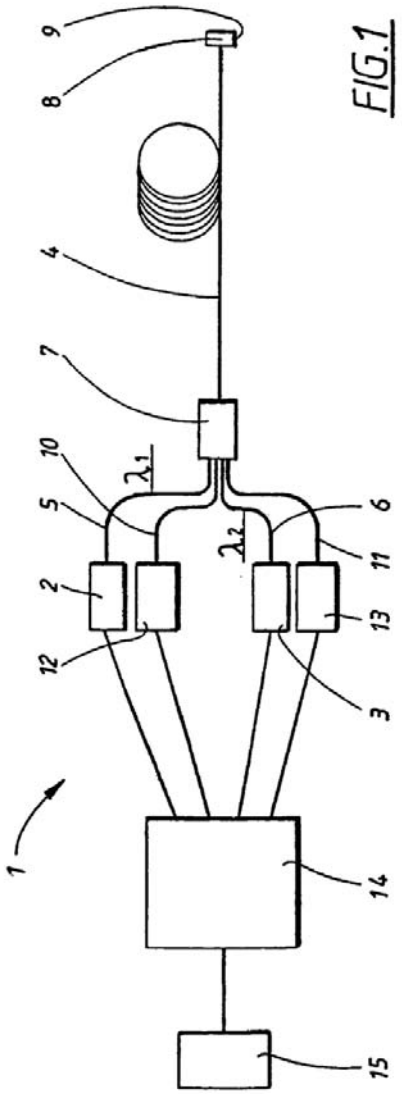
(57) **ABSTRACT**

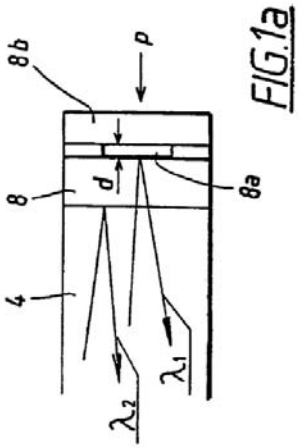
Compensation is provided for bending of an optical fibre in intensity-based optical measuring systems. A measuring signal and a reference signal of different wavelengths are generated and transmitted through an optical connection towards a sensor element. The reference signal is not influenced in the sensor element. The measuring and reference signals are detected and compensation is carried out for bending of the optical connection using correction data. The correction data is based upon pre-store data concerning the relationship between the measured reference signal and the measured measuring signal as a function of the bending influence on the optical connection. Devices and methods according to the invention allow for measurements with an optical pressure measuring system that exhibit effective compensation for any bending of the optical connection.

16 Claims, 3 Drawing Sheets



U.S. Patent Aug. 23, 2005 Sheet 1 of 3 US 6,934,015 B1





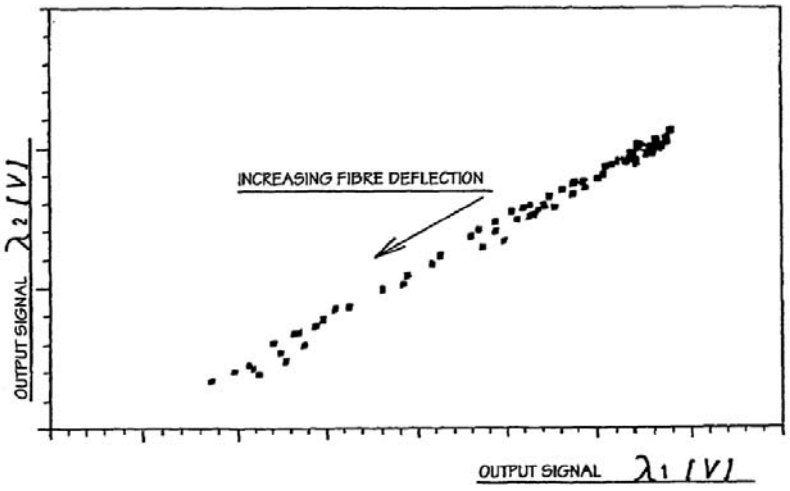

INCREASING FIBRE DEFLECTION
OUTPUT SIGNAL λ2 [V]
OUTPUT SIGNAL λ1 [V]

FIG. 2

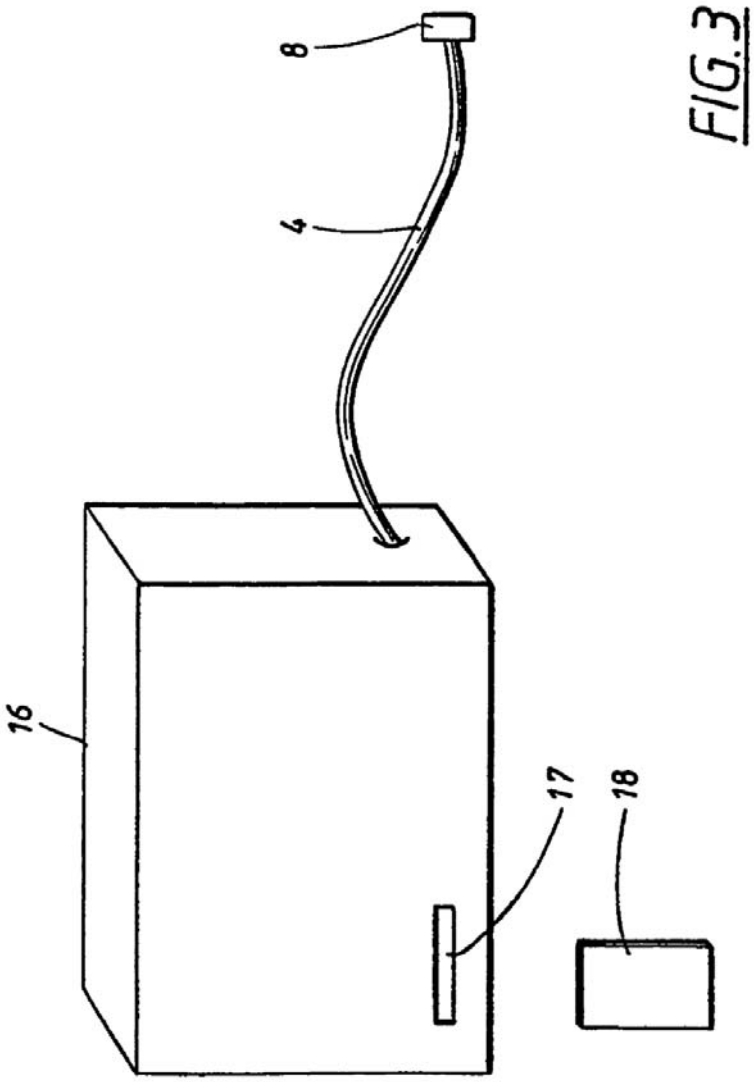


FIG.3

METHOD AND A DEVICE FOR BENDING COMPENSATION IN INTENSITY-BASED FIBRE-OPTICAL MEASURING SYSTEMS

TECHNICAL FIELD

The present invention relates to a method for measuring systems intended for use with intensity-based fibre-optical measuring systems for pressure measurements. The invention also relates to a device for carrying out such a method.

BACKGROUND ART

In connection with measuring physical parameters such as pressure and temperature, it is previously known to utilise various sensor systems by which the optical intensity of a ray of light, conveyed through an optical fibre and coming in towards a sensor element, is influenced due to changes in the respective physical parameter. Such a system may for example be used when measuring the blood pressure in the veins of the human body. Said system is based upon a transformation from pressure to a mechanical movement, which in turn is transformed into an optical intensity, conveyed by an optical fibre, which is in turn transformed into an electrical signal that is related to the measured pressure.

According to known art, such a fibre-optical measurement system may comprise a pressure sensor, an optical fibre connected to said pressure sensor, and at least one light source and at least one light detector located at the opposite end of the fibre, in order to provide the pressure sensor with light, and to detect the information-carrying light signal returning from the pressure sensor, respectively.

One problem occurring with previously known systems of the above kind relates to the fact that interference may occur in the signal transmission path, for example caused by fibre couplings or through bending, intentionally or unintentionally, of the fibre. Already at a light deflection of the fibre, a reduction of the light signal occurs. This signal damping, caused by the bent fibre, entails that the light signal detected in the light detector, which is related to the pressure detected in the sensor element, will have a value that does not coincide with the real pressure. The size of the deviation will then depend on how much the fibre was deflected.

Through EP 0 528 657 A2 a fibre-optical measurement system for measuring pressure is known. Said system comprises a pressure sensor with a membrane, three LED:s emitting light at different wavelengths, and two photo detectors. The system is arranged so that a computing algorithm is used for correction of such temperature effects that may have been superimposed on the output pressure signal. This algorithm is based upon the relationship between membrane deflection, pressure and temperature. Correction data obtained experimentally may also be used as input data to the algorithm regarding temperature compensation.

DISCLOSURE OF INVENTION

A primary object of the present invention is to compensate, by means of a method and a device, for interference in intensity-based fibre-optical sensor systems, caused by intentional or unintentional bending of the optical fibre. This is achieved by means of a method and a device in accordance with the present invention.

The invention is intended for bending compensation in intensity-based optical measurement systems comprising a sensor element connected to a measuring and control unit via an optical connection and adapted for providing a signal

corresponding to a measurement of a physical parameter in connection with the sensor element. The invention comprises; the generation of a measuring signal that is brought to come in towards the sensor element; the generation of a reference signal that is transmitted through the optical connection without being influenced in the sensor element, said measuring signal and said reference signal having different wavelengths; and the detection of said measuring signal and the detection of said reference signal. The invention is characterised by comprising bending compensation through correction data based upon pre-stored data concerning the relationship between the measured reference signal and the measured measuring signal as a function of the bending influence on said optical connection.

Advantageous embodiments of the invention are defined by the subsequent dependent claims.

BRIEF DESCRIPTION OF DRAWINGS

The invention will be explained in more detail below, with reference to a preferred embodiment and to the enclosed drawings, in which:

FIG. **1** shows, schematically, a pressure measuring system according to the present invention;

FIG. **1***a* shows an enlarged view of a sensor element intended for use in connection with the invention;

FIG. **2** shows a graph illustrating the relationship between a measured reference signal and a measured measuring signal as a function of the bending influence, in accordance with a method according to the invention; and

FIG. **3** shows, in principle, a pressure measuring system in which a so-called "smart card" can be used as the information-carrying memory unit.

PREFERRED EMBODIMENTS

FIG. **1** shows, schematically, an intensity-based fibre-optical measuring system **1** according to the present invention. According to a preferred embodiment, the arrangement is used in connection with a fibre-optical measuring system of an as such previously known kind, which could preferably, but not exclusively, consist of a pressure measuring system. Alternatively, the invention could be used e.g. for measuring temperature and acceleration.

Two light sources belong to the system **1**, comprising a first LED **2** and a second LED **3**, the first LED **2** functioning to emit a first light signal of a first wavelength λ_2, and the second LED **3** functioning to emit a second light signal of a second wavelength λ_2, said wavelengths being different. The LED:s **2**, **3** are connected to an optical conduit, preferably in the form of an as such previously known optical fibre **4**, by means of a first link **5** and a second link **6**, respectively, and also via a fibre coupling **7**. The optical fibre **4** is connected to a sensor element **8**, schematically illustrated in FIG. **1**.

According to what is shown in detail by FIG. **1***a*, which is an enlarged view of the sensor element **8**, said element comprises a cavity **8***a*, for example obtainable (according to known art) through construction by means of molecular layers (primarily silicone, alternatively silicone dioxide or a combination of the two) and an etching procedure. Preferably, a bonding procedure is also utilised in assembling the various layers of the sensor element **8**. The manufacture of such a sensor element **8** is as such previously known, e.g. from the patent Document PCT/SE93100393. In this way, a membrane **8***b* is also created within the sensor element **8**, the deflection of which membrane will depend on the pressure p surrounding the sensor element **8**.

According to what will be described in detail below, the first light signal with the first wavelength λ_1 will come in and be reflected against the cavity **8***a* within the pressure sensor **8**, whereas the second light signal with the second wavelength λ_2 is brought to come in onto the bottom side of the sensor element **8**, i.e. towards the interface between the pressure sensor **8** and the optical fibre **4**. Hereby, the first light signal will be modulated by the pressure p acting on the membrane **8***b*. When the membrane **8***b* is influenced, the dimensions of the cavity **8***a*, primarily its depth d, will change, entailing a modulation of the first light signal through optical interference inside the cavity **8***a*.

The second light signal will be reflected against the bottom side of the sensor element **8**, due to the fact that the silicone defining the sensor element **8** will only allow transmission of light with a wavelength longer than a certain limit value (e.g. 900 nm). Consequently, said first wavelength λ_1 will be selected so as to exceed this limit value. Contrary to this, said second wavelength λ will be selected so as to fall below this limit value. After having determined the two wavelengths λ_1, λ_2, appropriate dimensions of the cavity **8***a* are determined. For example, the depth of the cavity **8***a* is selected to be a value of substantially the same magnitude as the two wavelengths λ_1, λ_2. The sizing of the cavity **8***a* is made considering the required application range for the sensor element **8** (in the current case primarily the pressure range to which the sensor element **8** is to be adapted).

The light signal (λ_1) emitted from the first LED **2** defines a measuring signal that is thus transmitted through the fibre **4** to the sensor element **8**, where said light signal will be modulated in the manner described above. The second light signal (λ_2) will then define a reference signal, transmitted through the fibre **4** and being reflected by the bottom side **9** of the sensor element **8**. The light signal modulated in the sensor element **8** and the light signal reflected from the bottom side **9** of the sensor element are then transmitted back through the fibre **4**. The returning light signals will, through the fibre coupling **7**, be conveyed into fibre links **10**, **11**, connected to the detectors **12** and **13**, respectively. The detectors **12**, **13** will detect the measuring signal and the reference signal, respectively.

The four links **5**, **6**, **10**, **11** preferably consist of optical fibres, the fibre coupling **7** thereby preferably consisting of an as such known fibre junction device designed so as to transfer the four fibre links **5**, **6**, **10**, **11** into the fibre **4** leading to the sensor element **8**.

The system **1** also comprises a computerised measuring and control unit **14**, to which the LED:s **2**, **3** and the detectors **12**, **13** are connected. Said unit **14** comprises means for processing the values detected by said detectors **12**, **13**. According to the invention, the processing of the detected values includes a compensation for intentional or unintentional bending of the fibre **4**, by utilising correction data based upon pre-stored data concerning the relationship between a measured reference signal and a measured measuring signal as a function of the bending influence on the optical fibre **4**. Such correction data could for example be comprised of a table or a function defining values to be used during measurements to correct the detected measuring signal.

Finally, the system **1** comprises a presentation unit **15**, e.g. a display, allowing a measurement of the sensed pressure p to be visualised for a user.

FIG. **2** graphically illustrates how the above relationship between a measured reference signal and a measured measuring signal is changed during increased bending of the fibre **4**. In the figure, the reference signal is referenced as "Output signal λ_2 [V]" and the measuring signal as "Output signal λ_1 [V]". Said measured relationship can be described by a function, so as to correct the measuring signal continuously with a specific value depending on the reference signal. Alternatively, the measured relationship can be used for defining a mathematical function, which in turn is used for producing corrected values during measurements with the system according to the invention. As a further alternative, a number of measurement values may be registered in a table, into which the value of the reference signal is entered, to obtain a value (with the aid of interpolation, if necessary), with which the current measuring signal is corrected. Independently of the correction procedure used, it is performed in the above-mentioned measuring and control unit **14**.

FIG. **3** shows, in principle, a pressure measuring system according to the invention, comprising an alternative measuring unit **16** to which the sensor element **8** is connected, via the optical fibre **4**, in an exchangeable manner via an optical coupling (not shown in FIG. **3**). Said measuring unit **16** also comprises a reader unit **17** for insertion and reading of a separate unit in the form of an information-carrying card **18** (also called "smart card"). Said card **18** comprises a memory device where data regarding the sensor element **8** are stored for use. During measurements, these data may be read by the measuring unit **16** and be used for example for bending compensation in dependence of which specific sensor element **8** that is being used for the moment. The invention thus provides a further advantage, in that different sensor elements **8** can be connected to said unit **16** without calibration, thanks to data stored on the information-carrying card **17**. Said data preferably define the relationship between predetermined correction data, produced through measurements of the first as well as the second light signal at various degrees of bending of the optical fibre.

The invention is especially suitable in case a single measurement station with one measuring unit **16** is used together with several exchangeable sensor elements. In such a case, data corresponding to properties, measuring range, etc. of each sensor element, can be stored on a corresponding number of information-carrying cards, each then corresponding to (and being used together with) a specific sensor element.

As an alternative to an information-carrying unit in the form of a card, the invention can also be used with other types of separate data carriers. Further, the measuring system according to FIG. **3**, as opposed to what is shown in FIGS. **1** and **2**, is not limited to measurements of the kind using two different wavelengths, but can also be used when measuring with for example only one wavelength.

It should be mentioned, that the card **18** may also contain other stored information than that mentioned above, e.g. information regarding the sensor type, calibration data, etc. The basic principle is, however, that the card **18** is coordinated with a specific sensor element such that it will comprise stored data regarding the function of the specific sensor element. Preferably, the card **18** will be provided with information—in the form of a set of parameters—allowing the properties of the sensor element **8**, together with the properties of the measuring unit **16**, to provide a suitable linearisation of the characteristics of the specific sensor element during measurements.

The invention is not limited to the embodiment described above, but may be varied within the scope of the appended claims. For example, the principle for data storage regarding

a specific sensor on a separate information-carrying card can be used also for systems not intended for pressure measurements.

What is claimed is:

1. A method of compensating for bending of an optical fibre in light intensity-based optical measuring systems, said light intensity-based optical measuring systems comprising a sensor element connected to a measuring and control unit via optical fibre and being adapted for providing a signal corresponding to a measurement of a physical parameter, said method comprising

generating a measuring light signal;

transmitting the measuring light signal through the optical fibre towards the sensor element;

generating a reference light signal;

transmitting the reference light signal through the same optical fibre without being affected by the sensor element due to the measuring light being separated from the reference light, wherein said measuring light signal and said reference light signal have different wavelengths;

detecting said measuring light signal after being influenced by the sensor element;

detecting said reference light signal after being transmitted through the optical fibre and after being reflected by said sensor element;

compensating for bending of the optical fibre by reference to correction data based upon pre-stored data concerning a relationship between the measured reference light signal and the measured measuring light signal as a function of the bending influence upon said optical fibre, wherein said measuring light signal causes optical interference in a cavity associated with the sensor element.

2. The method according to claim **1**, wherein said correction data includes a stored table or function, describing a relationship measured beforehand, between the reference light signal and the measuring light signal, as a function of the bending influence.

3. A method according to claim **1**, wherein said sensor is utilized for pressure measurements, said sensor element including a membrane being affected by the pressure surrounding the sensor element.

4. The method according to claim **1**, further comprising guiding the measuring light signal into the cavity of the sensor element; and reflecting the reference light signal from the sensor element without entry into the cavity.

5. The method according to claim **1**, wherein characteristics of material forming at least one surface of said cavity permits guiding the measuring light signal into the cavity and causes reflectance of the reference light signal from the cavity.

6. The method of claim **1**, wherein the wavelength of the measuring light signal is selected to exceed a limit value and the wavelength of the reference light signal is selected to be less than said limit value.

7. The method of claim **6**, wherein said limit value is based on a characteristic of the senor element material.

8. The method of claim **6**, wherein dimensions of the cavity are determined based on a selected wavelength of the measuring light signal, a selected wavelength of the reference light signal and the limit value.

9. A device for measurements in optical measuring systems comprising:

a sensor element adapted for providing a signal corresponding to a measurement of a physical parameter in connection with the sensor element;

an optical fibre connected to the sensor element;

a first light source and a second light source arranged at the opposite end of the optical fibre and functioning to emit a first light signal and a second light signal, respectively, at different wavelengths, the first light signal defining a measuring signal, transmitted towards the sensor element through the optical fibre, and the second light signal defining a reference signal, transmitted through the optical fibre without being affected by the sensor element due to the measuring light being separated from the reference light;

a first detector intended to detect a light signal modulated by the sensor element;

a second detector intended to detect a light signal reflected by the sensor element; and

a measuring and control unit, to which said detectors are connected, whereby said measuring and control unit comprising means for processing the values detected by said detectors, means for storing data concerning the relationship between the measured reference signal and the measured measuring signal as a function of the bending influence upon said optical connection, and means for correcting the value detected by the first detector in dependence of said correction data, wherein said sensor element comprising a cavity, shaped so as to create optical interference when feeding said measuring signal into the cavity.

10. The device according to claim **9**, wherein said cavity includes a plurality of molecular silicone and/or silicone dioxide layers which have been etched.

11. The device according to claim **10**, whereby said cavity includes bonding layers.

12. The device of claim **9**, wherein the measurement light signal is guided into the cavity, whereas the reference light signal is reflected by the sensor element without entering the cavity.

13. The device of claim **9**, wherein characteristics of material forming at least one surface of said cavity permits guiding of the measuring signal into the cavity and causes reflectance of the reference signal from the cavity.

14. The device of claim **9**, wherein the wavelength of the first light signal exceeds a limit value and the wavelength of the second light signal is less than the limit value.

15. The device of claim **14**, wherein said limit value is based on a characteristic of the sensor element material.

16. The device of claim **14**, wherein dimensions of the cavity are determined based on the first wavelength, the second wavelength and the limit value.

* * * * *

4.8. Appendix H: Excerpt from international search report

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/01296

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: G01L 11/02, G01D 5/26
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: G01L, G01D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4356396 A (H.RUELL ET AL), 26 October 1982 (26.10.82), abstract ---	1-8
A	US 5280173 A (T.F.MORSE ET AL), 18 January 1994 (18.01.94), abstract ---	1-8
A	US 4924870 A (WLODARCZYK ET AL), 15 May 1990 (15.05.90), abstract ---	1-8
A	US 5422478 A (M.T.WLODARCZYK ET AL), 6 June 1995 (06.06.95), abstract ---	1-8

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 Sept 2000	29 -11- 2000
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Lars Jakobsson Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/01296

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5089979 A (A. MCEACHERN ET AL), 18 February 1992 (18.02.92), figures 2-4, abstract	9
	--	
X	US 4418392 A (Y. HATA), 29 November 1983 (29.11.83), abstract	9
	--	
X	US 5249143 A (J. STALEY, III), 28 Sept 1993 (28.09.93), abstract	9
	--	
X	US 5857777 A (W. SCHUH), 12 January 1999 (12.01.99), abstract	9
	--	
X	US 4858615 A (A. MEINEMA), 22 August 1989 (22.08.89), abstract	9
	--	
A	EP 0326309 A2 (HEWLETT-PACKARD COMPANY), 2 August 1989 (02.08.89), abstract	9-10
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Form PCT/ISA/210 (continuation of second sheet) (July 1998)

4.9. Appendix I. Rejected and abandoned patent US2009/0027659A1

US 20090027659A1

(19) **United States**

(12) **Patent Application Publication**

Naevius

(10) **Pub. No.: US 2009/0027659 A1**

(43) **Pub. Date: Jan. 29, 2009**

(54) **MEASURING SYSTEM FOR MEASURING A PHYSICAL PARAMETER INFLUENCING A SENSOR ELEMENT**

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(21) Appl. No.: **12/155,936**

(22) Filed: **Jun. 11, 2008**

Related U.S. Application Data

(60) Continuation-in-part of application No. 11/175,171, filed on Jul. 7, 2005, now abandoned, which is a division of application No. 10/018,220, filed on Apr. 26, 2002, now Pat. No. 6,934,015, filed as application No. PCT/SE00/01296 on Jun. 16, 2000.

(30) **Foreign Application Priority Data**

Jun. 18, 1999 (SE) 9902320-2

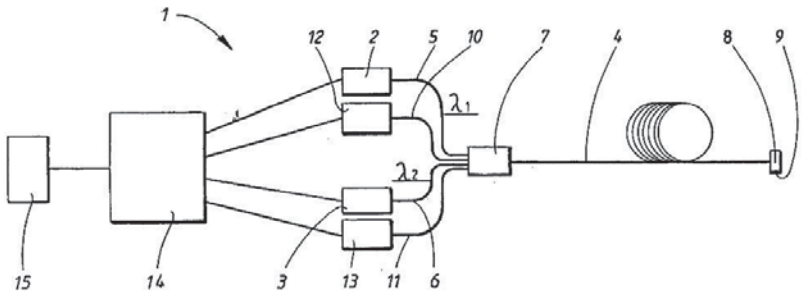
Publication Classification

(51) **Int. Cl.**
G01N 21/25 (2006.01)

(52) **U.S. Cl.** **356/73.1**

(57) **ABSTRACT**

A measuring system is disclosed for measuring a physical parameter influencing a sensor element adapted to be connected to a measuring and control unit. The system comprises an information-carrying unit comprising a memory and being adapted to be associated with said measuring and control unit, said information-carrying unit being coordinated with the sensor element by containing stored information regarding the properties of the measuring system and the sensor element during measurements, and said information-carrying unit being supported by a connector for connecting said sensor element with said measuring and control unit.



Patent Application Publication Jan. 29, 2009 Sheet 1 of 5 US 2009/0027659 A1

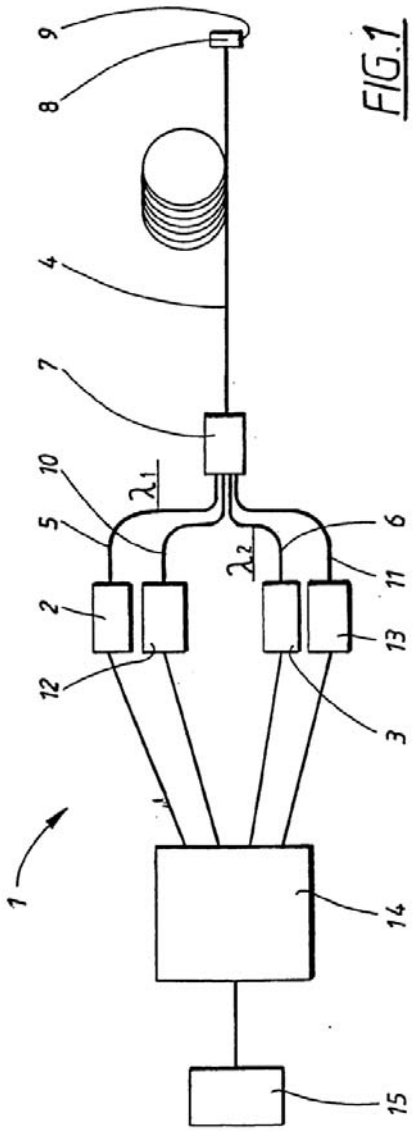


FIG.1

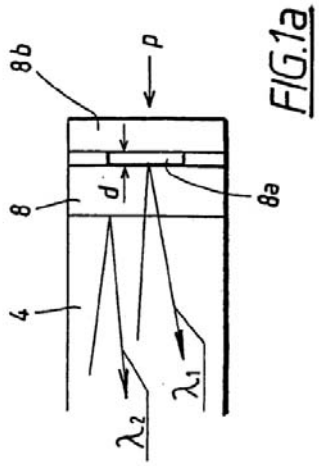


FIG.1a

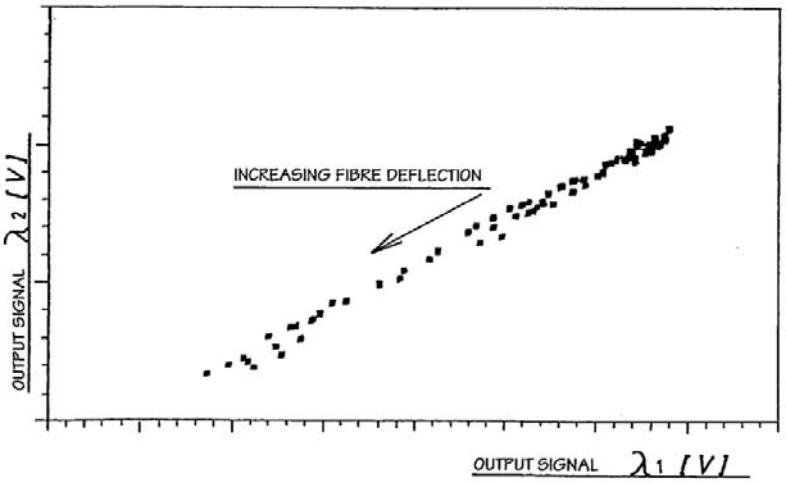

INCREASING FIBRE DEFLECTION
OUTPUT SIGNAL λ_2 [V]
OUTPUT SIGNAL λ_1 [V]

FIG. 2

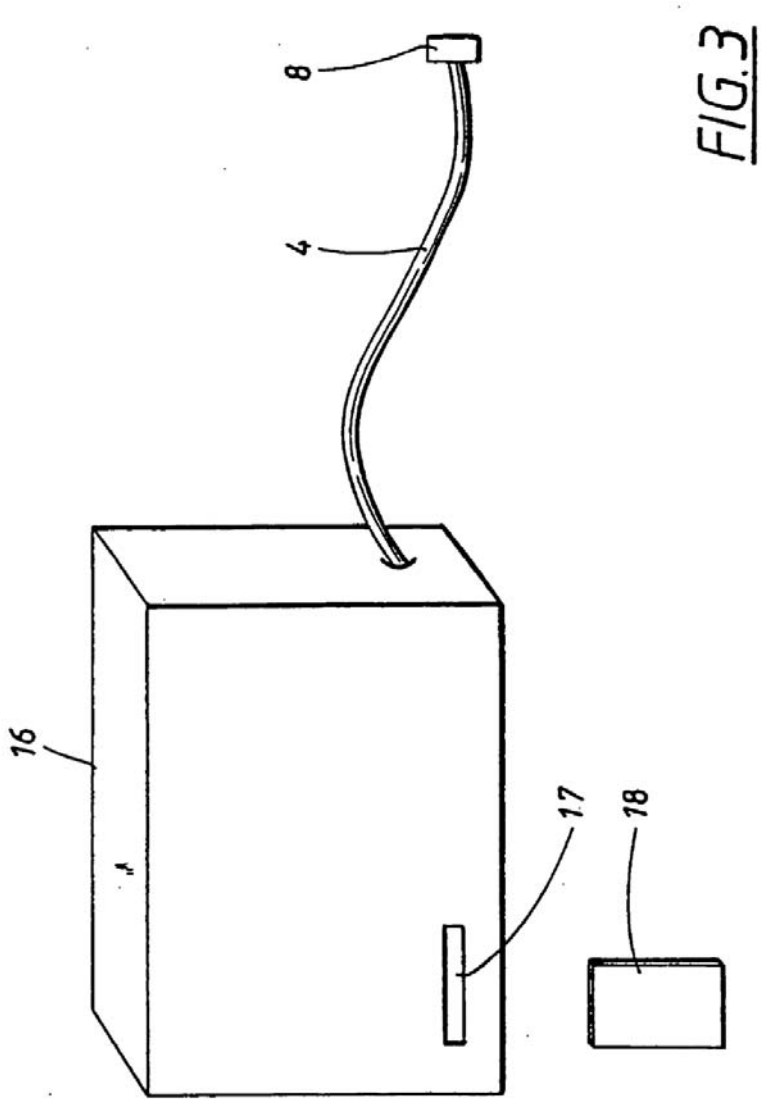


FIG.3

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Fig. 4

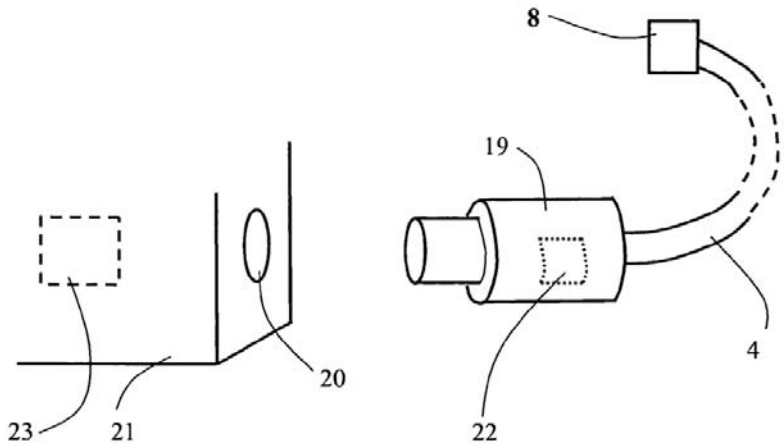
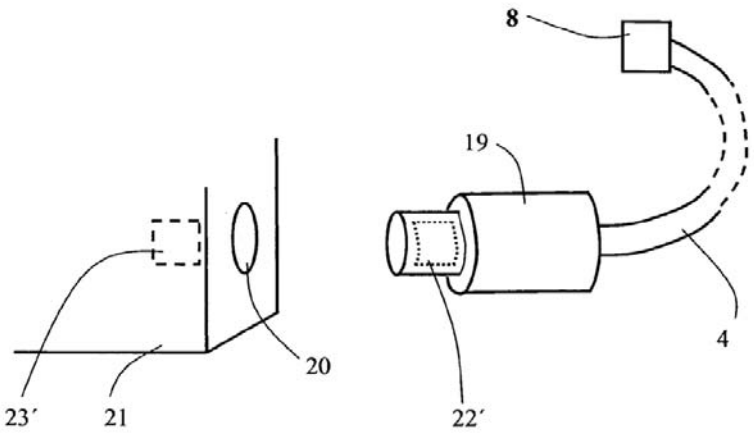


Fig. 5



US 2009/0027659 A1 Jan. 29, 2009

MEASURING SYSTEM FOR MEASURING A PHYSICAL PARAMETER INFLUENCING A SENSOR ELEMENT

RELATED APPLICATIONS

[0001] This application is a Continuation-In-Part application of U.S. patent application Ser. No. 11/175,171, filed in US on Jul. 7, 2005; which is a Divisional Application of U.S. patent application Ser. No. 10/018,220, filed in US on Apr. 26, 2002, and issued as U.S. Pat. No. 6,934,015 on Aug. 23, 2005; which is a national stage of PCT/SE00/01296 having an international filing date of Jun. 16, 2000, and claiming priority under 35 U.S.C. §119 to Swedish application 9902320-2, filed in Sweden on Jun. 18, 1999.

TECHNICAL FIELD

[0002] The present disclosure relates to measuring systems. For example, the disclosure relates to a measuring system for measuring a physical parameter influencing a sensor element adapted to be connected to a measuring and control unit.

BACKGROUND ART

[0003] In connection with measuring physical parameters such as pressure and temperature, it is previously known to utilise various sensor systems by which the optical intensity of a ray of light, conveyed through an optical fiber and coming in towards a sensor element, is influenced due to changes in the respective physical parameter. Such a system may for example be used when measuring the blood pressure in the veins of the human body. Said system is based upon a transformation from pressure to a mechanical movement, which in turn is transformed into an optical intensity, conveyed by an optical fiber, which is in turn transformed into an electrical signal that is related to the measured pressure.

[0004] According to known art, such a fiber-optical measurement system may comprise a pressure sensor, an optical fiber connected to said pressure sensor, and at least one light source and at least one light detector located at the opposite end of the fiber, in order to provide the pressure sensor with light, and to detect the information-carrying light signal returning from the pressure sensor, respectively.

[0005] One problem occurring with previously known systems of the above kind relates to the fact that interference may occur in the signal transmission path, for example caused by fiber couplings or through bending, intentionally or unintentionally, of the fiber. Already at a light deflection of the fiber, a reduction of the light signal occurs. This signal damping, caused by the bent fiber, entails that the light signal detected in the light detector, which is related to the pressure detected in the sensor element, will have a value that does not coincide with the real pressure. The size of the deviation will then depend on how much the fiber was deflected.

[0006] Through EP 0 528 657 A2 a fiber-optical measurement system for measuring pressure is known. Said system comprises a pressure sensor with a membrane, three LED:s emitting light at different wavelengths, and two photo detectors. The system is arranged so that a computing algorithm is used for correction of such temperature effects that may have been superimposed on the output pressure signal. This algorithm is based upon the relationship between membrane deflection, pressure and temperature. Correction data obtained experimentally may also be used as input data to the algorithm regarding temperature compensation.

SUMMARY

[0007] The present disclosure relates to compensating, by means of a method and a device, for interference in intensity-based fiber-optical sensor systems, caused by intentional or unintentional bending of the optical fiber.

[0008] In one aspect, bending compensation in intensity-based optical measurement systems is disclosed, comprising a sensor element connected to a measuring and control unit via an optical connection and adapted for providing a signal corresponding to a measurement of a physical parameter in connection with the sensor element. This aspect comprises the generation of a measuring signal that is brought to come in towards the sensor element; the generation of a reference signal that is transmitted through the optical connection without being influenced in the sensor element, said measuring signal and said reference signal having different wavelengths; and the detection of said measuring signal and the detection of said reference signal. This aspect is characterised by comprising bending compensation through correction data based upon pre-stored data concerning the relationship between the measured reference signal and the measured measuring signal as a function of the bending influence on said optical connection.

[0009] A measuring system is disclosed for measuring a physical parameter influencing a sensor element adapted to be connected to a measuring and control unit. The system comprises an information-carrying unit comprising a memory and being adapted to be associated with said measuring and control unit, said information-carrying unit being coordinated with the sensor element by containing stored information regarding the properties of the measuring system and the sensor element during measurements, and said information-carrying unit being supported by a connector for connecting said sensor element with said measuring and control unit.

BRIEF DESCRIPTION OF DRAWINGS

[0010] The invention will be explained in more detail below, with reference to a preferred embodiment and to the enclosed drawings, in which:

[0011] FIG. **1** shows, schematically, a pressure measuring system according to the present invention;

[0012] FIG. **1***a* shows an enlarged view of a sensor element intended for use in connection with the invention;

[0013] FIG. **2** shows a graph illustrating the relationship between a measured reference signal and a measured measuring signal as a function of the bending influence, in accordance with a method according to the invention;

[0014] FIG. **3** shows, in principle, a pressure measuring system in which a so-called "smart card" can be used as the information-carrying memory unit;

[0015] FIG. **4** shows, an exemplary embodiment in which a connector is associated with an information-carrying unit; and

[0016] FIG. **5** shows an alternative exemplary solution in which an information-carrying unit is constituted by a memory chip being arranged for cooperating with a detector unit in the form of a card reader.

DETAILED DESCRIPTION

[0017] FIG. **1** shows, schematically, an intensity-based fiber-optical measuring system **1** according to the present invention. According to a preferred embodiment, the arrangement is used in connection with a fiber-optical measuring system of an as such previously known kind, which could preferably, but not exclusively, consist of a pressure measuring system. Alternatively, the invention could be used e.g. for measuring temperature and acceleration.

[0018] Two light sources belong to the system **1**, comprising a first LED **2** and a second LED **3**, the first LED **2** functioning to emit a first light signal of a first wavelength λ_1 and the second LED **3** functioning to emit a second light signal of a second wavelength λ_2, said wavelengths being different. The LED:s **2**, **3** are connected to an optical conduit, preferably in the form of an as such previously known optical fiber **4**, by means of a first link **5** and a second link **6**, respectively, and also via a fiber coupling **7**. The optical fiber **4** is connected to a sensor element **8**, schematically illustrated in FIG. **1**.

[0019] According to what is shown in detail by FIG. **1***a*, which is an enlarged view of the sensor element **8**, said element comprises a cavity **8***a*, for example obtainable (according to known art) through construction by means of molecular layers (primarily silicone, alternatively silicone dioxide or a combination of the two) and an etching procedure. Preferably, a bonding procedure is also utilised in assembling the various layers of the sensor element **8**. The manufacture of such a sensor element **8** is as such previously known, e.g. from the Patent Document PCT/SE93/00393. In this way, a membrane **8***b* is also created within the sensor element **8**, the deflection of which membrane will depend on the pressure p surrounding the sensor element **8**.

[0020] According to what will be described in detail below, the first light signal with the first wavelength λ_1 will come in and be reflected against the cavity **8***a* within the pressure sensor **8**, whereas the second light signal with the second wavelength λ_2 is brought to come in onto the bottom side of the sensor element **8**, i.e. towards the interface between the pressure sensor **8** and the optical fiber **4**. Hereby, the first light signal will be modulated by the pressure p acting on the membrane **8***b*. When the membrane **8***b* is influenced, the dimensions of the cavity **8***a*, primarily its depth d, will change, entailing a modulation of the first light signal through optical interference inside the cavity **8***a*.

[0021] The second light signal will be reflected against the bottom side of the sensor element **8**, due to the fact that the silicone defining the sensor element **8** will only allow transmission of light with a wavelength longer than a certain limit value (e.g. 900 nm). Consequently, said first wavelength λ_1 will be selected so as to exceed this limit value. Contrary to this, said second wavelength λ_2 will be selected so as to fall below this limit value. After having determined the two wavelengths λ_1, λ_2, appropriate dimensions of the cavity **8***a* are determined. For example, the depth of the cavity **8***a* is selected to be a value of substantially the same magnitude as the two wavelengths λ_1, λ_2. The sizing of the cavity **8***a* is made considering the required application range for the sensor element **8** (in the current case primarily the pressure range to which the sensor element **8** is to be adapted).

[0022] The light signal (λ_1) emitted from the first LED **2** defines a measuring signal that is thus transmitted through the fiber **4** to the sensor element **8**, where said light signal will be modulated in the manner described above. The second light signal (λ_2) will then define a reference signal, transmitted through the fiber **4** and being reflected by the bottom side **9** of the sensor element **8**. The light signal modulated in the sensor element **8** and the light signal reflected from the bottom side **9** of the sensor element are then transmitted back through the fiber **4**. The returning light signals will, through the fiber coupling **7**, be conveyed into fiber links **10**, **11**, connected to the detectors **12** and **13**, respectively. The detectors **12**, **13** will detect the measuring signal and the reference signal, respectively.

[0023] The four links **5**, **6**, **10**, **11** preferably consist of optical fibers, the fiber coupling **7** thereby preferably consisting of an as such known fiber junction device designed so as to transfer the four fiber links **5**, **6**, **10**, **11** into the fiber **4** leading to the sensor element **8**.

[0024] The system **1** also comprises a computerised measuring and control unit **14**, to which the LED:s **2**, **3** and the detectors **12**, **13** are connected. Said unit **14** comprises means for processing the values detected by said detectors **12**, **13**. According to the invention, the processing of the detected values includes a compensation for intentional or unintentional bending of the fiber **4**, by, utilising correction data based upon pre-stored data concerning the relationship between a measured reference signal and a measured measuring signal as a function of the bending influence on the optical fiber **4**. Such correction data could for example be comprised of a table or a function defining values to be used during measurements to correct the detected measuring signal.

[0025] Finally, the system **1** comprises a presentation unit **15**, e.g. a display, allowing a measurement of the sensed pressure p to be visualised for a user.

[0026] FIG. **2** graphically illustrates how the above relationship between a measured reference signal and a measured measuring signal is changed during increased bending of the fiber **4**. In the figure, the reference signal is referenced as "Output signal λ_2 [V]" and the measuring signal as "Output signal λ_1[V]". Said measured relationship can be described by a function, so as to correct the measuring signal continuously with a specific value depending on the reference signal. Alternatively, the measured relationship can be used for defining a mathematical function, which in turn is used for producing corrected values during measurements with the system according to the invention. As a further alternative, a number of measurement values may be registered in a table, into which the value of the reference signal is entered, to obtain a value (with the aid of interpolation, if necessary), with which the current measuring signal is corrected. Independently of the correction procedure used, it is performed in the above-mentioned measuring and control unit **14**.

[0027] FIG. **3** shows, in principle, a pressure measuring system according to the invention, comprising an alternative measuring unit **16** to which the sensor element **8** is connected, via the optical fiber **4**, in an exchangeable manner via an optical coupling (not shown in FIG. **3**). Said measuring unit **16** also comprises a reader unit **17** for insertion and reading of a separate unit in the form of an information-carrying card **18** (also called "smart card"). Said card **18** comprises a memory device where data regarding the sensor element **8** are stored for use. During measurements, these data may be read by the measuring unit **16** and be used for example for bending compensation in dependence of which specific sensor element **8** that is being used for the moment. The invention thus provides a further advantage, in that different sensor elements **8** can be

connected to said unit **16** without calibration, thanks to data stored on the information-carrying card **17**. Said data preferably define the relationship between predetermined correction data, produced through measurements of the first as well as the second light signal at various degrees of bending of the optical fiber.

[0028] The invention is especially suitable in case a single measurement station with one measuring unit **16** is used together with several exchangeable sensor elements. In such a case, data corresponding to properties, measuring range, etc. of each sensor element, can be stored on a corresponding number of information carrying cards, each then corresponding to (and being used together with) a specific sensor element.

[0029] As an alternative to an information-carrying unit in the form of a card, the invention can also be used with other types of separate data carriers. Further, the measuring system according to FIG. **3**, as opposed to what is shown in FIGS. **1** and **2**, is not limited to measurements of the kind using two different wavelengths, but can also be used when measuring with for example only one wavelength.

[0030] It should be mentioned, that the card **18** may also contain other stored information than that mentioned above, e.g. information regarding the sensor type, calibration data, etc. The basic principle is, however, that the card **18** is coordinated with a specific sensor element such that it will comprise stored data regarding the function of the specific sensor element Preferably, the card **18** will be provided with information—in the form of a set of parameters—allowing the properties of the sensor element **8**, together with the properties of the measuring unit **16**, to provide a suitable linerisation of the characteristics of the specific sensor element during measurements.

[0031] According to a further embodiment of the invention, which will now be described with reference to FIG. **4**, the sensor element **8** and the optical fiber **4** are associated with a connector **19**. The sensor element **8** is arranged at one end of the optical fiber **4** and the connector **19** is arranged at the opposite end of the optical fiber **4**.

[0032] The connector **19** as shown in FIG. **4** is formed in a manner (suitably as a conventional plug) so as to cooperate with a socket **20** by inserting it into the socket **20**. To this end, the connector **19** is formed so as to fit into the socket **20** in order to transmit signals between the sensor element **8** and the measuring and control unit **21**.

[0033] According to the embodiment shown in FIG. **4**, the connector **19** is associated with an information-carrying unit **22** which is supported by, and suitably physically integrated with, the connector **19**. According to the embodiment, the information-carrying unit **22** is in the form of a RFID tag (Radio Frequency Identification tag), which is a previously known type of microchip circuit which is combined with an antenna so as to form a single unit. The information-carrying unit **22** is designed to be physically integrated with the connector **19**, suitably in a manner wherein it is embedded into the connector **19**.

[0034] Generally, a RFID tag is previously known as such, and for this reason it is not described in greater detail here. However, it should be mentioned that the information-carrying unit **22** has an antenna (not shown) which cooperates with a detector unit **23** in the form of an RFID reader **23** which is provided in the measuring and control unit **21**. More precisely, the RFID reader **23** is arranged for transmitting signals to be picked up by the information-carrying unit **22**, which returns the signal, suitably with additional data included in the returned signal. Such additional data can suitably be in the form of stored information related to the sensor element **8**, i.e. data relating to the type of sensor element used, and data related to bending compensation corresponding to that which has been explained above. Also, such stored data may comprise calibration data and other data related to the function of the sensor element **8**. Consequently, the information-carrying unit **22** operates as a memory unit which stores data to be fed to the measuring and control unit **21** through operation of the RFID reader **23**.

[0035] According to an alternative solution, shown in FIG. **5**, the information-carrying unit **22'** is constituted by a memory chip being arranged for cooperating with a detector unit **23'** in the form of a card reader. This embodiment is consequently of generally the same type as a conventional contact smart card being used as a credit card or being used as mobile telephone SIM cards. This means that according to this embodiment, the connection between the information-carrying unit **22'** and the card reader **23'** is not wireless but is based on a mechanical contact between contact pads (not shown) in the information-carrying unit **22'** and corresponding contact surfaces in the card reader **23'**.

[0036] Accordingly, the exemplary embodiments described with reference to FIGS. **4** and **5** are generally based on a device for connecting the sensor element to a measuring and control unit, said device suitably being in the form of a connector **19** to be connected with a socket **20** formed in the measuring and control unit **21**. The connector **19** carries an information-carrying unit **22** (**22'**). The transmission of information between the information-carrying unit can be wireless, as explained with reference to FIG. **4**, or through physical contact, as explained with reference to FIG. **5**.

[0037] In a manner which corresponds to the embodiment shown in FIG. **3**, the embodiments shown in FIGS. **4** and **5** also comprise a measuring unit **21** which is arranged to read data stored in the information-carrying unit **22** (**22'**) so as to be used, for example, for bending compensation during measurements, depending on which sensor element **8** is used for the moment.

[0038] Alternatively, the embodiments shown in FIGS. **4** and **5** are also useful in a situation in which a measuring unit **21** is used together with a number of different sensor elements. In such a case, various data corresponding to the properties of each specific sensor element can be stored in an information-carrying unit like the one shown in FIGS. **4** and **5**. In this manner, each sensor element is associated with an information-carrying unit, physically integrated into the connector which is connected to the sensor element and being provided with stored information which in a unique manner represents the properties of the corresponding sensor element.

[0039] The invention is not limited to the embodiment described above, but may be varied within the scope of the appended claims. For example, the principle for data storage regarding a specific sensor on a separate information-carrying card can be used also for systems not intended for pressure measurements.

What is claimed is:

1. A measuring system for measuring a physical parameter influencing a sensor element adapted to be connected to a measuring and control unit, wherein said system comprises an information-carrying unit comprising a memory and being adapted to be associated with said measuring and control unit,

said information-carrying unit being coordinated with the sensor element by containing stored information regarding the properties of the measuring system and the sensor element during measurements, and said information-carrying unit being supported by a connector for connecting said sensor element with said measuring and control unit.

2. The measuring system according to claim **1**, wherein said sensor element is connected to said measuring and control unit via a connector adapted for cooperating with a socket being part of said measuring and control unit and wherein said information-carrying unit is physically integrated with said connector.

3. The measuring system according to claim **2**, wherein said information-carrying unit is constituted by an RFID tag cooperating in a wireless manner with an RFID reader forming part of said measuring and control unit.

4. The measuring system according to claim **2**, wherein said information-carrying unit is constituted by a memory chip cooperating with a reader unit forming part of said measuring and control unit.

5. The measuring system according to claim **1**, wherein said connector which connects said sensor element to said measuring and control unit is an optical connection, wherein said stored information includes pre-defined correction data concerning the relationship between the measured reference signal and the measured signal as a function of the bending influence upon said optical connection, or calibration data for said sensor element.

6. The measuring system according to claim **2**, wherein said connector which connects said sensor element to said measuring and control unit is an optical connection, wherein said stored information includes pre-defined correction data concerning the relationship between the measured reference signal and the measured signal as a function of the bending influence upon said optical connection, or calibration data for said sensor element.

7. The measuring system according to claim **3**, wherein said connector which connects said sensor element to said measuring and control unit is an optical connection, wherein said stored information includes pre-defined correction data concerning the relationship between the measured reference signal and the measured signal as a function of the bending influence upon said optical connection, or calibration data for said sensor element.

8. The measuring system according to claim **4**, wherein said connector which connects said sensor element to said measuring and control unit is an optical connection, wherein said stored information includes pre-defined correction data concerning the relationship between the measured reference signal and the measured signal as a function of the bending influence upon said optical connection, or calibration data for said sensor element.

9. The measuring system according to claim **5**, wherein said connector and said sensor element are mounted to the opposing ends of an optical fiber.

* * * * *

4.10. Appendix J. Claim 1 comparison between filed (10/018220) and granted (US6934015B1) application

10/018220	US6934015B1 (granted)
Claim 1	
A method for bending comensation in intensity-based optical measuring systems, comprising a sensor element (8) connected to a measuring and control unit (16) via an optical connection (4) and being adapted for providing a signal corresponding toa measurement of a physical parameter in connection with the sensor element (8), said method comprising generation of measuring signal (Λ_1) that us brought to come in towards the sensor element (8), generation of a reference signal (Λ_2) that is transmitted through the optical connection (4) without being influenced in the sensor element (8), said measuring signal and said reference signal having different wavelengths, detection of said measuring signal (Λ_1) and detection of said reference signal (Λ_2), CHARACTERISED BY comprising bending compensation through correction data based upon pre-stored data concerning the relationship between the measured reference signal (Λ_2) and the measured measuring signal (Λ_1) as a function of the bending influence upon said optical connection (4).	A method of compensating for bending of an optical fibre in light intensity-based optical measuring systems, said light intensity-based optical measuring systems comprising a sensor element connected to a measuring and control unit via optical fibre and being adapted for providing a signal corresponding to a measurement of a physical parameter, said method comprising generating a measuring light signal; transmitting the measuring light signal through the optical fibre towards the sensor element; generating a reference light signal; transmitting the reference light signal through the same optical fibre without being affected by the sensor element due to the measuring light being separated from the reference light, wherein said measuring light signal and said reference light signal have different wavelengths; detecting said measuring light signal after being influenced by the sensor element; detecting said reference light signal after being transmitted through the optical fibre and after being reflected by said sensor element; compensating for bending of the optical fibre by reference to correction data based upon pre-stored data concerning a relationship between the measured reference light signal and the measured measuring light signal as a function of the bending influence upon said optical fibre, wherein said measuring light signal causes optical interference in a cavity associated with the sensor element.

5. Tasks

1. What purposes did C-Sensus patent application serve during the development of their business? What aspects are important in the design of a patent for the different purposes?

2. Why were some of the claims in the patent application rejected? What arguments could be used to counter such rejections?

3. What control position did C-Sensus have in relation to Geven and the sub-contractors?

    - How did the claim coverage change from the initial filing to the final issued patent, and how these changes affect C-Sensus control position?
    - What other intellectual assets can be defined in C-Sensus technology portfolio? Would you advise C-Sensus to patent any of those?

« Alterniity,
Marketing an innovative solution for
Alzheimer's disease »

Case study in the framework of the Health-2-Market project seminar
"Marketing of Innovative products in Health/Life sciences"

Author: White Research SPRL

"Health-2-Market is supported by the European Commission under the FP7-HEALTH programme"

Table of content

1. Case objective

Marketing is a vital element of the commercialization process, especially when referring to the launch of innovative products into highly intricate environments such as the health care market. This case study presents an example of how health researchers can incorporate the marketing process in their entrepreneurial ventures in order to substantially raise the likelihood of the successful commercial exploitation of their research outputs. Specifically, it describes the marketing process that a recently established start-up, Alterniity GmbH, has adopted so far for the scope of bringing to market its innovative solution to dementia and Alzheimer's disease[1].

The case of Alterniity GmbH addresses the participants of seminar 7: Marketing of innovative products in Health/Life sciences. After discussing the case participants will be able to:

- Understand basic concepts and principles of the marketing process.
- Apply the marketing process on their health research.
- Identify potential customers and their latent or existing needs.
- Recognize and assess competitors.
- Develop a marketing mix for their innovative product.

2. Introduction

A few decades ago, a teenage boy, Ioannis Tarnanas, observed his grandmother's agonizing struggle with Alzheimer's disease (AD) on a daily basis. Little did he imagine, that his grandmother's disease would ultimately determine his career path. Today, health researcher and aspiring entrepreneur, Dr. Ioannis Tarnanas, has already been researching virtual reality applications for the intervention of AD and other types of dementia for over 12 years. Full by his research achievements, he now envisions the development and commercialization of a product that will provide seniors and elderly people with an effective solution to delay or even prevent the onset of cognitive decline and counteract the degenerative process of dementia. The entrepreneur was contented to see his vision becoming a business venture with the establishment of Alterniity GmbH. Now, he wants to take a step further; He is investigating ways to ensure the long term viability of the endeavour. To succeed, he must decide and implement an effective marketing plan of the company's promising solution to dementia and Alzheimer's disease. Specifically, Ioannis will have to answer the following questions:

- What is needed to develop an intelligent and evidence based marketing strategy?
- Who are the potential customers and competitors of Alterniity?
- Which segment of its market should the company target first?
- How should Alterniity adapt its product and marketing strategy in order to better meet the needs of its targeted customers?

[1] Dementia is affecting over 44 million people worldwide with an estimated increase of 4.6 million new cases every year. According to the World Health Organization it is "a syndrome (typically of chronic or progressive nature) in which there is a deterioration in cognitive function beyond of what might be expected from normal aging". Alzheimer's disease (AD) is the most prevalent type of dementia accounting for almost 60 to 70 percent of cases. It is a currently incurable neuro-degenerative disease preceded by 5 to 6 years of accelerated decline of multiple cognitive functions (e.g. memory, thinking, social behaviour and the ability to perform everyday activities) that leads to the loss of the patient's ability to leave independently and eventually to death.

3. Alterniity GmbH company

3.1. Profile of the company

Alterniity was established in early 2014 as a spin-off from the ARTORG Centre for Biomedical Engineering of the University of Bern (Switzerland) in the form of a limited liability company (GmbH). The vision of the company is to become the leading edge non-pharmaceutical solution provider for dementia and Alzheimer's disease.

The mission of Alterniity is to promote the healthy aging of the brain by providing a solution with no side effects that will improve and maintain the fitness of the brain as a means to counteract age related cognitive decline and dementia. As thus, Alterniity can empower seniors and elderly people to self-care prolonging their ability to live independently at home and raising their quality of life. At the same time the company is able to alleviate the immense societal burden and health care costs associated with providing care to dependent people who suffer from dementia and Alzheimer's disease.

3.2. Alterniity's serious gaming solution

Alterniity's solution is a **serious game**[2] that is specifically designed to **monitor**, **assess**, **enhance** and even **rehabilitate** the neuro-cognitive state and functions of the patient/user through a **virtual reality experience** based on activities of daily living[3]. It is the result of 12 years of in-house scientific research backed by 4 years of empirical data collection via clinical trials conducted in the Inselspital Memory Clinic of the University of Bern, Switzerland.

The core of Alterniity's serious gaming experience comprises a suite of science-fuelled tools that provide a holistic solution to the burden of dementia by creating impact in 3 distinct dimensions:

- **Very Early Dementia Screening**: Alterniity offers fully 3D virtual worlds where users perform activities of daily living and get assessed for clinically validated early signs of dementia.
- **Dementia Prevention**: Alterniity's virtual simulations of activities of daily living offer an effective and fun method for users to train their brain as to build-up their cognitive reserve and exploit the effects of neuro-plasticity. The result is the fortification of the brain against cognitive decline delaying the onset of dementia and Alzheimer's disease.
- **Early Alzheimer's disease intervention and delay of dementia progression**: Alterniity's intervention suite trains the cognition of the patient directly in activities of daily living, a rehabilitation practice common amongst physicians. This type of intervention enables the simultaneous training of multiple cognitive functions facilitating the transferability of the results to real life every day activities.

The serious game of Alterniity was demonstrated with 1200 real users at the **iENA international trade fair 2013** and won the **bronze medal award among 1150 inventions** from 35 countries worldwide, gaining valuable recognition in mass media channels such as Germany's Spiegel. Furthermore, Ioannis received honorary second place for his submission "Alterniity - Virtual Reality

[2] Serious games are computer or video games that are designed for a primary purpose other than pure entertainment.

[3] Activities of daily living (ADLs) is a term used in healthcare in reference to daily self care activities that can be divided into basic and instrumental ADLs. Basic ADLs consist of self care activities necessary for the fundamental functioning (e.g. bathing, dressing, eating, etc.) of an individual whereas instrumental ADLs encompass activities that allow an individual to live independently within a community (e.g. housework, shopping for groceries, taking medication, etc.).

Serious Games for Dementia Intervention" in the Call to Innovation Award of the Global Impact Competition organized by the Singularity University (USA) and the TEDx Academy in Greece.

3.3. Profile of the founders and the management team

CEO

Dr. Ioannis Tarnanas (PhD) is the Chief Executive Officer (CEO) and main shareholder of Alterniity GmbH. He is a Senior Researcher at the ARTORG Centre for Biomedical Engineering of the University of Bern. His PhD concerns neuroscience focusing on new means to improve and maintain cognitive performance and prevent cognitive decline as long as possible. Application areas for his work include quantitative assessment of human performance, augmentative communication systems, serious games for the older people, medical communications and integrated interactive educational systems.

Operations Management

Dr. Veronika Petrova (PhD) is responsible for managing the company's daily business operations as the Chief Operating Officer (COO). She has more than 10 years experience in managing projects and was previously working in the Risk Remediation Programme at Erste Group Bank AG. She has also served as an analyst at Goldman Sachs and as a consultant at the Boston Consulting Group (BCG).

Financial Management

Mr. Basil Vetas serves as the Chief Financial Officer (CFO) of the company. He has more than 6 years experience in impact investing. He has worked for almost two years with the Sorenson Global Impact Investing Centre, evaluating dozens of social enterprises for early stage investment. Previously, he worked for the University Venture Fund, a student-run venture capital fund, where he was exposed to many industries including online education, medical devices, genetic testing, and 3D software animation.

Marketing Management

Ms. Willemien van den Toorn is in charge of the marketing department of Alterniity. She has more than 16 years of experience in health marketing. She has worked for Straumann Group (a global leader in the field of implant, restorative and regenerative dentistry) as Marketing Director at Straumann Benelux and as Marketing Manager (Surgical Business Unit Western Europe & Latin America) at Institut Straumann AG.

Advisor/Networking

Mr. Nikolaus Hutter is the appointed advisor of Alterniity and contributes to the networking efforts of the company. He is the Director Europe for Toniic LLC, a leading global impact investor network, and serves on the board and as an advisor to several organizations in the social entrepreneurship and impact investment field. He has worked for over 10 years as a Venture Capital investor (most recently as Sector Partner Cleantech with CEE investment firm 3TS Capital Partners) and has close to 15 years international experience as an investment executive and entrepreneur.

Scientific Board

The scientific board of Alterniity is an essential part of the company and is comprised of esteemed expert scientists from the Gerontechnology and Rehabilitation group of the ARTORG Centre. Specifically, the board comprises **of Professor Dr. Tobias Nef**, **Professor Dr. Urs Mosimann**, MD (Psychiatrist, expert in Old Age Psychiatry), and **Professor Dr. Rene Muri**, MD (Neurologist, expert in Cognitive and Restorative Neurology), all of whom are founding members of Alterniity and participate in the company's share capital.

4. Alterniity's approach to marketing

4.1. Analysis of the market

Ioannis figured that the first thing to do in order to design a successful marketing plan is to assess the current situation of the company's environment. He had to analyze the brain fitness market along with the existing global and local trends that may greatly influence the future development of Alterniity. The goal was to get a deeper understanding of the market that the company was going to operate in, spot potential customers, identify their needs and as a result prepare an evidence based marketing strategy to meet them effectively. Additionally, a comprehensive market analysis would allow the entrepreneur to assess existing and potential competitors and differentiate Alterniity's value proposition from them. The analysis that Alterniity has conducted for its market so far is provided below:

The brain fitness market

Brain fitness applications in health care aim to train and improve various cognitive functions and generally to maintain the user's brain health. The market encompasses both software and hardware applications: On one hand, **software** applications involve digital and online applications that can be accessed through a variety of platforms (e.g. personal computers, laptops, tablets, smart phones, etc.) and are designed to monitor, assess, enhance and/or rehabilitate the cognition of the user. On the other hand, **hardware** applications involve applications that utilize hardware components (biometrics) for the sake of measuring the physiological response (e.g. heart rate variability) linked to a cognitive outcome. Specialized brain fitness applications such as Alterniity's solution target impaired patients suffering from age related cognitive decline, traumatic brain injuries or dementia.

The **global brain fitness market** accounted for **over $1 billion** in terms of revenue **in the end of 2012** and is forecasted to grow to **over $6 billion by 2020** (Appendix A). The market is growing rapidly posing a very promising business opportunity for Alterniity.

The main factor driving the growth of the brain fitness market regards the increasing prevalence of dementia and especially Alzheimer's disease. As there is no available treatment for dementia, research for a pharmaceutical solution is still ongoing. In the meantime, the number of people suffering from dementia is already substantial and expected to triple by 2050. In third world countries this number is calculated to quadruple. The 2013 World Alzheimer Report found that there is a global shortage of caregivers for people with dementia meaning that the traditional system of 'informal' (unpaid) care provided by family, friends, and community alone will not be sustainable in the future. Alzheimer's disease has become a health priority in many countries where governments and health systems are seeking for novel non-pharmaceutical methods to alleviate the immense societal burden and health care costs that the disease implies. Accordingly, people are starting to recognise the importance of adopting a proactive lifestyle that involves improving and maintaining the fitness of their brain in order to prevent dementia and delay the onset of cognitive decline.

Customers

Alterniity has identified the following consumer groups (**B2C**) as potential customers for its solution within the brain fitness market:

Early patients: This end user segment consists of elderly people who suffer from mild cognitive impairment. They are typically above 60 years old and are at the early stages of Alzheimer's disease or other types of dementia. Chronic cognitive impairing conditions such as dementia can have adverse effects to the patient's ability to execute activities of daily living (ADLs) compromising their ability to live independently. The toll (physical and psychological) of cognitive impairment and the

consequent increase in the dependency of the patient can be immense. Therefore, early patients need to delay the cognitive decline and decrease their dependency on formal and informal care by empowering themselves to live independently and self care. Accordingly, they can purchase and utilize the solution of Alterniity to train their cognition as a means to delay the progress of dementia and at the same time enhance their ability to perform ADLs.

Informal caregivers: This consumer segment is comprised of informal caregivers of elderly people that suffer from dementia. Informal care essentially refers to people who provide voluntary care to cognitive impaired people without charging a fee for their services. The principal informal caregivers are close family members such as adult children or spouses, but other relatives, friends and neighbours can potentially provide informal care as well. Providing care for elders suffering from cognitive decline can prove to be a very strenuous challenge both physically and psychologically requiring from the caregiver to dedicate a substantial share of his/her time. Therefore, informal caregivers need a solution to empower the independent living of their loved ones and consequently decrease the time and cost (psychological and financial) requirements of the informal care they provide.

Healthy seniors and elderly people: This end user segment regards healthy seniors and elders that are usually 55 years old and above. They are concerned about the "healthy aging" of their brain due to the increasing prevalence of dementia. Therefore, they are interested in maintaining a healthy and proactive life style that will keep them fit both mentally and physically and in result prolong the maintenance of their independent living.

All the aforementioned customer groups are quite appealing. However, **which one is the ideal segment that will facilitate the rapid future development of Alterniity?** Ioannis will have to carefully evaluate the attractiveness of each one before selecting the B2C segment to target initially: On one hand, early patients are the core end user segment of Alterniity and stand to benefit the most of the company's solution. But, will a sufficient number of consumers be able to purchase the product considering their condition (cognitive impairment)? On the other hand, informal caregivers are also a very interesting segment. They may act as the buyers of Alterniity's solution as most of the time it is the informal caregivers that are responsible for managing the financial resources of dependent elderly people. They may even purchase Alterniity's serious game as a present to their loved ones suffering from AD or other types of dementia. The demographics of this segment, however, are very diverse and Ioannis will have to come up with a different approach to further segment this broad customer group if he is to address it effectively. Finally, targeting healthy seniors and elderly people can help the company significantly expand its customer base but the concern about the prevalence of dementia and AD might not be motivating enough to lead customers from this group to purchase Alterniity's serious game. Ioannis must find the benefits that Alterniity can offer these consumers and communicate them effectively through the company's marketing efforts.

Alterniity is also wondering whether it should focus on marketing solely to consumers or, if they should target business clients (B2B) as well. The **B2B market segment** regards a blend of public and private organizations that constitute the health and social care system associated with providing care to elderly people. Potential customer groups for Alterniity within this segment encompass **health care providers** (e.g. hospitals, memory clinics, etc), **social care providers** (e.g. senior living providers and communities) and **health care professionals** that diagnose and treat cognitively impaired elderly people. **Pharmaceutical companies** can serve as potential customers as well. The screening aspect of the company's serious game can be utilized to provide an accurate and reliable method to measure and keep track of the progression and effectiveness of AD drug related treatments in the framework of clinical trials. As the information about this segment is much less, Alterniity considers undertaking some market research to understand these segments more.

Competition

Alterniity's market analysis would not be complete without a thorough assessment of the company's competition. Thus, Ioannis carefully examined the brain fitness market in order to identify and evaluate the strengths and weaknesses of potential competitors.

The analysis of the competition (Appendix B) revealed that despite the many existing brain fitness companies the market is still fragmented. The vast majority of the existing brain fitness companies offer digital cognitive tests to assess the cognitive state and needs of the patient (cognitive assessment). Some companies go a step further providing cognitive training aiming to delay the onset of cognitive decline and/or improve the patient's cognitive functions. However, their software is designed either in 2D or 3D, typically targeting a wide audience (i.e. not a specific target age group) and providing exercises that improve specific cognitive abilities and functions one by one (memory, attention, planning, etc), detached from activities of daily living which is the predominant source of the societal burden and costs of dementia. Furthermore, even though most competing companies provide a scientific evidence base (e.g. scientific and white papers) showing evidence of their product's temporal benefit to the cognitive functions of the patients, they do not necessarily imply that this benefit has the far transfer effect on activities of daily living that the market requires.

Ioannis was finally able to verify with concrete evidence that Alterniity would essentially be the first to offer the brain fitness market a scientifically proven and clinically validated serious game designed specifically for seniors and elderly people suffering from Alzheimer's disease, utilizing 3D Virtual Reality technology to simultaneously train various cognitive functions of the users directly in activities of daily living in a fun, immersive and engaging environment. Thus, Alterniity's serious game would not only assess and keep track of the cognitive state of the patient but also improve it in a way that will have a direct impact on the ability to execute of activities of daily life.

4.2. Alterniity's marketing mix

After gaining valuable insights about the brain fitness market, potential customers and competitors, Ioannis had to face the challenge of developing an appropriate **marketing mix** that would enable Alterniity to effectively reach its target audience and create the impact on society that the entrepreneur has been seeking for so long now. The concept of the marketing mix was not entirely alien to him. He knew that in theory it consisted of the four Ps, notably **product**, **price**, **place** and **promotion**. Now, however, it was time for him to develop an actual mix and for his own company to boot. Furthermore, the diversity of the different customer segments within the brain fitness market did not allow for a standardized marketing mix to fit the needs of all the customer segments. Therefore, Ioannis had to make some important decisions concerning how to specifically tailor each element of the marketing mix to Alterniity's targeted market segments.

Product

Alterniity's prototype solution has been showing promising results in a clinical environment. However, the current version is not suitable for release to the general public. Therefore before launching its solution into the B2C brain fitness market, Alterniity will need to perform further R&D work applying additional modifications and simplifications to its serious game. The aim is to create a version of the solution customized for home use that will be **affordable** and **easy to use.** Furthermore the product will have to be **fun** and **engaging** in order to increase the chances of widespread adoption amongst the elderly people. Ioannis is considering a variety of components that he could potentially incorporate in Alterniity's serious game in order to better appeal to potential customers:

- **Cloud computing technology** to ensure processing requirements are kept to the minimum possible from the user's point of view meaning that a mediocre internet device (e.g. tablet, old PC, etc.) can run the state of the art serious game of the company with no problems.
- **Fun and engaging in-game objectives** that along with the immersive game play will motivate the user to adhere to the training and ultimately achieve better performance and results.
- **Support of low cost gesture recognition hardware**. This type of innovative hardware will enable the interpretation of human gestures as input allowing the controller free interaction of the user with the serious game thus ensuring that even people with limited or no computer skills are able to utilize the solution of Alterniity.
- **Automatically adjusted difficulty settings** that will enable the real-time customization of the cognitive exercise suite to fit exactly the personalized needs of each patient/user.
- **Physical training objectives** in order to combine physical and cognitive exercise aimed at providing an integrated approach to the healthy aging of the user through the maintenance of both physical and mental fitness.
- **Collaborative game play option** (multiplayer) that will allow multiple users to play simultaneously in the same virtual environment aiming to enhance the involvement of the user.

Price

The pricing goal of the company, set forth by Ioannis, is to provide target customers with an affordable solution in order to magnify the beneficial impact to society and at the same time facilitate the company's entry to the market. Towards this goal Alterniity has decided to adopt a subscription based pricing model with a small twist adapted from the free to play model (f2p) that is gaining increased popularity in the video gaming market. The aim is to attract additional customers by providing a basic version of the serious game for free while offering a premium version that requires a subscription. According to this "**freemium**" model, prospective subscribers are able to access the free version of the serious game designed for trial and promotional purposes. Those who are interested in seriously improving their brain fitness via the elite exercise suites will need to subscribe to the core cognitive training program gaining unlimited access to cognitive exercises that facilitate the transition of acquired skills to the real world. The premium version will also include the cognitive tracking aspect of the solution to document processes and make recommendations on how to further train with the game.

Alterniity will provide potential subscribers with two different subscription programmes, notably either a monthly or a yearly subscription plan, to ensure that the customer has the option to make the financial commitment he/she desires. The subscription fee will be within the price range of competitive products (i.e. about 100€ per year).

Place (Distribution)

The distribution of Alterniity's serious game will be realized via digital means. Specifically, the customer will be able to access the serious game online. The purchase of the subscription will be made online as well.

Ioannis insisted that Alterniity should adopt this relatively novel method of digital distribution as it can offer substantial benefits to the company when compared to more traditional physical distribution means (e.g. wholesalers, physical transportation, brick and mortar retail stores). Most notably it helps reduce operating costs (e.g. manufacturing and logistics costs) and eliminates the need for distribution intermediaries (e.g. transportation companies, technology brokers etc.). In addition, the digital distribution of the serious game along with the cloud computing technology the company employs will allow Alterniity to minimize the risk of software piracy.

Promotion

The promotion element of Alterniity's marketing mix is of vital importance as it is the tool that will enable the company to convey its marketing communications to targeted audiences and "pull" prospective customers to its solution. Specifically, the goals of Alterniity's promotional strategy are to:

- Raise awareness on the problem of dementia and the solution Alterniity offers.
- Lead customers towards taking action against this problem by purchasing Alterniity's solution.
- Build up a respectable and trustworthy brand image for Alterniity amongst target audiences.

The promotional channels that will be employed are mainly online. The company will develop a **web portal** through which prospective customers will be able to access Alterniity-related content such as Alterniity's **serious game web page** as well as **newsletters** and **blogs** that the company will maintain.

Apart from the development and maintenance of the company's personal web portal, other marketing techniques that Alterniity will employ encompass:

- Social Media Marketing
- Online Advertising
- Viral Marketing
- Search Engine optimization

Ioannis realised that the proliferation of social media and their increasing adoption rate amongst older age groups require Alterniity to establish a firm presence in the social media environment. Therefore the company will develop and maintain **social media pages** in mainstream social networks (Facebook, Twitter and Google+) including key niche social networks that focus on seniors. Furthermore, careful placement of **online advertisements** in key web sites (e.g. ThirdAge.com) and especially search engines will raise the company's visibility amongst targeted audiences and attract the attention of prospective customers. **Promotional videos** will be posted in popular sites such as YouTube exploiting the potential of viral marketing and aiming to build up brand recall while highlighting the unique characteristics of Alterniity's serious game by including footage of actual game play content. Especially the promotional videos will be made available prior to the initial launch of the serious game for the scope of generating anticipation (buzz), a practice quite common in the video gaming industry. Last but not least, Alterniity will utilize **search engine optimization** tactics in order to ensure that potential customers will be able to easily locate the company's solution amongst the vast number of brain fitness games and programs offered via the internet.

The social media aspect of Alterniity's promotion will serve as a tool for building and maintaining a brand community that will allow end users to engage with the company's serious game even when not playing. Furthermore, it will allow users to share their experiences increasing their involvement and motivation. Elderly people satisfied with the results of Alterniity's solution can potentially act as informal sellers through word of mouth advertising providing positive reviews and referrals.

Alterniity will also utilize **offline promotion** channels in order to complement its internet marketing efforts. Specifically, the company will launch a **brand ambassador programme** in order to incorporate into its promotion strategy a panel of clinically appropriate individuals (healthy and impaired elderly people) and influential health care professionals. Additional offline promotional actions will include promotion through patients' organizations (e.g. Alzheimer's Europe) and other below the line marketing tactics such as physical participation in **exhibitions**, **trade fairs** and **scientific conferences**.

5. Business development and financial planning

The business strategy and plan of Alterniity have been formulated with the support of the EC funded Health-2-Market project. The company is still at a very early point of its business development. Alterniity will tailor its solution to the B2C market during the first year of its operation. A German version of the serious game will be launched online initially into the the DACH region (Germany, Austria and Switzerland). Once the product is pre-tested and is on the market for 3-6 months the company will expand to additional international markets with a translated (and potentially updated) version. The product will be continuously upgraded to sustain its competitive advantage. Beyond software upgrades, hardware upgrades will be considered as well, mainly in cooperation with established game providers (collaborators). Additional financial resources will have to be procured in order to finance the implementation of the marketing plan. Alterniity has prepared an extensive financial model based on a scenario analysis aiming to ensure the robustness of its commercial endeavour and appeal to prospective investors. An overview of Alterniity's financial projections (on the base case scenario that was examined) can be found in Appendix C. Overall, the financial analysis has shown that Alterniity poses a very profitable business venture even in the most adverse scenarios and market circumstances. The company has also developed an exit plan for potential investors according to which payback will be realized either on the 4th or 5th year. The company is considering an Initial Public Offering or directly selling the investors' share to a strategic or financial investor such as a pharmaceutical company wanting to enter the brain fitness market.

6. Lessons learnt and thinking further

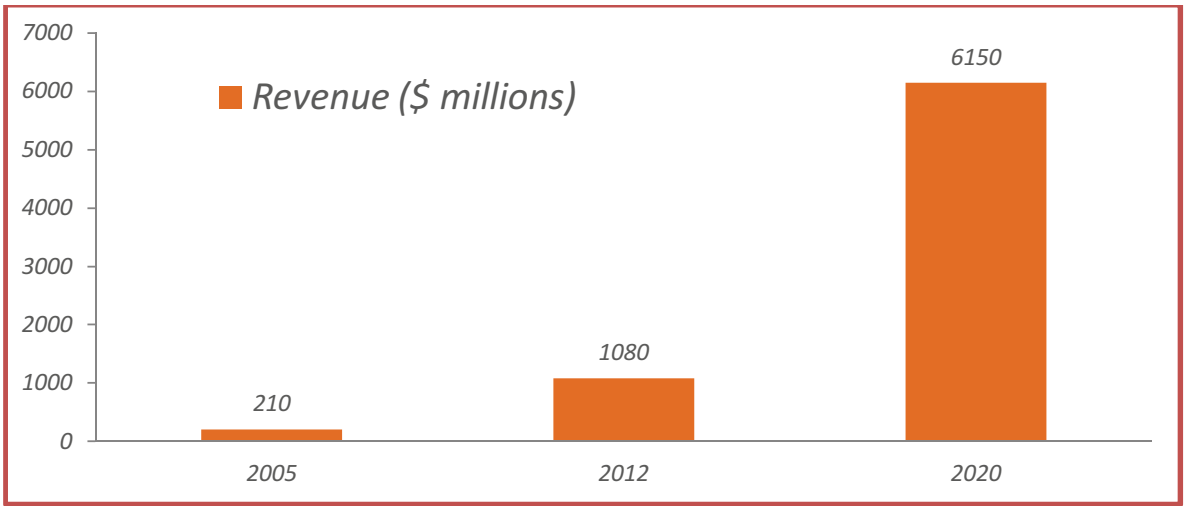
The adoption of an effective marketing process (Appendix D) has significantly helped Ioannis so far with the commercialization of Alterniity's promising solution to dementia and Alzheimer's disease. The analysis of the brain fitness revealed valuable insights regarding the dynamic of the brain fitness market and led to the identification of several potential customers groups that the company can target. The competitive environment is also clearer now. As a result, the entrepreneur has been able to adapt the marketing mix of Alterniity accordingly, to effectively market the company's solution, increase the prospect of successful market deployment and ultimately take a step closer towards materializing his vision.

Some questions to spark further thinking are:

- *Evaluate the market analysis of Alterniity. Do you think it is sufficient? Suggest further aspects of the market that require analysis but the company might have overlooked.*
- *What bases can Ioannis use in order to further segment informal caregivers? How will this help Alterniity? What aspects of the company's serious game do you think would better appeal to healthy seniors and elderly people?*
- *Suggest the segment (or segments) of the B2C market that you think Alterniity should target. What elements would you advise Ioannis to incorporate in the serious game to better adapt it to the target segments you have suggested.*
- *The company needs more information to enter the B2B market. What kind of information do you think is required? How would you find it?*

APPENDIX

Appendix A: Brain Fitness Market Revenue 2005 – 2020[4]

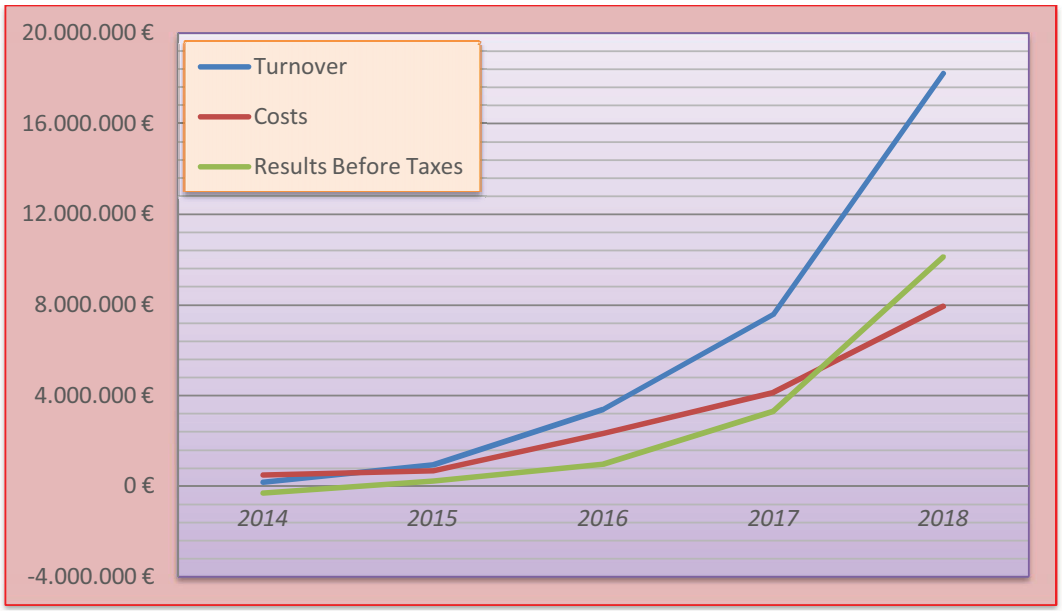


Appendix B: Overview of Alterniity's Competition Matrix

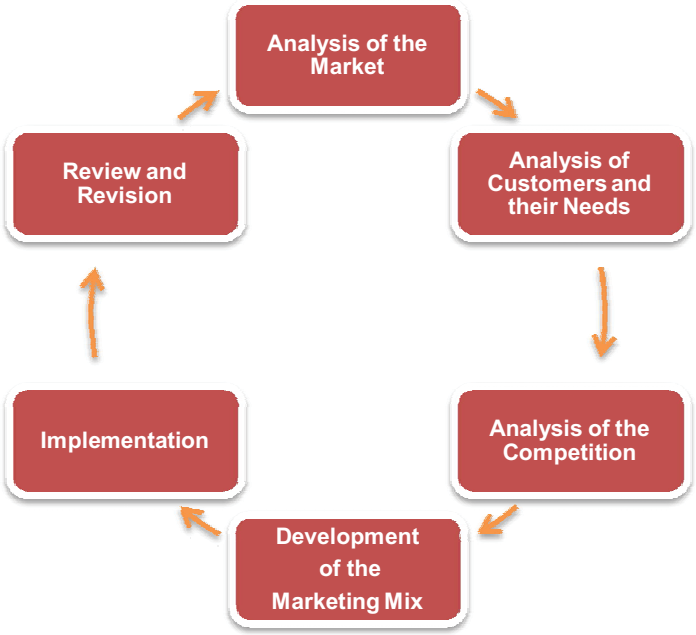
Brain Fitness Company	Cognitive Assessment	Cognitive Training	ADL Training	Progress Record	Scientific Evidence Base	3D Virtual Reality	Focus On Alzheimer's Disease	Target Age Group
Lumos Labs	✓	✓		✓	✓			All
Cambridge Cognition	✓							All
CogniFit	✓	✓		✓	✓			All
Posit Science	✓	✓		✓	✓			All
Blue Marble Game co.	✓	✓		✓	✓			All
Dakim	✓	✓		✓	✓		✓	55+
Neo Corta	✓							All
NeuroTrax	✓							All
HappyNeuron	✓	✓		✓	✓			All
Vivity Labs (FitBrains)	✓			✓				All
Alterniity	✓	✓	✓	✓	✓	✓	✓	55+

[4] Source: Sharpbrains (2013), "The Digital Brain Health Market 2012-2020: Web-based, mobile and biometrics-based technology to assess, monitor and enhance cognition and brain functioning", accessible at: http://sharpbrains.com/market-report/

Appendix C: Alterniity's Financial Projections Overview



Appendix D: Alterniity's Marketing Process



« Utilising market research to enhance decision making* »

Case study in the framework of the Health-2-Market project seminar
"Marketing of innovative products in Health/Life sciences"

*all names of actors have been changed for publication

Author: White Research SPRL

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Key concepts addressed by the case

Market research can prove to be invaluable for practically every commercial venture but even more so for aspiring entrepreneurs in the field of Health / Life sciences who seek to commercially exploit the innovative outcomes of their research.

Researching your target market can shed ample light to key factors that may influence the commercialisation process including the needs and requirements of prospective customers. An effective market research, however, is not limited to investigating the demand side only (customers). It also involves an in-depth look at the supply side (competitors) and should address aspects such as the regulatory framework of the market as well as trends and forces that drive its development in order to reveal valuable insights regarding the market environment of the proposed venture and generate the necessary knowledge to make evidence-based business decisions.

The current case study follows the endeavours of Dr. Robert Malcolm, a European scientist in the field of epigenetics who, after carefully researching his target market, must now rethink his initial commercialization plan and select the most appropriate route to market his innovative solution. The case of Robert highlights the importance of researching your target market at an early stage of the entrepreneurial venture and will introduce you to some basic elements of market research that if carried out properly can enhance your decision-making in a business setting.

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1. Having second thoughts about a past decision

The familiar hang-up sound of Skype signals the end of an important conference for health-researcher and aspiring entrepreneur, Dr. Robert Malcolm. For over 3 hours he was discussing the findings that emerged from his market research with Ted Humphrey, a close friend and seasoned business consultant. Robert values Ted's suggestions but knows that in the end it is no other than him that will have to make the final decisions on how to proceed with the valorisation of his health-research findings. "If only it was that easy. These decisions will determine the future of my entrepreneurial career", thinks Robert while reflecting back on his long and vigorous research career in epigenetics[1], a rapidly growing scientific field that presents great potential for understanding the basis of cancer and various other diseases (e.g. Alzheimer's disease, cardiovascular diseases, etc.) as well as for developing applications for diagnosis and drug discovery for them.

Indeed, for more than 20 years now, Robert has been a committed scientist in the field of epigenetics, or how he frequently calls it, "the mechanisms that switch genes on and off". Fuelled by his passion of exploring the effect of epigenetic mechanisms on health (see Annex) and expanding human knowledge of molecular life, Robert was able to develop an advanced screening technology. This innovative result of his health research held the potential to significantly improve the means that are currently employed for studying and understanding epigenetic mechanisms by allowing for more accurate and reliable measurements of epigenetic changes and overcoming several shortcomings of other contemporary technologies (e.g. measurement bias and false positive results).

Leveraging his innovative technology, Robert envisioned the development and commercialization of epigenetics-based In Vitro Diagnostics[2] (IVD) intended for use in diagnosis of cancer and other diseases (e.g. autoimmune diseases, inflammatory diseases, neurological disorders, etc.). In order to realize his vision, he planned to gain support from a large company already operating in the market so as to access valuable financial backing and marketing connections in the healthcare sector. In early 2009 Robert had already established contact with a large biotechnology company that was highly interested in the application of the technology within a clinical context in the form of IVDs that would enable the detection of specific epigenetic cancer biomarkers (i.e. a substance or process that is indicative of the presence of cancer in the body). Negotiations showed promising potential for the proposed venture but in the end came to a halt as the patent that Robert had filed a year ago (2008) in the United States (US) had not been granted at the time and therefore the technology lacked crucial Intellectual Property (IP) protection.

In the beginning of 2014 the US patent was finally approved and Robert was presented with the opportunity to once again proceed with the commercialisation of his promising technology. However, uncertain as he was on whether the large biotech company he approached 5 years ago would still be interested in the venture, this time he paid heed to Ted's advice: "Consider examining alternative choices. Do some market research on those. Collaborating with a larger company can prove rather complicated and you could end up with the short end of the stick in a potential agreement". Indeed, Robert himself was not entirely fond of negotiating with intimidating legal

[1] "As an organism grows and develops, carefully orchestrated chemical reactions activate and deactivate parts of the genome at strategic times and in specific locations. Epigenetics is the study of these chemical reactions and the factors that influence them". Source: The Genetic Science Learning Center of the University of Utah, United States, available at http://learn.genetics.utah.edu/content/epigenetics

[2] Epigenetic-based in vitro diagnostics are tests performed outside of a living body in an artificial environment and enable the detection of epigenetic changes in a variety of samples (e.g. whole blood, plasma, urine, tumor, tissue samples, cell extracts, etc.) offering promising application opportunities in many aspects of the patient care process (e.g. prevention, diagnosis, prognosis, etc.).

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departments and signing complex long-term contracts as such an approach would imply but how else was he going to find the support he required to successfully market his IVDs?

After thinking long and hard, Robert realised that a possible alternative would be to employ his innovative technology to produce ready-to-use epigenetics kits. These could be utilised by scientists in Life Sciences laboratories as valuable tools intended for Research Use Only (RUO) in epigenetic studies and experiments. This alternative approach would provide him with access to a segment of the epigenetics market that even though relative smaller is also considerably less regulated than the market for IVDs and would not involve costly market approval processes or the more often than not challenging task of marketing to the healthcare sector. Thus, Robert would not necessarily need to partner with an over-powered large company. Of course targeting the RUO epigenetics market would require him to put his vision to commercialize IVDs on hold for the moment and potentially to develop an entirely new business model for his entrepreneurial venture. This implied relying on his own powers to set up a marketing department, develop distribution channels and hire the right personnel among several other business planning aspects and all these with significantly limited financial resources at hand.

In order to make an evidence-based decision, Robert agreed to follow Ted's suggestion to undertake some market research. In fact, he had already investigated the market for epigenetics 5 years ago but in this rapidly evolving field, information collected that long ago may just as well be considered vastly outdated. Therefore, a fresh look into his target market would enable Robert to reassess his business strategy and find the most appropriate route to market his innovative health research outcome. Constrained by lack of financial resources and in order to save time, Robert focused his market research on secondary sources and went online with the aim to find freely available and easily accessible information about his target customers and future competitors via a thorough internet search. Online sources that he consulted included synopses of market research reports, websites and published annual reports of competitors, government websites and statistics as well as the press including newspapers and popular business journals.

Now, in light of the new insights that his market research has revealed, Robert is having second thoughts about his originally planned approach with respect to the commercial exploitation of the innovative outcome of his health research: What is the most appropriate route to market for his novel technology? Partnering with a large biotechnology company in order to enter the market for epigenetics-based cancer IVDs or relying on his own powers and targeting the market for epigenetics RUO tools instead?

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2. Looking into the epigenetics market

2.1. Market size and growth potential

The exponentially increasing scientific literature in the field of epigenetics over the past few years was for Robert a clear initial indication of the growth of the epigenetics market which includes epigenetic screening technologies, instruments, kits and consumables used in gene regulation studies, biomarker detection and drug discovery. However, it was time for him to take a closer look into his target market and gather sufficient evidence in order to determine its size and growth potential.

A careful internet search revealed that in 2012, the global epigenetics market was valued at US$2.6 billion in terms of revenue and is expected to reach US$8 Billion by 2017[3]. These figures included both the research and diagnostics market segments whose projected growth translated into a compound annual growth rate of more than 25%, implying a promising potential for Robert's entrepreneurial venture**.** From a geographic perspective, the most appealing market appeared to be North America that accounted for the largest portion of the epigenetics market (almost 40%), followed by Europe that also held a significant share of the market in 2012.

The increasing incidence rate of cancer and the accompanying raised public awareness for timely diagnosis and cure are the main drivers of the epigenetics market. Worldwide, an estimated 8.2 million people died from cancer in 2012, whereas 14.1 million new cases of cancer occurred[4]. The realization that epigenetic mechanisms play a crucial role in oncology drives the development of novel diagnostic as well as therapeutic strategies through the discovery and application of epigenetic cancer biomarkers. Consequently, the growing list of discovered biomarkers are fueling the next generation of cancer diagnostics presenting a lucrative business opportunity.

Therapeutic applications of epigenetics in non-oncology settings as well as in personalized medicine are also emerging areas that receive increasing investments and funds. Due to their promising research in cancer and other diseases, these areas are expected to enhance the growth of the market in coming years. As there is a strong correlation between cancer and other diseases and aging the prevalence of these diseases is constantly growing along with the increasing aging population. According to the World Health Organization[5], the global population aged 60 years and over is expected to double from 11% (2000) to 22% by 2050, an astounding increase that can have not only immense implications for healthcare and societal costs, but also great opportunities for health business.

In this rapidly changing environment, pharmaceutical and biotech companies are undertaking initiatives and forming alliances for the development and commercialization of epigenetics drugs. Collaborations among and investments from such companies are expected to further enhance the growth of this market. Finally, countries within the Asia-Pacific region are expected to greatly drive the growth of the epigenetics market in the future due to the favorable regulatory landscape, rising disposable incomes and growing population suffering from diseases such as cancer, diabetes, etc.

[3] Markets and Markets (2013), "Epigenetics Technology Market (Epigenomics, DNA Methylation, Histone Modifications, RNA Interference, Cancer Therapeutics, Personalized Medicine) 2012 - 2017".
[4] Cancer Research UK, "Worldwide cancer statistics", available at: www.cancerresearchuk.org/cancer-info/cancerstats/world/cancer-worldwide-the-global-picture
[5] World Health Organization, "Facts about ageing", available at: www.who.int/ageing/about/facts/en/

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2.2. Customers, needs and requirements

Faithful to his original commercialization plan that involved the development of In Vitro Diagnostics (IVD), Robert first started researching prospective customers that could be interested in next generation epigenetics-based IVDs for various cancer types (e.g. breast, cervical, prostate, colorectal, etc.). These were healthcare professionals and physicians as well as public or private hospitals and healthcare providers. This customer group appeared to be highly interested in the accuracy and effectiveness of a potential cancer IVD, a quite promising finding for Robert as, employing his cutting-edge technology, he could provide them with highly accurate next generation IVDs that would allow for the systematic elimination of false positive results. In addition, his IVDs would equip healthcare practitioners with the tools required to improve their decision-making in the patient care process and achieve better health outcomes through early cancer screening enabled by the detection of epigenetic biomarkers which are ideal targets for early stage cancer detection. Furthermore, epigenetic-based IVDs allow for convenient and rapid detection of epigenetic cancer biomarkers in a broad range of samples that do not require uncomfortably invasive medical practices. This implies a potentially increased compliance rate of patients with screening guidelines that hints to a promising adoption rate of Robert's IVDs amongst health practitioners.

The market research came up with exciting evidence for the size of this customer segment as well since in 2013, the estimated value of the global market for next generation cancer diagnostics was US$1.6 billion in terms of revenue[6]. However, it also reminded Robert that despite the appealing profitability that this market segment can offer to his entrepreneurial venture, commercializing IVDs can prove to be a quite challenging task. The market is geographically fragmented and in many parts of the world marketing of IVDs is highly regulated by relevant authorities. For instance, the gatekeeper of market entry for IVDs in the United States (US) is the Food and Drug Administration (FDA). Marketing an IVD within the US would require Robert to obtain a premarket approval from the FDA, a complex process that involves submitting a respective application that must be supported by detailed and comprehensive scientific evidence (including clinical data) that demonstrates the safety and efficacy of the IVD for its intended purpose. In practice, such premarket approval applications to the FDA take, on average, as long as 13 months to be successfully reviewed[7] and as Robert observed similar long bureaucratic processes exist in many of the major geographical markets. Therefore, much to his dismay, Robert realized that the development of an IVD does not necessarily imply its commercialization as the process of applying for regulatory approval may take a significant amount of time and money with no guarantee that the application will be eventually approved.

In sharp contrast, Robert observed that devices which are considered to be in the laboratory phase of development and are marketed for research use only (RUO) are exempt from most regulatory controls. This translated into a promising business opportunity that involved developing and marketing ready-to-use epigenetics kits based on his innovative technology to scientists and researchers at Life Sciences laboratories either in the private or the public sector, a market that, in terms of revenue, was estimated at US$410 million in 2014[8]. Prospective customers could encompass universities, research institutes, pharmaceutical and biotechnology companies as well as individual scientists and health-researchers that engage in epigenetic research and/or epigenetics-fueled drug

[6] BCC Research (2014), "Next Generation Cancer Diagnostics: Technologies and Global Markets".
[7] Cairns, E. (2014), "FDA medtech approval slowdown hits surgical devices hardest", EP Vantage, available at: http://www.epvantage.com/Universal/View.aspx?type=Story&id=525375&isEPVantage=yes
[8] Markets and Markets (2014), "Epigenetics Market by Product (Modifying Enzymes, DNA Polymerase, Acetylase, Methyltransferase, Instruments & Consumables, Kit, Bisulphite Conversion Kit, Reagents), Research Area (Developmental Biology, Oncology) & by End User - Global Forecast to 2019".

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discovery and development, aimed at the generation of groundbreaking medical breakthroughs for the benefit of society.

The market research revealed that the key audience that Robert would have to influence by targeted marketing efforts in this customer segment are epigenetics researchers. These RUO customers appeared to be highly interested in the prevalence of the epigenetic screening technology in relevant scientific literature as well as its cost as they are typically faced with research budget constraints. Robert had already achieved several scientific publications in prominent medical journals with a high impact factor that could serve as valuable levers for the promotion of his innovative technology among the epigenetics research community. Furthermore, Robert's ready-to-use kits could provide epigenetics researchers with an effective way to screen for epigenetic events producing reliable, accurate and rapid results at a competitive price through an easy and standardized procedure that has the potential to replace the labor-intensive and time-consuming methods that they currently employ. According to Robert's estimations, by utilizing his ready-to-use kits, epigenetics researchers and by extension their labs could decrease their annual spending on epigenetic screening products and services as much as 37%. This was possible due to the high sensitivity and reliability of the screening technology that implied a lower number of experiments required to reach satisfactory results as well as less quantity of input (e.g. reagents) for each test. The cost effectiveness of the innovative technology could provide Robert with a considerable competitive advantage and potentially serve as an essential driving force for his entrepreneurial venture in the RUO segment.

2.3. Competition

In order to obtain valuable insight into the competitive landscape of his target market, Robert carefully studied the websites and published annual reports of some prominent epigenetics companies that would be his main potential competitors.

A representative example is Epigenomics[9], a German molecular diagnostics company focused in the IVD segment of the epigenetics market and especially in the field of early cancer diagnosis. Even though in 2013, the company reported revenues equal to €1,588,000 (almost 50% more than 2012), Epigenomics has been suffering losses over the past few years. These losses , however, are slowly decreasing as Epigenomics develops its business activities worldwide by establishing customers and partners through out-licensing in many strategic geographic markets in Europe, Asia and the US. After achieving approval in Europe to market its IVD for colon cancer screening based on the detection of its patented epigenetic biomarker, Epigenomics is now pursuing its approval in the US market as well. Another important competitor, MDxHealth[10], is headquartered in Belgium and is utilizing its patented technology to develop and commercialize IVDs with emphasis on prostate, colorectal and lung cancer. MDxHealth has out-licensed many of its cancer screening products as well as biomarkers to several strategic partners and its revenues have grown from US$3,740,000 in 2011 to US$7,554,000 in 2013. However, similarly to Epigenomics, it is also suffering losses for the last three years.

The analysis of his competitors showed Robert that the majority of epigenetics companies drawn by the potential high profitability that the IVD market promises have several products that are currently in development and/or in pursuit of regulatory approval. However, an alarming finding was that even though their revenues are growing rapidly they appear to be suffering losses for several years after market entry. This means that the IVD market requires substantial financial resources to cover the losses that a small company may face during its very first years of operation. In addition, the

[9] www.epigenomics.com
[10] www.mdxhealth.com

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relatively limited number of the epigenetics-based cancer IVDs that have finally achieved regulatory approval and are available in the market convinced Robert that there is a great risk and that the considerable constraints set by regulatory authorities could threaten the viability of his entrepreneurial venture.

With these in mind Robert proceeded to investigate the competitive landscape of the RUO segment of his market. As a seasoned researcher himself, he was already well aware that there is a wide array of research tools and services available to epigenetics scientists. An analysis of the competitive landscape of the RUO segment, however, further evidenced the fragmented structure of the market, as no competitor seemed to have the market lead.

Several Life Science laboratories provide epigenetic screening services while others have developed and employ their own methods for studying epigenetic events. However, such services and methods are typically quite expensive and/or time consuming for epigenetics researchers and thus would not pose a serious threat to Robert's low cost ready-to-use kits. The competitors that Robert will have to worry the most about are the many multinationals and molecular diagnostics companies which are operating in the RUO market by licensing the patented technologies of relatively smaller epigenetics companies (e.g. MDxHealth) for the development of RUO epigenetics kits. Robert observed that one of the major competitors that he will have to face in this segment of the market is Qiagen[11], a large multinational provider of sample and assay technologies for molecular diagnostics, applied testing, academic and pharmaceutical research headquartered in the Netherlands. Qiagen reported net sales of US$1,302 million in 2013 and net profits equal to US$69,073 million. The company has been steadily growing over the last 5 years offering a wide array of RUO products. Its large size and scope of activities allows Qiagen to benefit from economies of scale and thus to offer rather competitive prices for its products worldwide.

The market research made it evident that the competition in the RUO segment was significantly more intense than the clinical setting of the epigenetics market. Would the competitive advantages of his technology suffice for Robert to successfully compete with the intimidating larger companies and profitably market his ready-to-use epigenetics kits to prospective RUO customers?

[11] www.qiagen.com

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3. Identifying alternative routes to market

Robert had to utilize the information collected through his market research to put an end to his crucial dilemma regarding the introduction of his innovative technology into the market: Should he follow his original plan and market his solution to customers of the cancer In Vitro Diagnostics (IVD) market with the support of an already established large biotechnology company or change his approach and target the epigenetics market for research use only (RUO) tools, an option that could provide him with the opportunity to venture on his own?

In light of this important decision, Robert sought counselling from his close friend Ted Humphrey. Ted had been a business consultant for more than 20 years now and besides his key competence in marketing and business planning had also considerable experience in supporting innovative start-ups to acquire financing at the crucial first steps of their life cycle. Robert send over all relevant data to Ted and scheduled a Skype call to discuss on the most appropriate route to market. During the call, Ted highlighted that Robert's IVD and RUO customers appear to be rather different in terms of needs and requirements and therefore cannot be addressed with the same marketing approach or business model.

On the one hand, in the IVD segment of the market, the many regulatory requirements in conjunction with the time consuming procedure needed to obtain market approval can raise substantial barriers that might prove to be rather difficult for a young start-up such as Robert's to overcome alone due to the typically limited resources at its disposal. Therefore, if Robert decides to target IVD customers, the safest strategy would be for him to collaborate with an experienced, well-connected, and powerful strategic partner as the benefits of cooperating with a larger, already established company can greatly raise the probability of success in his entrepreneurial venture.

As a new entrant in the IVD market, Robert could leverage the strengths of a large biotechnology or molecular diagnostics company including established marketing channels and existing relationships with key influential actors in healthcare (e.g. health practitioners, hospitals, etc.) as well as potentially even benefit from its financial backing. In fact, as Ted suggested, Robert could out-license his technology to a number of selected strategic partners as many competing epigenetics companies already operate in the market and focus on the development of new IVDs as well as the discovery of novel epigenetic biomarkers for cancer. This business model would require relatively limited investments in terms of marketing or sales promotion and more importantly would allow Robert to avoid the establishment of an in-house manufacturing department that would require substantial financial resources and potentially relevant regulatory compliance. It also has the potential to allow for the creation of a significant Intellectual Property (IP) portfolio that Robert can later on leverage to attract additional potential collaborators but consequently will require effective IP management. On the negative side, as currently the innovative technology is only protected in the United States, Robert might encounter significant difficulties in expanding to international markets. This business model might also imply relatively lower revenue for Robert as he would not directly sell to the IVD customer segment and thus could influence the growth potential of Robert's start-up.

On the other hand, Robert can choose to target the epigenetics market for RUO tools which, even though more crowded in terms of competitive offers, appears to be rather fragmented with no significant entry barriers from a regulatory perspective. Therefore, by targeting this customer segment Robert has the option to assume direct marketing and distribution of his ready-to-use epigenetics kits without requiring the support of a strategic partner. Directly marketing to RUO customers would be more challenging but at the same time also rather promising as, due to the competitive advantages of Robert's technology, it holds the potential to generate the revenue

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required to fuel the rapid growth of his budding company before pursuing regulatory approval of his IVDs at a later stage of development.

Ted explained that choosing this route to market would involve the development of a marketing and sales department in-house as well as establishing distribution networks within the targeted markets from scratch. Robert would not be able to handle all these alone and thus would need a skilled team to work along with him in his entrepreneurial endeavour. He would need at least one person with business to business marketing and sales experience to help him create and develop a network of customers as well as someone to handle the daily administrative aspects of the venture. That would allow Robert to focus on the development of new epigenetics kits to enhance the product portfolio of his start-up. Furthermore, Robert would have to identify a viable business solution for manufacturing his epigenetics kits. A potentially cost-effective alternative to establishing a manufacturing department within his company would be to outsource the production to an appropriate manufacturer. Robert had already identified a few prospective manufacturers through his online search but he would have to determine the criteria based on which he would select the most appropriate. Finally, as this business model would involve increased initial funding needs for the start-up, financial resources would have to be procured from external sources. Towards this direction Ted volunteered to support Robert by introducing him to some angel investors with whom he has established contact through his past business experience. What if Robert could not convince them, however, and thus couldn't find the resources necessary to kick-start his entrepreneurial venture? Before approaching potential investors he would have to prepare a business plan that would make a strong business case for his proposed venture.

Based on the insights that emerged from his market research as well as Ted's concise recommendations during their conference, Robert will now have to carefully weigh the advantages and disadvantages involved in each case and make the right decisions setting his course towards a successful entrepreneurial endeavour.

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4. Lessons learnt and thinking further

Information derived from an effective market research are essential in guiding important strategic business decisions, even more so in budding entrepreneurial ventures. Furthermore, as evidenced through the case of Robert, market research is not an activity conducted only once. Especially in rapidly evolving markets where technological advances generate constant innovations, it should be an ongoing cycle and when carried out properly can lead to conclusions and decisions that may have a value that considerably exceeds the investment of the research itself.

Indeed, Robert made an organized effort to collect and analyze information regarding his targeted customers, potential competition and several other aspects of the environment of his entrepreneurial venture in order to gain a more in-depth understanding of his target market. The market research provided him with findings that pointed to alternative pathways that he could follow in order to introduce his innovative technology into the market thus leading him to challenge his original commercialization plan.

Based on the findings of his market research and taking into account the expert advice of his friend Ted, Robert will have to decide the most appropriate route to market for his innovative solution in order to safeguard the short-term viability and long-term sustainability of his entrepreneurial venture. Should he follow the route that seemed so promising back in 2009 and collaborate with a large biotech company to develop and produce IVDs for cancer or should he choose a different route and market off-the-shelf kits to epigenetics scientists that as unveiled by his market research would be possible without involving a strategic partner in his entrepreneurial endeavour?

Some questions to spark further thinking are:

- *Assume that Robert has decided to target customers in the epigenetics market for RUO tools and is now trying to determine an appropriate marketing strategy for his product. What type of customers should he go first? How should he approach them in terms of distribution and promotion? With what product and at what price? Suggest a marketing strategy that Robert could adopt in order to effectively reach the customers of the RUO segment of the epigenetics market.*

- *Are there any other types of strategic partnerships apart from licensing that Robert could consider in order to enter the IVD segment of the epigenetics market? What are the implications of each one for his entrepreneurial venture and which one would you recommend? How would your suggestions for the previous point change in case Robert decided to enter the IVD market through the strategic partnership that you suggested?*

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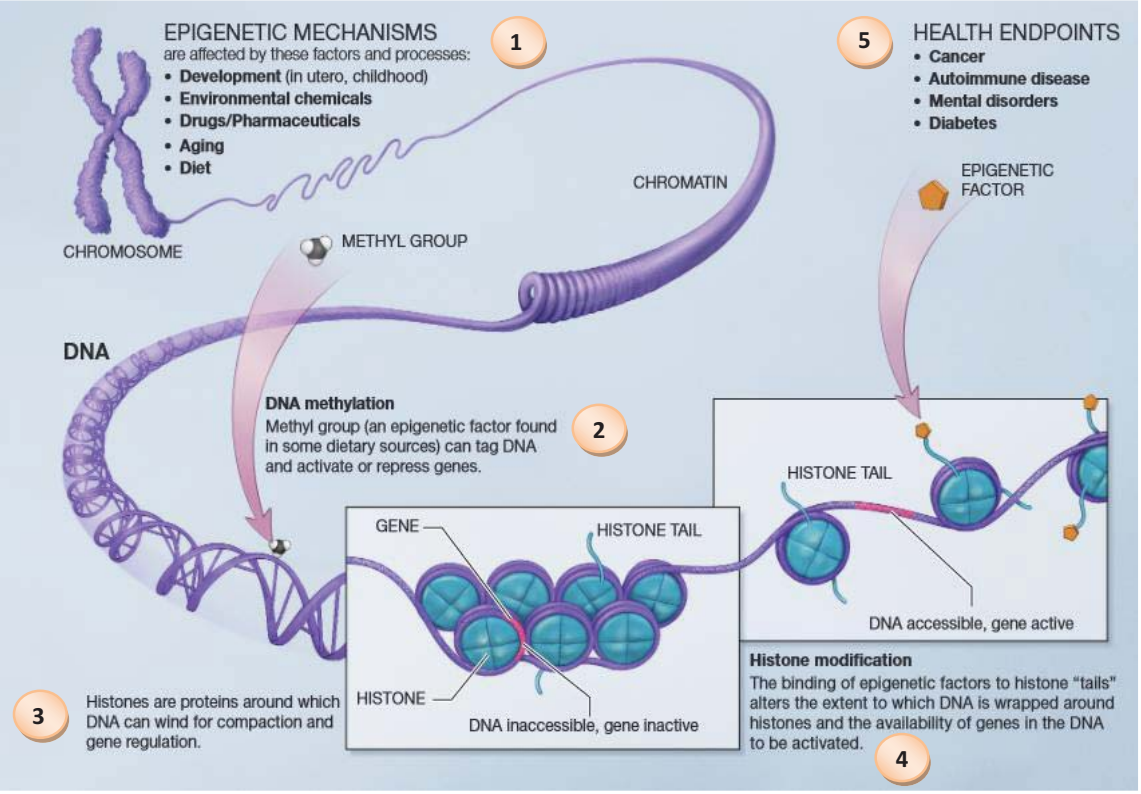
Annex

Overview of the way that epigenetic mechanisms can influence health



***Source**: Adapted from **National Institutes of Health**, available at:commonfund.nih.gov/epigenomics/figure*

1. Epigenetic mechanisms are affected by several factors and processes including **development in utero** as well as during **childhood**, **environmental chemicals**, **drugs** and **pharmaceuticals**, **aging**, and **diet**.

2. DNA methylation refers to the biochemical process that involves methyl groups, an epigenetic factor found in some dietary sources, tagging DNA and switching genes on and off.

3. Histones are high alkaline proteins that serve as spools around which DNA can wind enabling compaction and regulating genes as well.

4. Histone modification occurs when the binding of epigenetic factors to histone "tails" alters the extent to which DNA is wrapped around histones and the availability of genes in the DNA to be activated.

5. All of the abovementioned factors and processes can have an effect on people's health and may influence their health potentially leading to **cancer**, **autoimmune diseases**, **mental disorders**, or **diabetes** among other diseases.

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SEPTEMBER 2012 – AUGUST 2015

Health 2 Market

FROM HEALTH RESEARCH TO BUSINESS

Entrepreneurship & Business Planning Guidebook

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SKEMA Business School

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www.health2market.eu

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Health 2 Market — FROM HEALTH RESEARCH TO BUSINESS

Title:	**FROM HEALTH RESEARCH TO MARKET – ADVANCED SERVICES FOR THE IPR MANAGEMENT AND BUSINESS EXPLOITATION OF THE EU-FUNDED RESEARCH RESULTS IN HEALTH/LIFE SCIENCES**
Acronym:	**Health-2-Market**
Project Coordinator:	**Ms Svetlana Klessova** **Inno** ***S.Klessova@inno-group.com***
Contract No:	**305532**
Duration:	***36 months (September 1, 2012 – August 31, 2015)***
EC Contribution:	***€ 1.999.785***

Description:

Health-2-Market is a 3-year long Coordination and Support Action, funded by the Seventh Framework Programme of the European Commission (Grant Agreement No 305532), aiming at providing training and individual support to health and life science researchers in the process of transforming their research results into successful new business ideas. The duration of the project was 36 months (September 2012 – August 2015).

A portfolio of high-level services, training actions and tools were designed and offered free of charge (and some of them are still available), escalating to address the needs of all potential target groups (health/life science researchers, European health research institutes, Technology Transfer Organizations, EU health-related companies and entrepreneurs, health/life sciences European networks, NCPs etc). The most important Health-2-Market services and assets developed during the project were the following:

- 17 regional training seminars and 7 weeklong academies with more than 600 participants
- 20 individually tailored commercialization services to selected health research projects
- E-learning courses on "bringing research to market", still available free of charge on http://elearning.health2market.eu/ and on Googleplay and Applestore
- MOOC on "Roadmap to Entrepreneurial Mindset and Toolkit", available on Udemy (https://www.udemy.com/entrepreneurial-mindset-and-toolkit)
- "How to do" guide on Innovation strategy in R&D projects and annotated templates for Horizon 2020 proposals, available free of charge on http://www.health2market.eu.

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INTRODUCTION

1. Reference framework for the guide

This set of case studies presents a series of pitched business plans that were ranked as best practices by a jury of life science entrepreneurs and business angels as well as academics during the two Venture Academies that took place at SKEMA Business School, Sophia Antipolis, France. The first Pilot Academy took place from the 2nd to the 6th of September, 2013, the second took place from the 6th to 10th October, 2014 and the third and last took place from 1st to 5th June 2015, Rome, Italy.

The academies have taken participants through the process of formulating the framework of their entrepreneurial venture, from innovative idea creation to early start-up activities and acquisition of the first clients for a new business. Central to this process was the iterative creation and fine-tuning of a business plan, and understanding the uses of the business plan for management of key activities and for attracting outside investors.

Before pitching their business plans in real life situation, participants have experienced iterative construction of the different steps of the business plan with daily pitches and feedbacks from professionals as well as peer trainees. Action learning has structured the training in order to leverage cross-fertilization between participants. Testimonials from entrepreneurs have also enabled experience sharing on the entrepreneur's curriculum.

Each case study business plans articulates through a set of commonly agreed fourteen topics required by venture capitalists, business angels or incubator professionals when assessing the robustness of an entrepreneurial project.

1. Vision/mission
2. Business opportunities
3. Solution/offer
4. Value proposition/customer benefits
5. Targeted market
6. Competition
7. Simplified business model
8. Go to market strategy
9. The team
10. History of the project
11. The next 18 months
12. Key figures
13. Risks

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14. Demand

During the academies, participants have designed, challenged, and fine-tuned the content of each specific topic through daily pitches, peer evaluation and brainstorming with SKEMA experts, other entrepreneurs and fund raising specialists. Each participant eventually ended-up with a robust set of fourteen slides representing the framework for their pitched Business Plan and the skeleton for their in-depth detailed formalized Business Plan.

Each topic of the pitched business plan was previously introduced from a theoretical perspective in order for participants to anchor their work in relevant and legitimate academic background. Consequently, participants were also provided with academic insights on competitive and development strategy, strategic management of innovation, business model design, market research and analysis, sales management and organization, and basics of entrepreneurial finance and accounting. This academic knowledge was then used throughout the venture academies via action learning to design the pitched business plan.

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2. Case studies

Business Plan case 1: DENOVO SKIN

(2013 Edition)

DenovoSkin addresses the issue of patients with disfiguring, deep wounds and defects. It aims at solving the issues of skin donor-site shortage and complications, healing with scars, need for multiple surgeries during growth stage of patients, and patient social adapting problems.

The company will provide a new, minimally scarred skin which has great clinical and cosmetic outcome, which grows with the patient itself, thus reducing surgery and hospitalization, thus permitting normal social relations and dramatic improvement of patients' quality of life.

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denovoSkin
Vision & Mission

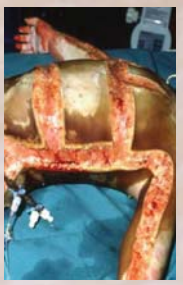
Dramatically improve quality of life of patients with disfiguring, deep wounds and defects

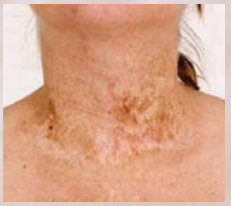
Provide a new, minimally scarred skin which:

- has great clinical and cosmetic outcome
- grows with the patient itself, thus reducing surgery and hospitalization
- permits normal social relations

Business opportunities

- Skin donor-site shortage and complications
- Healing with scars
- Need multiple surgery during growth stage of patients
- Patient social adapting problems





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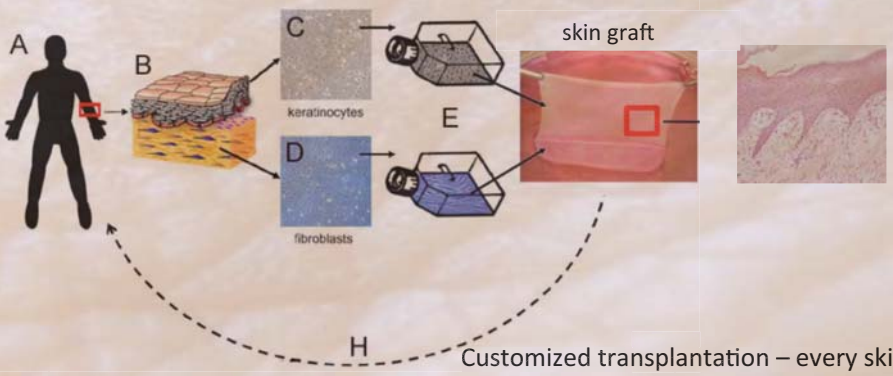
Offer: laboratory-grown skin with patient's own cells



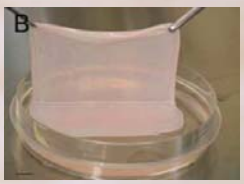
Customized transplantation – every skin graft is unique as every patient is!

Value proposition of denovoSkin

- Minimize scarring
  - Reduce number of surgeries
  - Reduce hospitalization time
  - Give back self and social confidence
- Minimize donor-skin area, only 1 cm

	Needed healthy skin from patient	
Wound Area	Gold standard	denovoSkin
10 cm^2	5 cm^2	1 cm^2
20 cm2	10 cm^2	1 cm^2

Dramatic reduction



- Provide surgeon-friendly skin tissue

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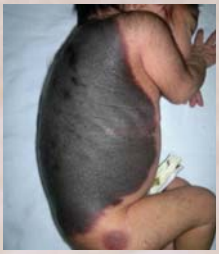
Targeted marked segments

- Burn and reconstructive surgeons



Patients

- 11 million people burned need hospital care/year world wide
- Patients with reconstructive surgery need
  - 1% of newborns

- Hospital associated production site outside Europe

Competition

- Full and split thickness skin transplants
- Dermal templates + Split thickness skin transplant
- Allogenic skin graft
- Epidermal templates

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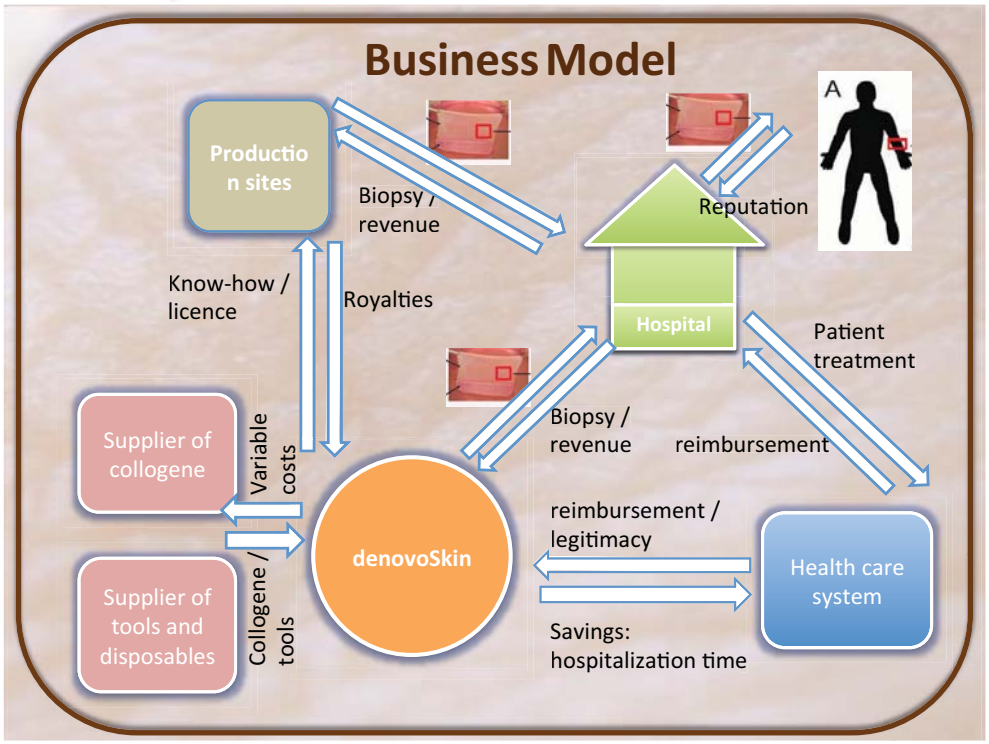

Go-to-market strategy

- Sale strategy: direct sales to hospitals
- Competitive strategy:
  - we offer a better product
- Development strategy
  - First focus on skin in Europe
  - Skin worldwide
  - Diversify product features
- Cooperate alliances
- Communication strategy:
  - On-site visits
  - Conferences
  - Key Opinion Leader
  - Publications
  - Media: internet, television, newspapers

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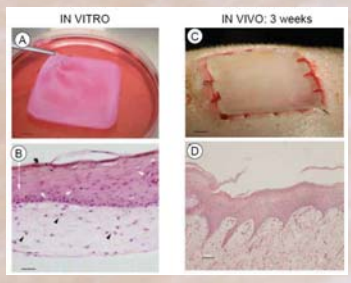
Team

- Dr. Daniela Marino (CEO)
- Prof. Martin Meuli (scientific board member)
- Prof. Ernst Reichmann (CSO)

- Tissue biology research unit – spin-off
- Launching customers: 70% burn treatment of Europe
  - Dutch burn Centre,
  - Trauma hospital Berlin,
  - University children's hospital Zurich
  - University hospital Zurich

History of project

- Track record the last 3 years: over 15 scientific papers



- Production time within surgeon's requirement

- Regulatory and ethical approval

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Next 18 months

- Phase 1 and 2 clinical trial – results expected by 2016 ->we are funded for this
- Patenting the production tools and then sell them, 2014

Key figures

	Before launching	1st year	2nd year	3rd year	4th year	5th year	6th year
Investments							
Sales in quantity of products or services sold							
Sales in value							
Total costs							
Including fixed costs							
Including variable costs of products or services sold:							
Including variable costs of products in stock							
Profit before income tax							
Cash at end of period							
Return (before income tax) On Sales							
Return (before income tax) On Equity							

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Risks

- Negative result out of clinical trials
  - Modify the product
  - Dermal template
  - Acellular template
- Lack of confidence of the patients in laboratory grown skin
  - Started with awareness program
  - Involvement of patient organizations
  - Disseminating trial results

Demand

- Network expansion
- CEO business coach

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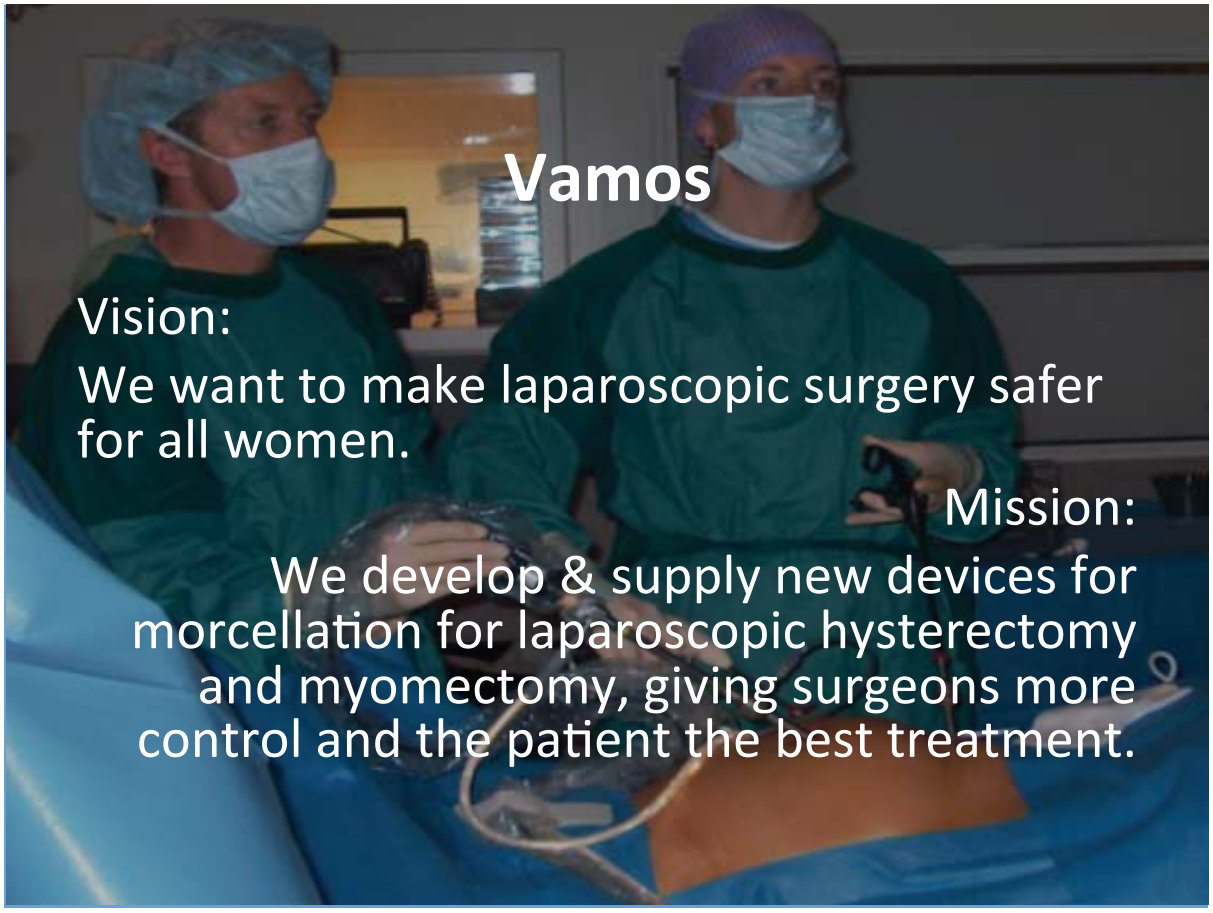
Business Plan case 2: VAMOS

(2013 Edition)

Vamos wants to make laparoscopic surgery safer for all women. Vamos develops and supplies new devices for morcellation for laparoscopic hysterectomy and myomectomy, giving surgeons more control and the patient the best treatment. The company provides both the conventional laparoscopic approach with oscillating cutting blades instead of rotating ones and the trans-vaginal approach with oscillating cutting blades.



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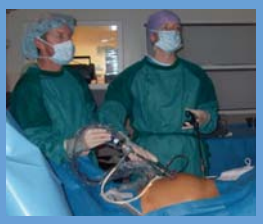
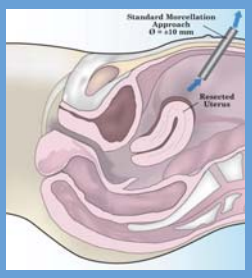
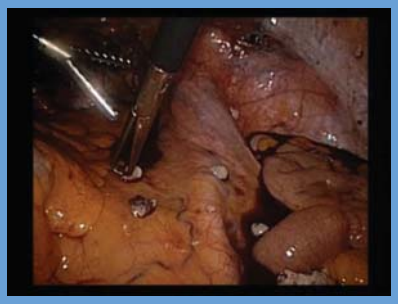
Health 2 Market

FROM HEALTH RESEARCH TO BUSINESS

VAMOS Business opportunity







Unsatisfied need:

Surgeons

struggle with morcellator during laparoscopy:
CONTROL & SPREAD

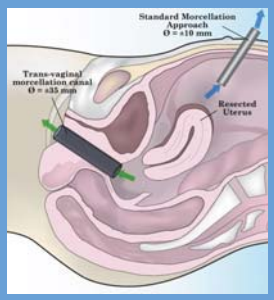
Patients

disadvantages open surgery

VAMOS Solution: Two approaches

VAMOS 1

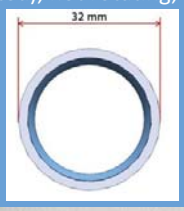
Conventional laparoscopic approach with oscillating cutting blade (patented) in stead of rotating;

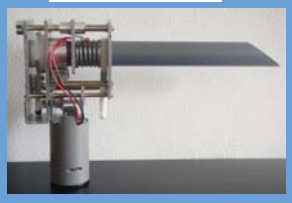


Patented oscillating knife

VAMOS 2

Trans-vaginal approach:
Larger diameter – larger tissue pieces;
With oscillating cutting blade (patented), not rotating;





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Value Proposition

VAMOS patented technology

VAMOS_1: laparoscopic

↑Improved performance

↓ complications

↑ patients benefit

REPUTATION

↑ **sales** of other laparoscopic devices

International MedTech

VAMOS_2: Vaginal

Advanced technology for future surgeons

International MedTech

Further improvement of procedure

VAMOS – targeted market

Laparoscopic Hysterectomy
Laparoscopic Myomectomy
Both US&EU

# interventions with morcellation Only hysterectomy	US& EU
2012	19.600
2018	50.960

<u>Surgeons</u> trained for laparoscopic hysterectomy or myomectomy;

REPUTATION

<u>Hospital management</u>

International MedTech

In gynaecology:

Ethicon (J&J), Olympus, Storz, Smith&Nephew, Hologic, Aesculap, Cook Medical.

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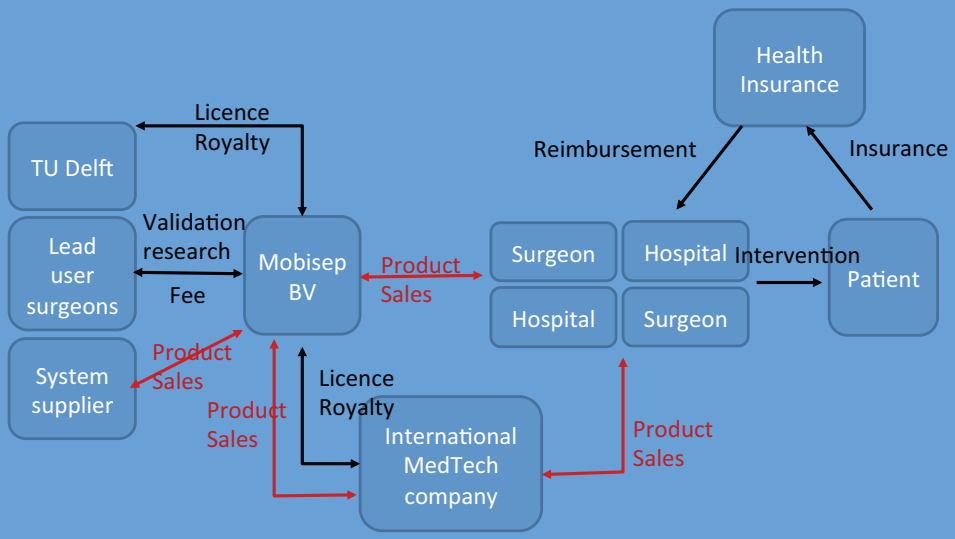
Competition (both EU & US)

- KarlStorz – two types
- Ethicon (J&J)
- Olympus

We compete with existing instruments so no complicated reimbursement issues because these are already in the reimbursement system.

VAMOS Business model



Cost structure is a combination of fixed & variable costs

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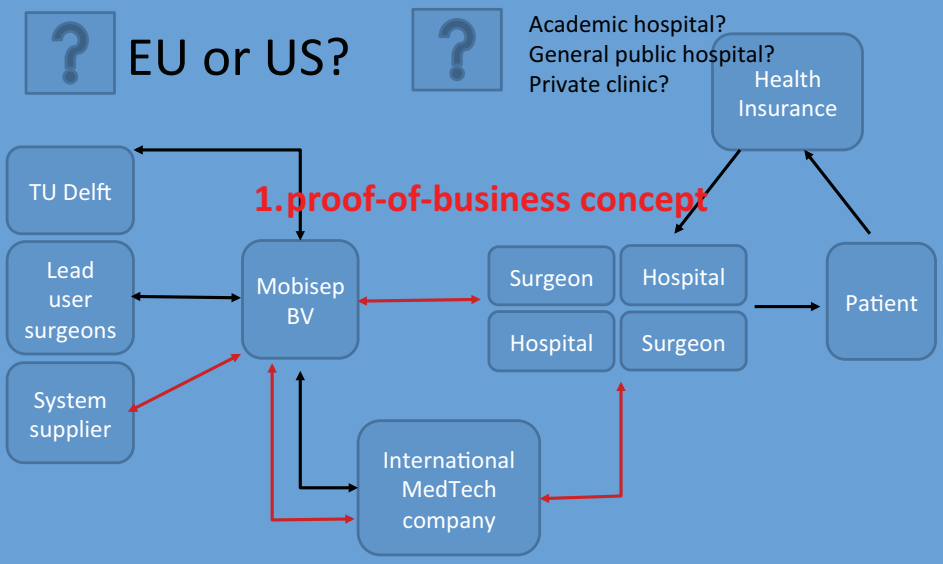
Go to market strategy



2. Fast market access: International MedTech

The Team

Mobisep B.V.

Malcolm Begeman	**Director & entrepreneur**
Wimold Peters	Medical Devices Engineer
Jules Scheltes	Medical Device Developer

Inventors & advisors:

Prof. Dr. Frank Willem Jansen	Gynaecologist, Leiden Ac. Med.Center
Ir. Ewout A. Arkenbout	PhD student, TU Delft
Ir. Caroline Duterloo	TU Delft, Valorisation Centre & NIMIT consortium

Exert user group:

Dr. Johan Rhremrev	Gynaecologist, Bronovo Hospital
Dr. Andreas Thurkow	Gynaecologist, Sint Lucas Andreas Hospital

Both are leading an extensive network of international gynaecologist;

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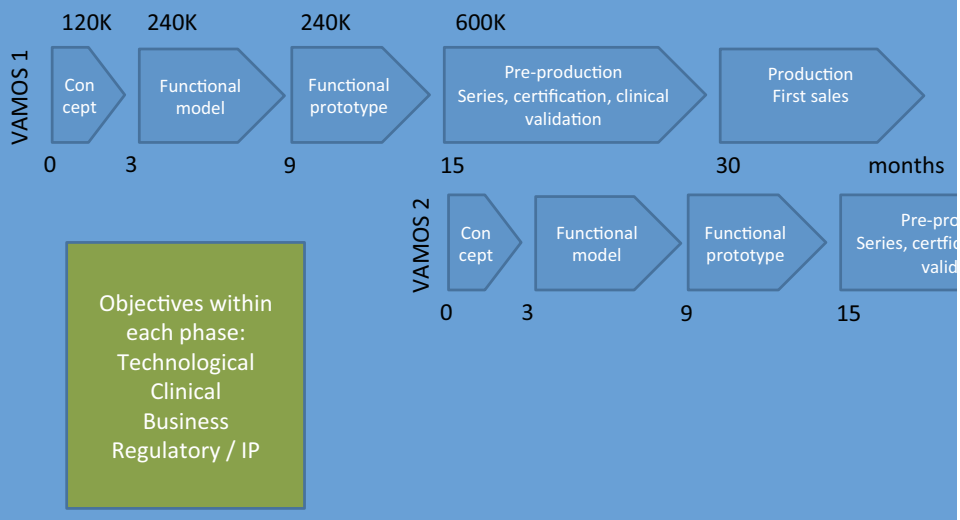
Genesis of project

Ewout Arkenbout – Masterstudent Biomedical Engineering
Prof. F.W. Janssen – Gynaecological surgeon
Prof. Dr. J. Herder – Biomedical Engineering

2009	Internship MIT
2011-2012	Master thesis
2010-2013	3 conference proceedings
Jan 2013	Patent application
2013 – 2015	clinical evaluation current Laparoscopic procedure
Aug 2013	Start cooperation with Mobisep B.V.

Next 18 months



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Key figures

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Profit before income tax							
Cash at end of period							
Return (before income tax) On Sales							
Return (before income tax) On Equity							

Confidential

Risks

VAMOS 1: incremental technological innovation

Risk: - not platform technology

- no exclusive technological skill needed,

get strong competitors on our side,
not against us

VAMOS 2: new approach, new procedure

Risk: embraced by key expert users?

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Demand

- Investment money: $1,5million – milestone based
  $75K for initial
- Entry to CEO MedTech in Women's Health
- Investors expertise to strengthen business case

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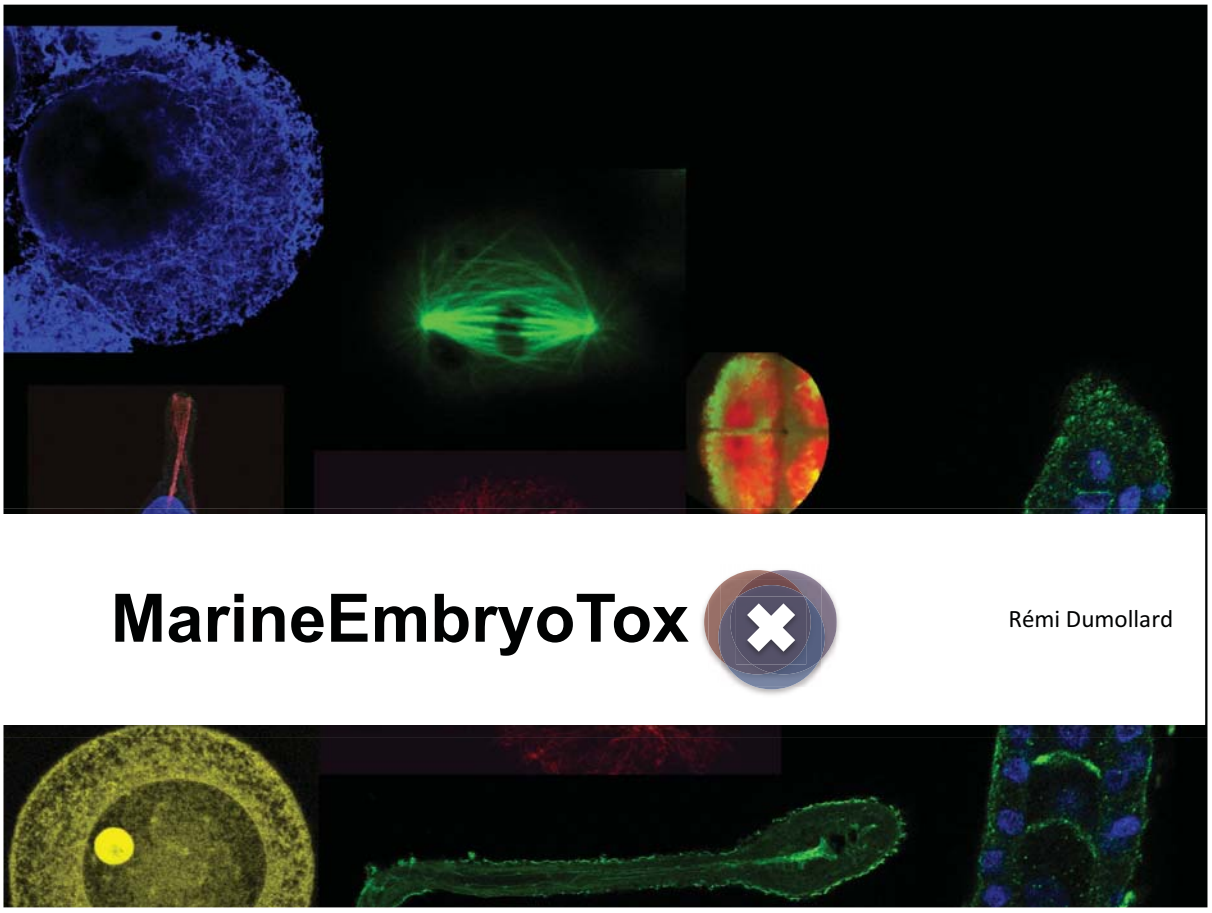
Business Plan case 3: MARINE EMBRYO TOX

(2013 Edition)

MarineEmbryoTox uses state-of-the-art molecular imaging techniques of transgenic marine embryos to characterise in depth the toxicity of marine samples and chemicals and its impact on human health. MarineEmbryoTox has developed a 3-in-1, highly sensitive, faster and a more cost-effective test for the evaluation of marine pollution. It uses human-model compatible, genetically engineered tools to perform customized analysis of marine toxicity.



Health-2-Market has received funding from the European Union's Seventh Programme for research, technological development and demonstration under Grant Agreement No 305532

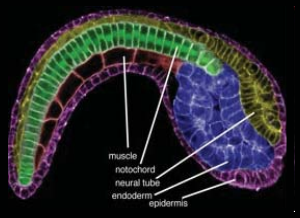
MarineEmbryo-Tox

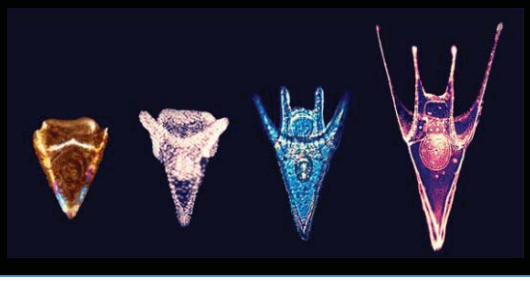
Vision

Using the knowledge of experienced academics on marine life to assess marine pollution and its impact on human health

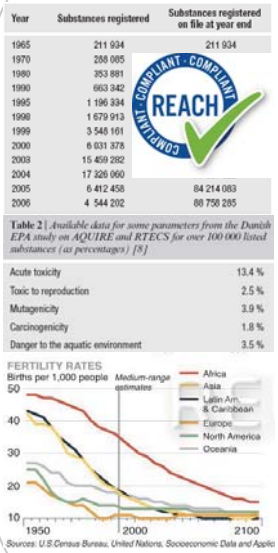
Mission

We use state-of-the-art molecular imaging techniques of transgenic marine embryos to characterise in depth the toxicity of marine samples and chemicals.





2-Business opportunities



Year	Substances registered	Substances registered on file at year end
1965	211 934	211 934
1970	288 085	
1980	353 881	
1990	663 342	
1995	1 196 334	
1998	1 679 913	
1999	3 548 161	
2000	6 031 378	
2003	15 459 282	
2004	17 226 060	
2005	6 412 458	84 214 083
2006	4 544 202	88 758 285

Table 2 | *Available data for some parameters from the Danish EPA study on AQUIRE and RTECS for over 100 000 listed substances (as percentages) [8]*

Acute toxicity	13.4 %
Toxic to reproduction	2.5 %
Mutagenicity	3.9 %
Carcinogenicity	1.8 %
Danger to the aquatic environment	3.5 %

1. Need for **new, sensitive toxicological tests** to cope with the overwhelming number of manufactured chemicals.
2. Such tests must be **fast, cost effective and amenable to high throughput**
3. Need for tests that **evaluate the impact of marine pollution on human health**
4. Need for an **alternative to animal-testing**

~3.4 billion people currently live in coastal areas

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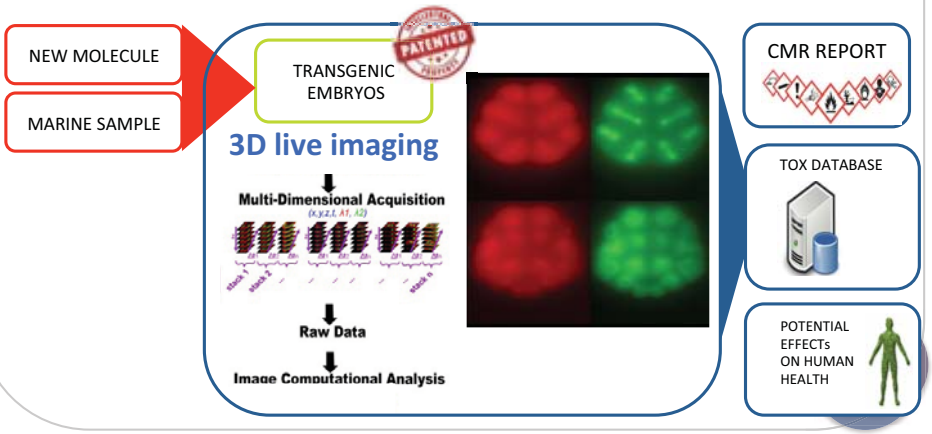
3-Solution

We offer:

- customized 3-in-1 CMR tests
- establishing the CMR toxicity of chemicals
- and their effect on marine life and human health



4-Value proposition / customer benefits

Our 3-in-1 test…….

•Combines determination of carcinogenicity, mutagenicity and reprotoxicity (CMR) of your sample

•Is a highly sensitive, faster and a more cost-effective evaluation of marine pollution

•Uses genetically engineered tools PATENTED to evaluate the impact of your sample on human health

•Performs customized analysis of toxicity

•Can be automated for high-throughput screens

•Will be embedded in the EMBRC network of marine stations all around Europe

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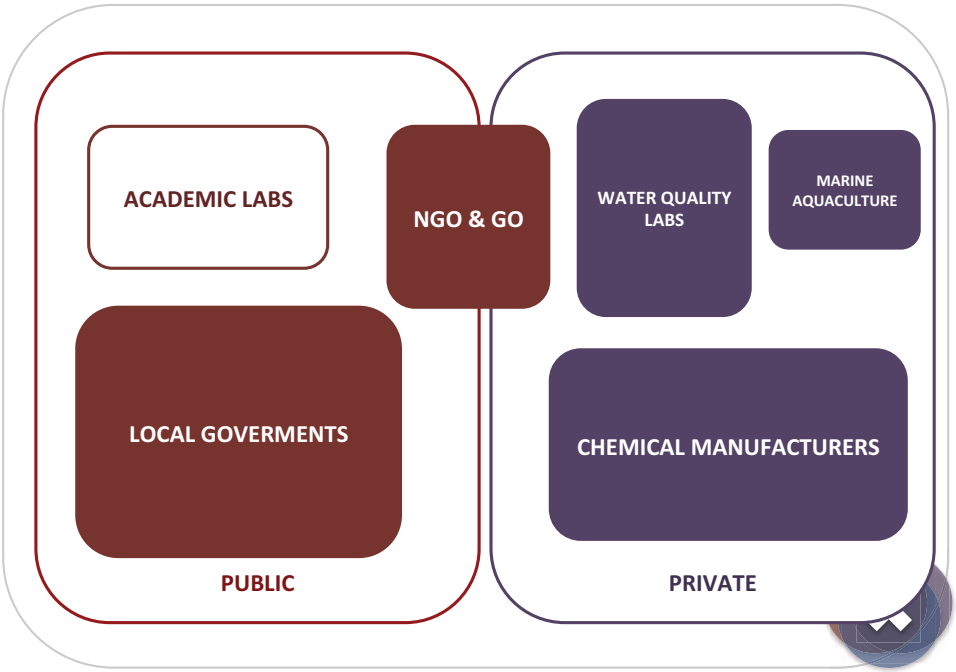
5-Targeted markets



National and international competition in toxicological testing

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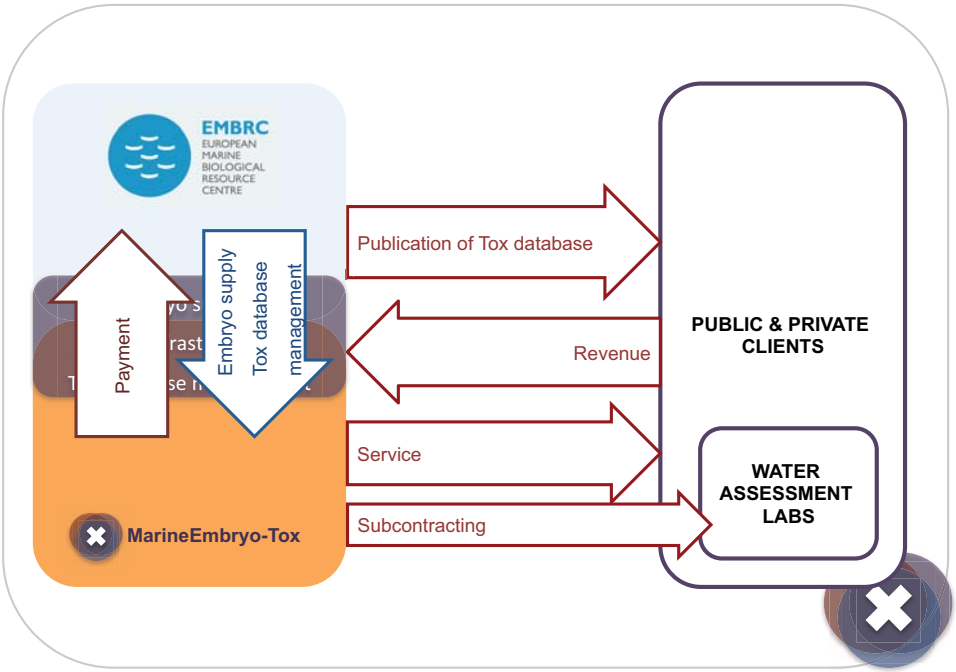
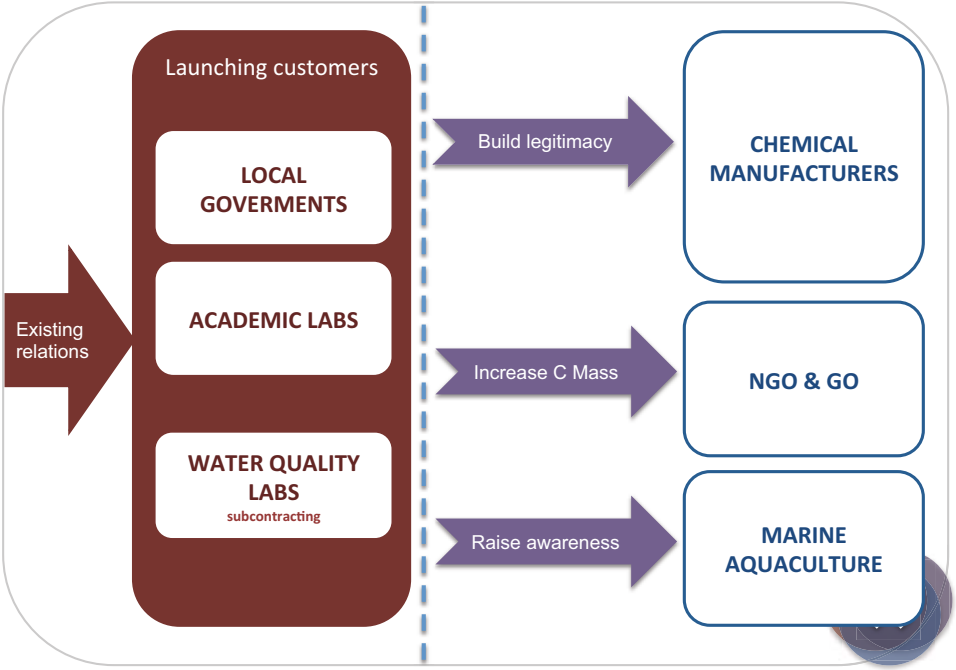
7-simplified BM



8-Go to Market strategy



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9-the team

MARINE EMBRYO TOX CO

- **CEO**
- **1 CSO** (inventors/founders)
- **1 Engineer**
  (performing CMR tests and reports)
- **From year 5 :**
- **+1 engineer**
- **+1 tech staff**
- **+1 Admin staff**

EMBRC & UPMC

- **Computer staff**
  (database management)
- **Infrastructure staff**
  (running lab and preparation of molecular tools)

10-history of the project

- 15 years experience in studying marine life by our team of scientists (LBDV)
- Molecular tests in the process of patenting (SATT Sud-Est)
- Labelling of MarineEmbryo Tox by Pole Mer PACA (Pole Mer France)
- Key partnership with EMBRC-Fr (Infrastructure d'Excellence 2011) & EMBRC-EU (ESFRI) and UPMC
- First clients from academic labs (University of Nice) and private (Loreal, sophia)

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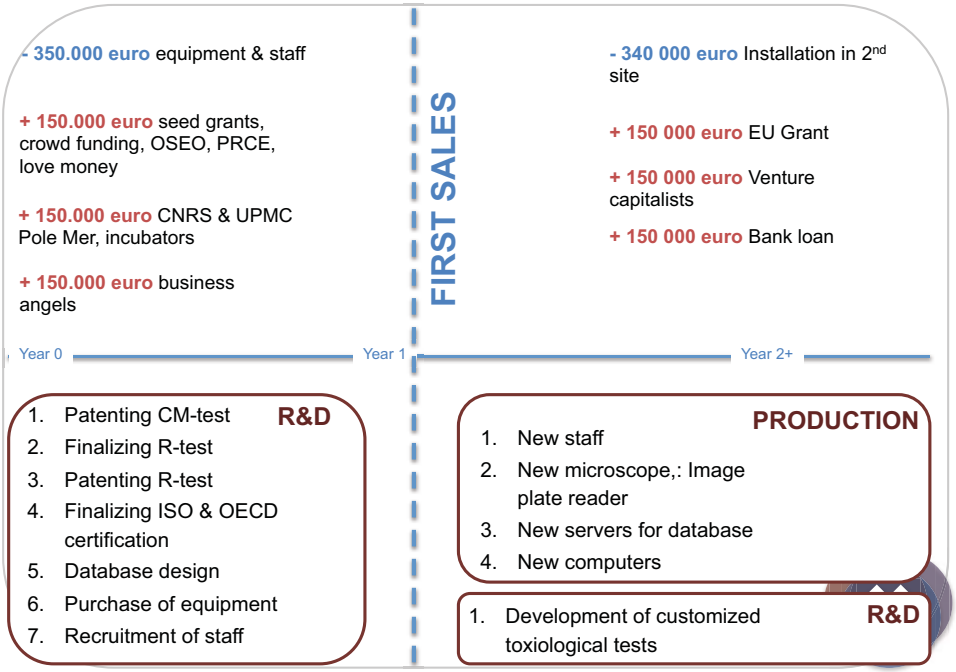
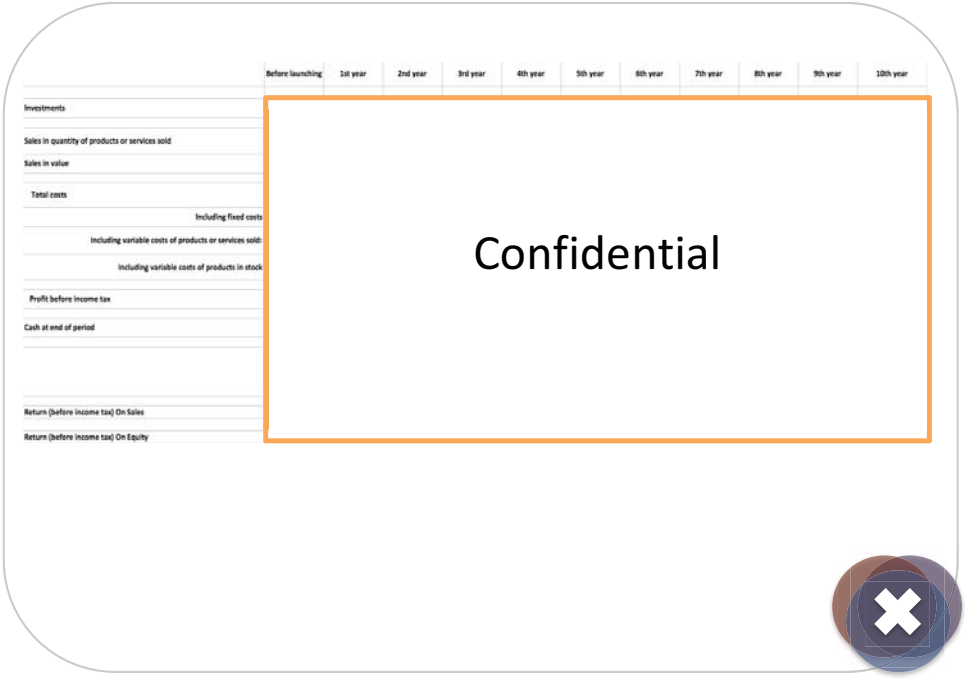
11-The next 18 months



12-key figures



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150 000 euros

(equipment and core staff) (co-financing the 450 000 initial investment)

CONTACTS

Business angels, Chemical manufacturers,
Consulting for market study

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Business Plan Case 4: SWEETCHECK

(2014 Edition)

SweetCheck aims at providing a solution to the growing trend in health issues related to diabetes in the World. SweetCheck is a pain-free, easy to use and discreet blood glucose measurement solution, which motivates diabetics & risk groups to keep better track of their blood sugar – anytime, anywhere.

Health-2-Market has received funding from the European Union's Seventh Programme for research, technological development and demonstration under Grant Agreement No 305532

VISION & MISSION

1. To improve the quality of life for diabetic patients.
2. Support risk groups in preventing to become diabetic.
3. Contribute to the survival of the endangered health care systems.

Our mission is to offer a pain-free, easy to use and discreet blood glucose measurement solution, which motivates diabetics & risk groups to keep better track of their blood sugar –
anytime, anywhere!

BUSINESS OPPORTUNITIES

1. Unsatisfying current blood glucose measurement systems

Invasive → painful, inconvenient & rather indiscreet in usage

↓

reduced daily measurement frequencies
increased treatment costs on the long term

Failure to stimulate diabetic **risk groups** to start monitoring themselves.

2. Emerging societal opportunities

Worldwide increase in diabetes and rapid extension of diabetic risk groups.

Over-stretched health care budgets.

Health-2-Market has received funding from the European Union's Seventh Programme for research, technological development and demonstration under Grant Agreement No 305532

SOLUTION & OFFER

We are pioneers in offering:

breath detector

for blood glucose measurement.

non-invasive

easy to use

social life compatible

VALUE PROPOSITION & CUSTOMER BENEFITS

The daily life of diabetics!

SweetCheck brings back Ease to patient's life!

Pain-free
Discreet
Easy to use
Fast and accurate
No test strips, no waste, low total costs

Risk groups don't measure themselves!

SweetCheck motivates them to keep track, raises awareness & helps to avoid developing diabetes!

Governments& health insurances with their stretched health care budgets

Health-2-Market has received funding from the European Union's Seventh Programme for research, technological development and demonstration under Grant Agreement No 305532

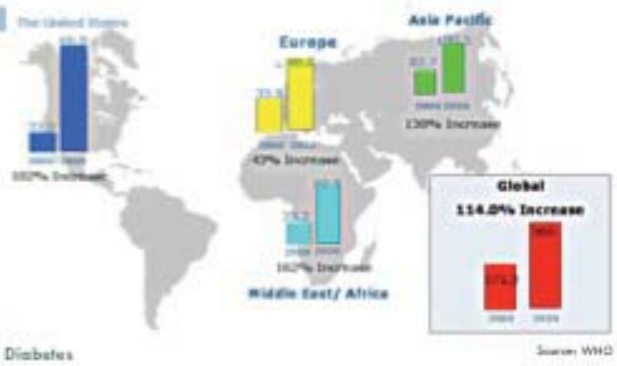
TARGET MARKET

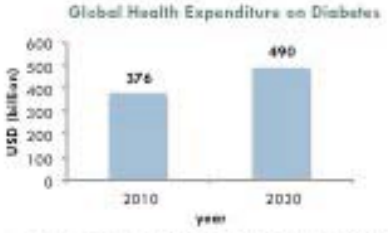
Our customers:

Diabetic patients

Pre-diabetics (Risk group)

Pharmacies





Data source: Zhang P et al. 2010, Diabetes Research and Clinical Practice.

Our related beneficiaries:

Worldwide welfare systems

COMPETITION on the blood glucose measurement market

Abbott Laboratories

Roche

Johnson&Johnson

Bayer HealthCare

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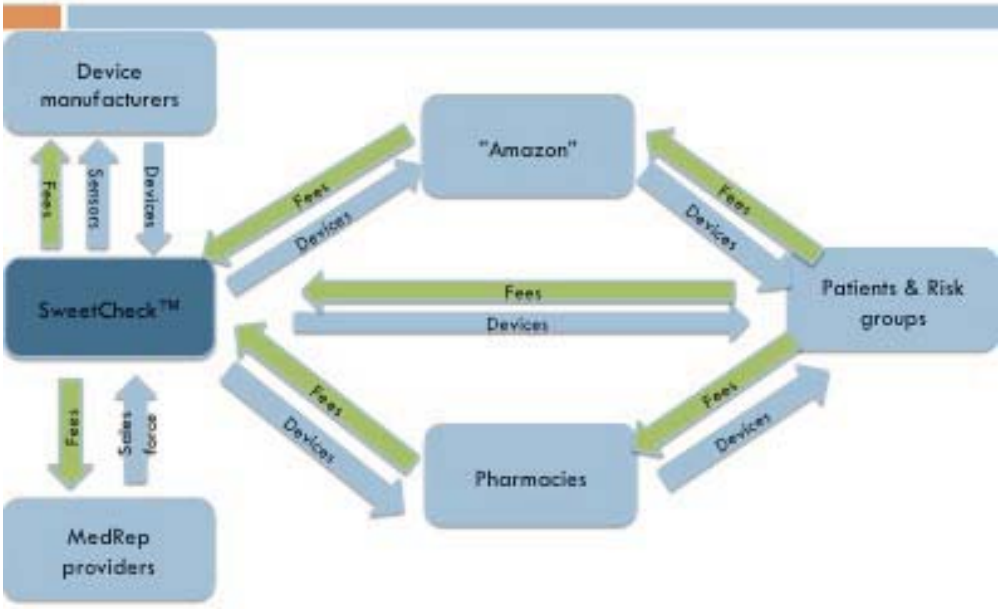
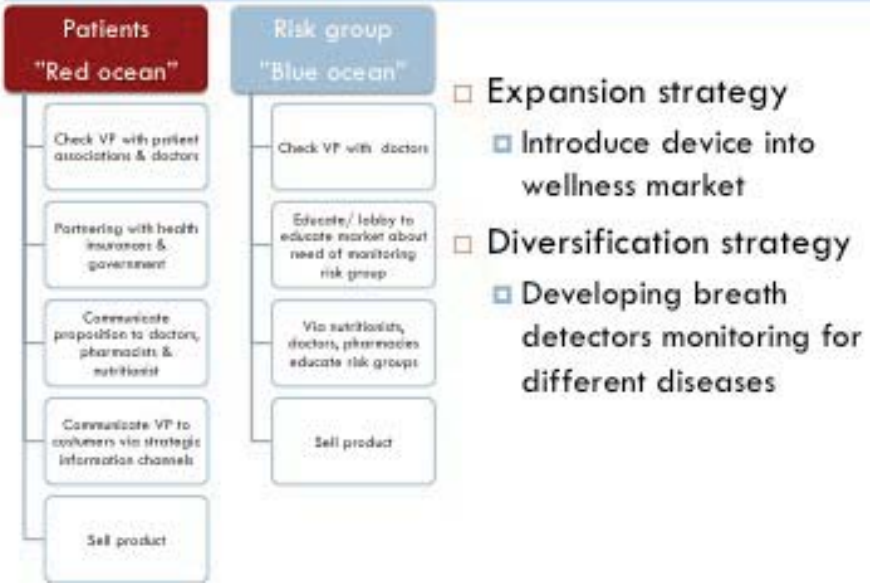
SIMPLIFIED BUSINESS MODEL



GO TO MARKET STRATEGY



- Expansion strategy
  - Introduce device into wellness market
- Diversification strategy
  - Developing breath detectors monitoring for different diseases

Health-2-Market has received funding from the European Union's Seventh Programme for research, technological development and demonstration under Grant Agreement No 305532

THE TEAM

Leading team:

Dorine du Mee, full time involvement as entrepreneur

MSc Biotechnology, 1 year in IP management

Dr. Olga Liska, full time involvement as entrepreneur

7 years of research experience in molecular

Scientist:

Peter Schmidt full time involvement in R&D

PostDoc researcher at the TU Delft

- Teams competences
  - Scientific background
  - Entrepreneurial skills
  - Willingness to engage in the development of the business
  - Experience with grant applications & fund raising
- Other capabilities needed
  - relevant network in the health care sector

HISTORY OF THE PROJECT

- TU Delft research on Nano-based sensor technology
- Key incentives to start development of our device
  - highly sensitive sensors available
  - emerging market of non-invasive diagnostics
  - growing diabetic market
- TU Delft in process of applying for a patent

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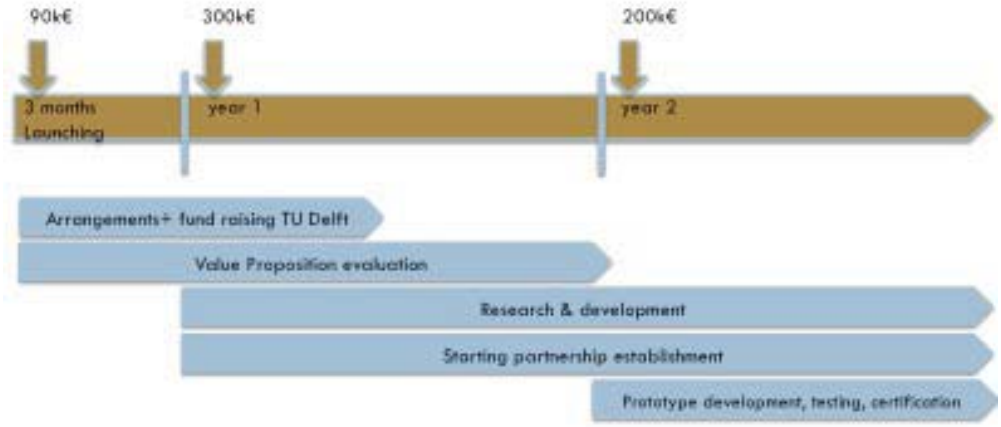
THE NEXT 18 MONTHS



KEY FIGURES

Confidential

Health-2-Market has received funding from the European Union's Seventh Programme for research, technological development and demonstration under Grant Agreement No 305532

RISKS

- Competitors launching different painless solution
- Product development taking more time and being more expensive
- Patients unwilling to change current habits/ to start using new device

DEMAND

- Business angel support
  - Help to contact decision makers in insurance companies and governments
  - Strategic advise
  - Financial support to nurture birth phase → 200.000€

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Business Plan Case 5: ALTERNATIVE NUTRITION

(2014 Edition)

Alternative Nutrition's goal is simple: Improve health using natural nutrition. They approach the age-old saying "you are what you eat" and the subsequent current planetary problem via a dual perspective by using expert, scientifically proven, dietary coaching and local natural foods. By giving people a customized evaluation, they will be able to recommend what kind of local and natural food they should eat in order to enjoy healthier lives.

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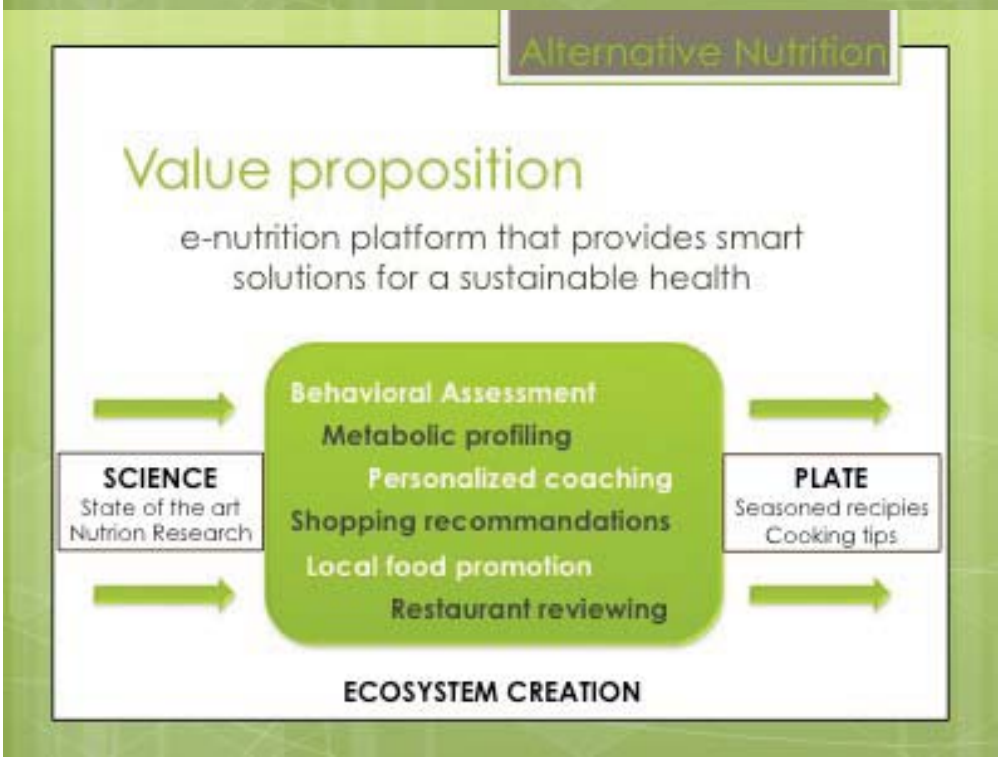

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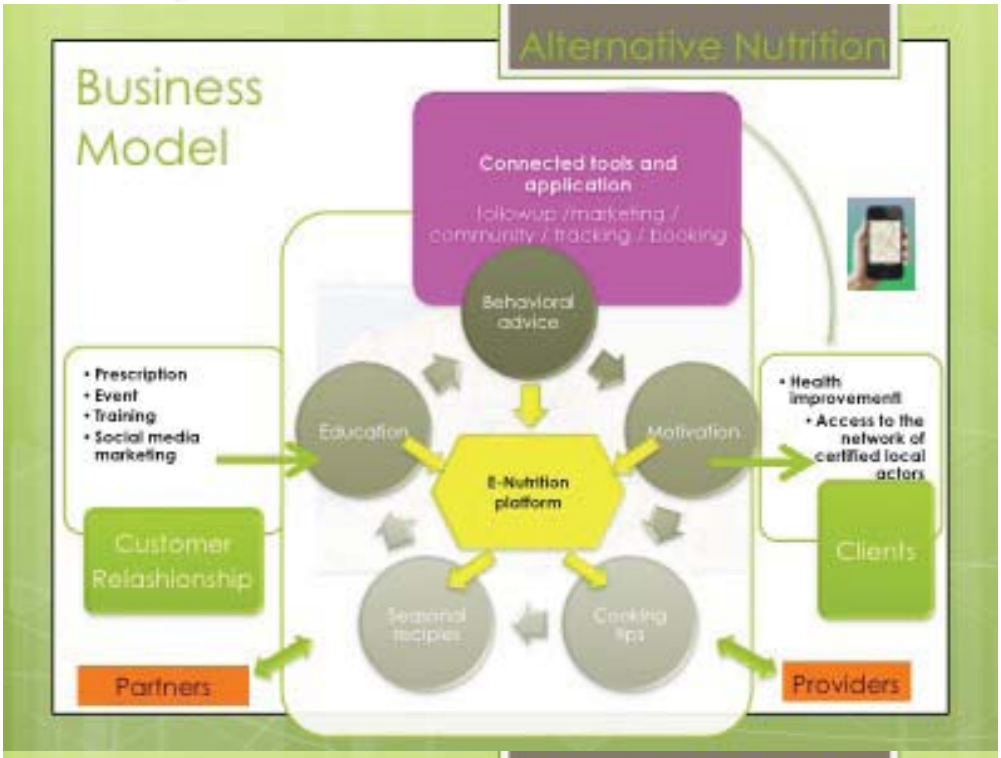

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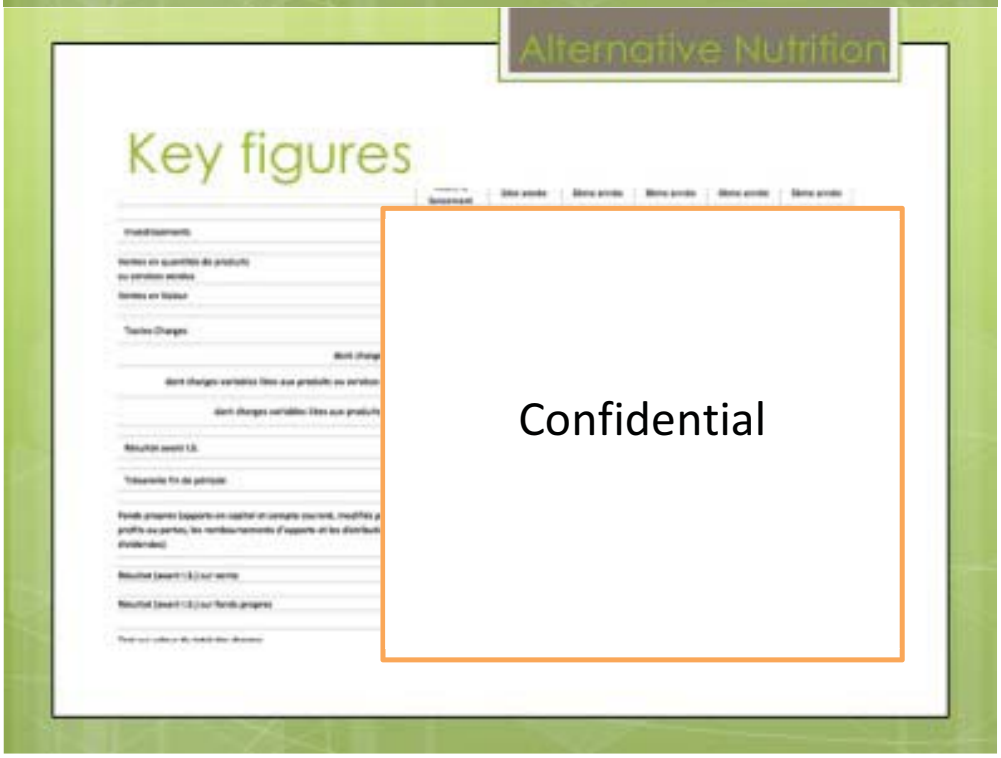

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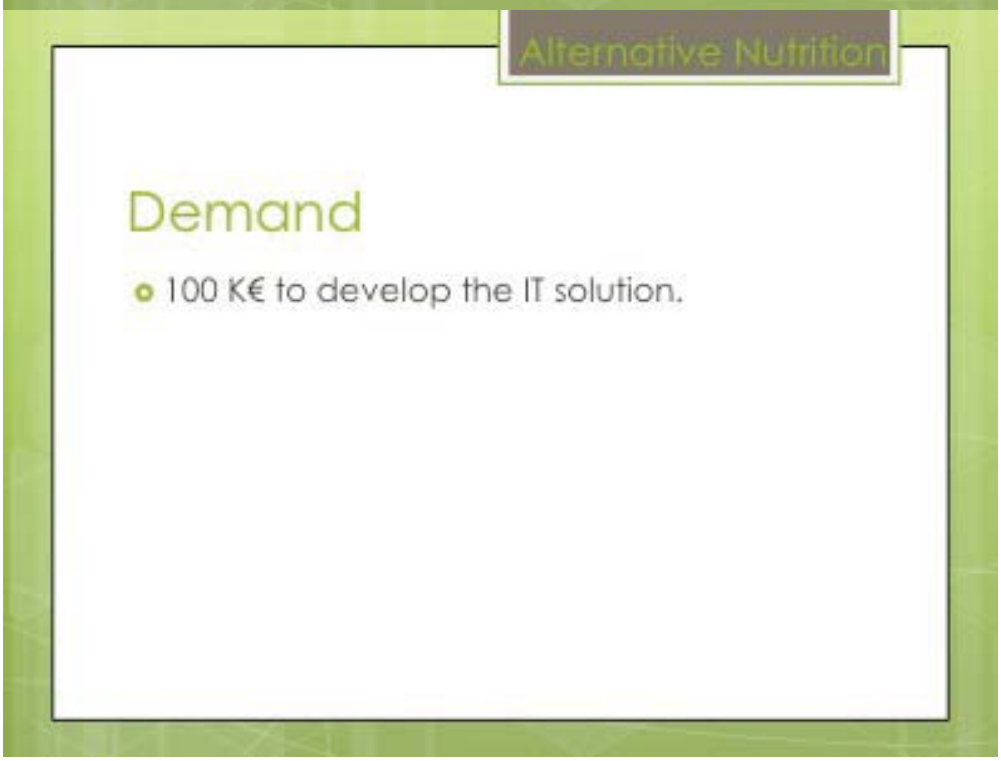


Health-2-Market has received funding from the European Union's Seventh Programme for research, technological development and demonstration under Grant Agreement No 305532

Business Plan Case 6: NODUS

(2014 Edition)

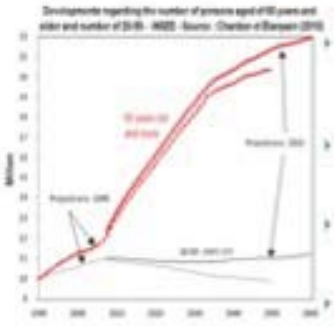
NODus addresses the problem of the growing amount of elderly people in the Western World who are unable to afford or find a place in retirement homes. NODus commits to enable any elderly person to stay safely in their home. Using smart home automations, non-invasive disruptive technologies and predictive algorithm, NODus learns from the person's habits, monitors real-time behaviors and anticipates risks.

Health-2-Market has received funding from the European Union's Seventh Programme for research, technological development and demonstration under Grant Agreement No 305532

Vision/Mission

- **NODus** commits to enable any elderly person to stay ageing in their home environment in full confidence and safety.
- Using smart domotics, non invasive disruptive technologies and predictive algorithm, **NODus** system learns from the person's habits, monitors realtime behaviors and anticipates risks.

Business Opportunities



EU faces a crucial social and unprecendent demographic change.

- In 2020 , 20 Millions individuals older than 65 in Europe, 80% wishing to stay ageing in their familiar home environment
- 26% are taken care by a relative, which represents strong responsibility and heavy commitment
- Meanwhile, the community faces a dramatic lack of available rooms in specialized retiring residences.
- Between 2010 and 2060 total government spending on pensions, healthcare, unemployment and education will increase by almost 20 %, while expenditures for long-term care will double.

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Solution/Offer

NODus system offers state of the art technologies:

- Innovative [redacted] Sensors
- [redacted]
- [redacted] and
- installation

Value proposition/ NODus Customer Benefits

For Individuals	• Keeping elderly people longer in their familiar environment safely, develop confidence & Wellbeing • Self functionning alert system in case of behavior change or real emergencies • Reassure users and their community by a secure life monitoring and continuous discrete care
For Heathcare organisations	• Improve intervention efficiency and productivity of personnal assistant organisms and heathcare firms • Alternative solution to the dramatic lack of rooms in elderly residences & specialized personal • Reduce heathcare expenditure related to domestic accidents of these vulnerable people living alone
For Authorities	• Anticipate health related risks (undernourishement, medical treatment omission, sadness, depression, unhealthy lifestyle… & falls) • Social security budget reduction in the highest expenses segment [60-85]

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Targeted market

NODus customers Base

Individuals	Healthcare organizations	Communities	Future segments To be explored
· End users [65-85] · Families* · Relatives* *[baby boomers & X generation]	· Home & Social care Associations · Elderly people help firms & private residences	· Territorial collectivities · Regional, National & EU Administrations	· Prisons · Banks · Nurseries

Phase 1 Exploration	Phase 2 Deploiement	Phase 3 Exploitation
Local test - 06	France - Région PACA	Autres Régions
Milieu urbain	Villes, Villages, Campagnes	Autres Pays

Competition

Since 2008, more than 200 concepts in the world aiming the better living of elederly are being studied. **NONE approaches *NODus***

NATIONAL:

- Gerhome (Sophia Antipolis, France) developed since 2007, mixes camera and "old" generation movement sensors information analysis
- Senior Adom (Balto project) focus on fall alert
- Catharis (IRLNX Grenoble) detect humans and animals,expensive thermal sensor, and lack of the predictive aspect.

INTERNATIONAL:

- MIT, Intel, Philips, Honeywell ("HomMed"), IBM ("Personal Care Connect"), Rosetta smart functions using video surveillance,
- Myguardian wearable devices,
- Hera3 (TV interactive, Alcatel Gmbh industrial partner),
- Nitics4 (Algorithm to find lost objects, Siemens Romania partner),
- Sonopa5 (habits analysis without outside communication tool)...

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Simplified Business Model

Go to market strategy

- FantasTIC SALES FORCE [Regional-National-EU-INT'L]
- ONLINE Direct Web Sales & support
- Dedicated Trade show
- INSTALLATION & MAINTENANCE contracts
- PRIVATE firms
- PUBLIC organisms
- STATE Tenders
- « Horse Troyes » Partners alliances (Insurances, Banks, IT sector, Building administration OPAM, Security firms, CNR Santé, Eurobiomed…)
- LICENCING / WHITE branding
- New Applications & Market Diversification (monitor other risks group)

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The Team

Co-founder of FantastIC Sourcing, **Mr Joel BERNIER** is NODus architect. 7 years managing an elderly residences, pioneer of Linux in France back in 1999, his company was sold to RED HAT USA. Endurance, tenacity,resourceful, bold, confident,initiative taker, pragmatic, well on earth, motivated, respectful of its engagements are some of his qualities.

James NICOLAÏ, Bachelor in Business Administration, graduated in 1995 (IGS Group). International business and Marketing, 1997-1999 ONYX (Veolia Environment), Madrid, Market intelligence investigations to answer public tenders.
2000 – 2003 Assistant General Manager, food industry, (Raviolis Perrin, Sophia Antipolis, Co-Founder of Fantastic Sourcing in 2004, Marketing and Business development Manager

Two positions will be created to start up:
R&D engineer in embedded computing
And Engineering Embedded

FantasTIC Sourcing, ISO9001:2008 is serving:

Aerospace (Thales, SYDERAL, éolane group), **Automation** (Schneider Electric), **Energy** (SPIE Nucléaire), **Transport** (Alstom, Rangsons), **Automotive** (Magneti Marelli, Huber AG, Maxima Technologies), **Medical** (Sedecal, Skanray, Larsen & Tubro), **Mobility** (Mobile Device Ingéniérie), **Photonics** (Spi Lasers, TURCK Duotec), **Telecom** (Sagemcom), **Wireless** (Vestel Digital, ALCOMA, SATIMO). Dedicated to the industry worldwide

History of the project

FantasTIC Sourcing R&D department has been driving since 2008 with its application engineers and students various projects, own products development (DyDomo, VOIP, Alarm system, Smoke detection, Infrared camera) and reports that led to shape *NODus* concept.

Recent major technological innovations in wireless connected smart objects permit to realize today what was costly and difficult to emplement yesterday.

The *NODus* project responds to some of the EU priority societal challenges, related to the demographic change, health, well-being and the creation of an French industrial offer based on research & innovation using emerging technologies that will be able to embrace the world, serve Mankind and bring utility while doing business.

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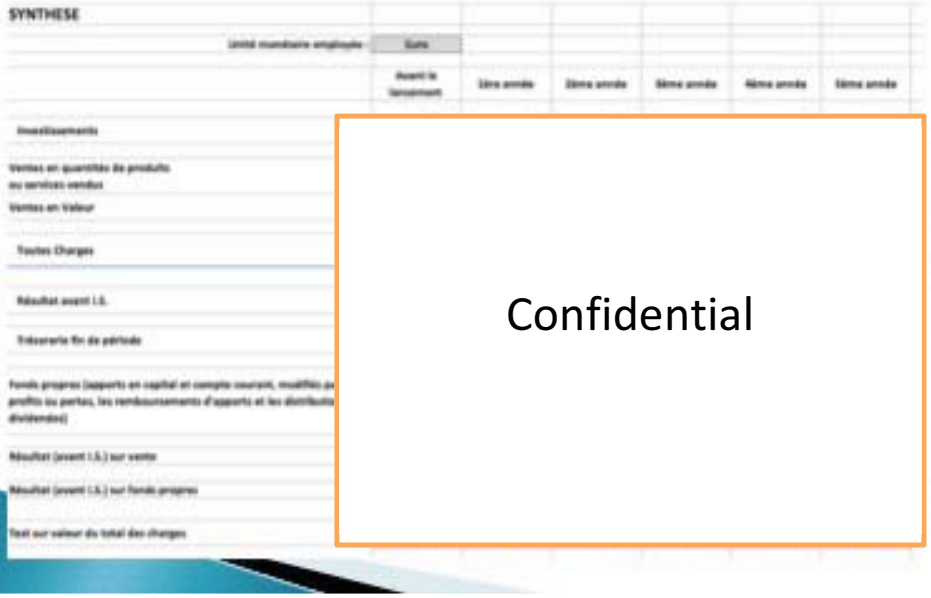
The next 18 months

Key figures



Confidential

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Risks

- International Competitors currently developping solution
- Technological risk (delay in Algorithm development, Sensors delivery)
- Financial risk
- Market readiness

Demand

- Funding the specific development of *NODus* algorithm (applied Artificial Inteligence)
- Funding 10 pre-series
- Teaming with French firm/Opinion leader
- Trust & support a Fantastic initiative !

Need for 70K € for product development finalisation:
- Algorithm engineer developper
- 10 pre-serie NODus systems for field test

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Business Plan Case 7: BioLAB

(2015 Edition)

BioLAB is a startup aiming to preserve costal environments by quickly detecting harmful cyanobacteria using infrared cameras and innovative software combined with drone technology. Unlike current solutions that offer only narrow analyses of contaminated regions, BioLAB provides a broader one thanks to drone technology. Furthermore, the real added value of BioLAB is its ability to preventatively scan regions before cyanobacteria epidemics occur thereby allowing authorities to take adequate measures faster.

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Health 2 Market

FROM HEALTH RESEARCH TO BUSINESS

BioLAB

Business Opportunity

Impact on **public health**

HUGE **economic** impact

(23% of water masses in Spain above WHO levels, 50% in Germany and Netherlands)

L. Carvalho *et al., Journal of Applied Ecology, 2013, 50 (2): 315*

EU directive 2006/7/EC

"appropriate Cyanobacterial monitoring shall be carried out to enable timely identification of health risks"

*BUT current technology too **SLOW***

BioLAB

www.health2market.eu

Health-2-Market has received funding from the European Union's Seventh Programme for research, technological development and demonstration under Grant Agreement No 305532

Our Solution

Infra-red thermal cameras with innovative software on drones scan large areas and quickly detect harmful blooms

Early reporting to appropriate stakeholders allow for intervention

Health-2-Market has received funding from the European Union's Seventh Programme for research, technological development and demonstration under Grant Agreement No 305532

Our value proposition

Large scale monitoring of bodies of water

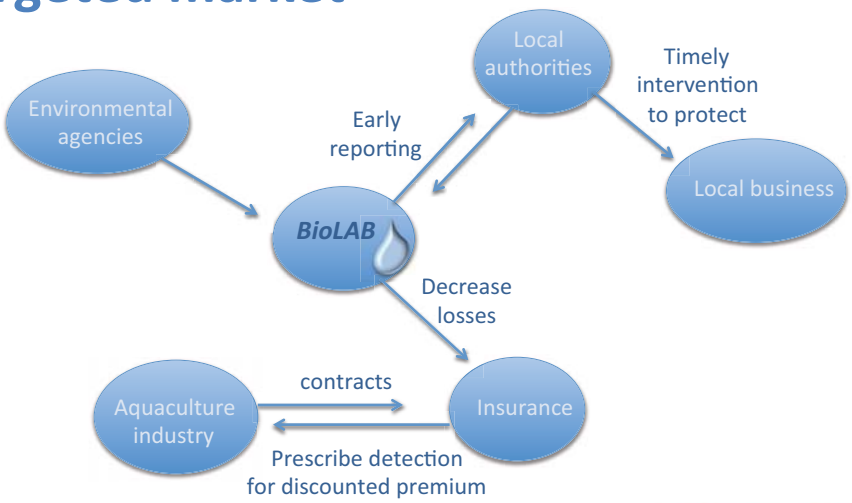
Early detection, risk assessment and communication to stakeholders

~ Saves lives and money ~

Risk evaluation for seafood producers

Health-2-Market has received funding from the European Union's Seventh Programme for research, technological development and demonstration under Grant Agreement No 305532

Targeted market



Competition

Environmental agencies now contract laboratories for water sampling and biomolecular assays

~ expensive
~ time consuming
~ only very small areas represented

Campain COST	15000,00 €	10000,00 €
Result timing	Seven working days	One day

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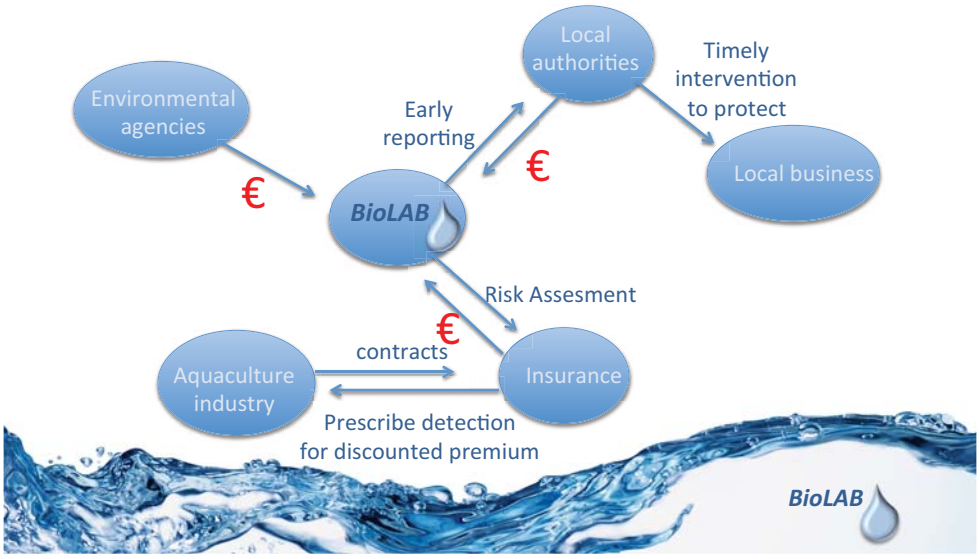
Simplified business model

Costs ~ cameras, drones, pilots, data analysis and staff ~



Go to Market Strategy

Sales Strategy

- Proof of concept pilot project in Basilicata (already financed)
- Present BioLAB at relevant workshops and conferences
- Local authorities (emphasize GROUP contracts because coastal provinces benefit only if adjacent province also monitors!!!)
- scan public tender

Communication Strategy

- Meet ANPA and public stakeholders
- One day workshop in the Frame of the annual CyanoCost Meeting
- Agreement with Legambiente, WWF etc

Development strategy

- Expansion to Italy
- Expansion to EU countries with a big aquaculture industry and an history of cyanobacterial blooms

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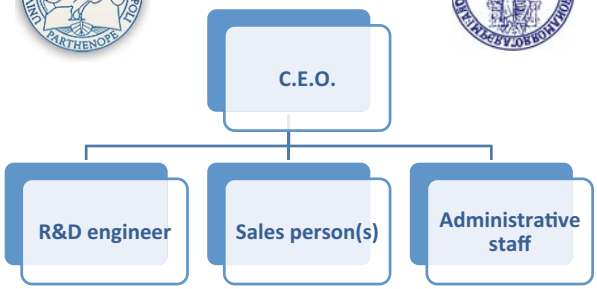
Health 2 Market

FROM HEALTH RESEARCH TO BUSINESS

Our Team



Partners

Dipartimento di Farmacia Università degli Studi di Napoli Federico II (Prof. Valeria Costantino)

Dipartimento di Scienze Ambientali Università Parthenope (Prof. Massimiliano Lega)

UNIBAS Dipartimento di Scienze

The BioLab Story

- Invited Speaker In 2014 annual CYANOCOST in Budapest
- Qatar University meeting and sampling 2014
- Sampling in Seattle (U.S.A.) 2014
- Sampling In Jeddah, Napoli and Potenza 2015
- Cooperation with Parthenope that work in environmental detection in collaboration with coastal law enforcement 2015
- Funded By Regione Basilicata for monitor deep and shallow water 2015

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The next 18 months

Start Up

Development of Sales Strategy (Goal: 20 contracts)

Dissemination/Communication

- Conferences
  - Water Innovation Europe 2015 - Brussels Water Conference 2015
  - World Water Congress XV Edinburgh
- Workshops
- One to one meetings
- Contact researchers in the field (screen literature)

BioLab BP Synthesis

Investments

Sales in quantity of products or services sold

Sales in value

Total costs

Including fixed cos

Including variable costs of products or services sol

Including variable costs of products in sto

Profit before income tax

Cash at end of period

Return (before income tax) On Sales

Confidential

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The demand

We require 100,000 euros

In return, we offer 50% return on investment by the 4th year

The risks

Local Government budget crisis….

BUT ….

legal obligation by EU directive!!

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Business Plan Case 8: JUMPO

(2015 Edition)

Jumpo is a startup that aims to improve people's health by encouraging sustained physical activity. Seeing the large amount of cancelation of gym subscribers, Jumpo will propose a smart and customized high-tech and wearable system which tracks movement via wearable wireless sensors and provides real-time feedback. This will not only allow to increase people's health but also gym's retention rate.

JUMPO

Sport engagement

Our vision:

«One day every person could use wearable technology as virtual personal coach for fitness, health or assistance»

Our mission:

We want to be the reference of technology solutions for body movement detection aiming at increasing motivation and engagement in physical activity

Giuseppe Cavallo, CEO
Tel: +39-320-4822-759
Email: g.cavallo@jumpo.it
Skype: peppecavallo

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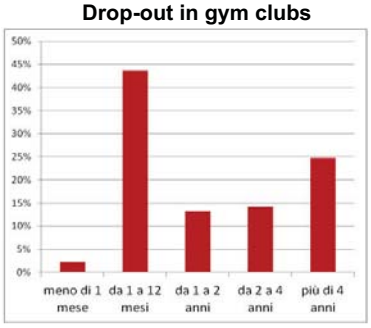
Business opportunity

- 44% of gym users cancel their subscription after 1 month (within 1 year)
- The top reason of drop-outs is lack of quick evident results (no motivation)
- A 2% increase in retention can deliver a 20% increase in profits

From research from Body Training Sytem, 2010

Drop-out in gym clubs

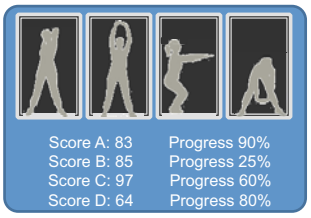


Solution/Offer

JUMPO is a smart and customized **high-tech** and **wearable system** which track movements of the body via wearable wireless sensors and provide you a **realtime feedback** on a screen

Main features:

- Wearable
- Movement reconstruction
- Quantitative data collection
- Realtime feedback
- Progress tracking
- Adaptive profile
- Group sessions
- Portable
- Small and lightweight



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Value Proposition

Gym clubs

- Retain customers, increase offer and profits

Users

- Reach goals, tracking your day by day progress and increasing motivation and engagement; enjoy a totally new fitness experience

Trainers

- Catch new users with a totally new and engaging technology; create tailored workouts to users and monitor their performances

Targeted market

CONTINENT	Total industry revenues (USD)	TOTAL # OF CLUBS	TOTAL # OF MEMBERS	REVENUE/ MEMBER
United Kindom	$5.551.053.350	5.885	7.400.000	$750
Spain	$5.035.570.000	5.800	7.980.000	$631
Germany	$5.207.839.500	6.703	7.900.000	$659
Italy	$3.721.021.200	7.500	5.200.000	$716
France	$3.179.087.856	2.940	4.000.000	$795

[International Health, Raquet & Sportclubs Association, 2013]

entring the Italian market

First 4 companies have 7% of the market
11 Million Italians are willing to pay up to 1,2k€/yr
[Il Sole 24 Ore, 2012 – Anif Eurowellness, 2013]

OUR CUSTOMERS

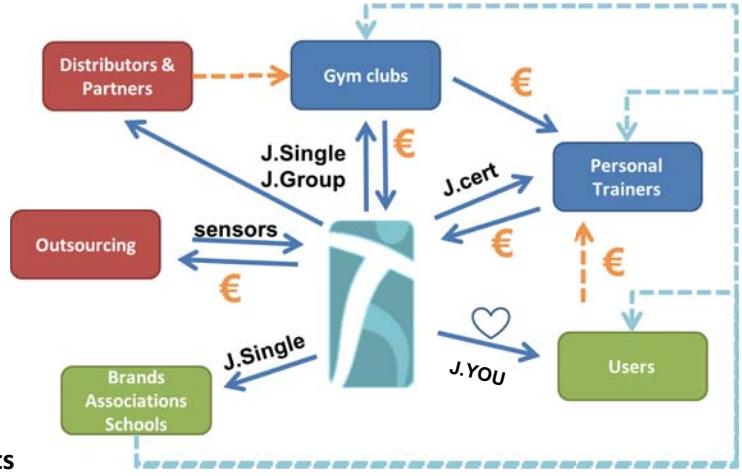
- Gym clubs and sport centers
- Personal Trainers and Coaches

Health-2-Market has received funding from the European Union's Seventh Programme for research, technological development and demonstration under Grant Agreement No 305532

Competitors

Company	Complete movement reconstruction	Track progress	Gamification	Online profiling	Group session	Realtime feedback
Polar	✗	✓	✓	✗	✓	✓
Preva	✗	✓	✗	✓	✗	✓
Exergame fitness	✗	✓	✓	✓	✓	✗
Digifit	✗	✓	✗	✗	✗	✗
Fitocracy	✗	✓	✓	✓	✗	✗
Dacadoo	✗	✗	✗	✓	✗	✗
Jumpo	✓	✓	✓	✓	✓	✓

Simplified business model



Products

J.Single: subscription fee (1.2k€ /yr)
J.Group: usage fee (20€/lesson)
J.YOU: free –user profile
J.cert: TBD – Certification for trainers
J.Adv: TBD – Advertising
J.API: free - Developers

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Go-to-market strategy

Development

- Partner with gym clubs and professional trainers for content development

Promotion

- Partner with industry suppliers (Technogym, LPG, ecc.)
- Offer technical courses to trainer schools and associations
- Develop our own sales network
- Indirect values to users (word-of-mouth)

Distribution

- Contract specialized distributors

The team

Giuseppe Cavallo, PhD
CEO, Business Developer
5+ yrs in Business Dvpt
in Medical Industy

Domenico Formica, PhD
CTO, Electronic Designer
10+ yrs mechatronic design

Fabrizio Taffoni, PhD
CSO, Biomechanical Expert
8+ yrs biomechanical research

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Health 2 Market — FROM HEALTH RESEARCH TO BUSINESS

The history of the project

- **ACHIEVEMENT**

Full working hardware prototype

- **AWARDS**

SMART & START — Winner "Invitalia – Smart&Start"

MIND THE BRIDGE — Winner "Mind the Bridge"

EIT ICT Labs IDEA CHALLENGE — Finalist "EIT ICT Labs – Idea Challenge"

The next 18 months

IPR

M1 — **m6** - Patent submission

R&D

M2 — **m8** – End of software development (**J.Single**)

Sales

M3 — **m10** - First **J.Single** contract

Marketing

M4 — **m12** – Launch on the market (i.e. Eurowellness)

Health-2-Market has received funding from the European Union's Seventh Programme for research, technological development and demonstration under Grant Agreement No 305532

Key figures

Investments	
Sales in quantity of products or services sold	
Sales in value	
Total costs	
Including fixed costs	
Including variable costs of products or services sold	
Including variable costs of products in stock	
Profit before income tax	
Cash at end of period	
Return (before income tax) On Sales	

Confidential

Risks

- **Acceptation by the market**
  - –There are other markets that can be targeted with the same technology
- **Human aspects (need for high quality people)**
  - –Hire international resources
- **Financial risks (lack)**
  - –Possibility to crowdfunding campaign

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Demand

- **Financial resources**
  - round I 90k€ for:
    - end of development of J.Single software
    - contract top level fitness professionals for content development
  - round II 250k€ for:
    - market development
    - development of J.Group and J.Trainer
- **Network resources**
  - contacts with main fitness industry players
    - Companies (Technogym, LPG, Panatta, ecc.)
    - Associations (Eurowellness,IHRSA, ecc.)
    - Distribution channels (Decathlon, Legea, ecc.)

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Business Plan Case 9: SPEAKY

(2015 Edition)

Speaky is an Italian company with over 10 years of experience in the field of facilitating communication the blind. They offer a fully integrated system that aims to allow blind people who are not technologically prone to use a personal computer through full speech recognition (speech synthesis and recognition). The company is now aiming to develop abroad and wanted to gain some expertise as to how to pitch to potential investors.

Speaky

Easy Personal Computer for Blind

Fabrizio Giacomelli and Paolo Bertuzzi

Health-2-Market has received funding from the European Union's Seventh Programme for research, technological development and demonstration under Grant Agreement No 305532

1 Vision/Mission

- Vision
  - To make blind and visually impared people able to acces to the digital world, enabling their fully INCLUSION in the modern world

- Mission
  - We develop and sell innovative and enabling solutions to make our Customers able to interact to the digital world in a natural way, simply by speaking, so without the need of learning computer skills

2 Business Opportunities

- Blind and visually impaired people are 5% of UE population.

- Blind and visually impared people without computer skills cannot access to the digital world. Those are about 50% of blind / visually impaired.

- Thus in UE there are about 12,5 millions persons for whom is not possible at all to partecipate to the modern digital world

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3 Solution / Offer

- Speaky: patented enabling technogy platform, solves the unsatisfied problem of digital access of blind without computer skills
- Developed with and validated by Italian Union of the Blind (UICI), is composed by a PC and several applications/services
- Current version is with TV, Audiobooks, Newspapers, Scanner, Screen Reader, Dictionary and translator, Screen Magnifier

4 Value Proposition / Customer Benefits

It is the first personal computer fully speech interactive with the user, designed for not computer skilled blind and viasually impared people

Easy to use: the user speaks to the Speaky remote control and the Speaky platform speaks to him/her, providing the content/services requested

Being Speaky'goal an important social/institutional goal, public health care in UE refund the cost for the Customer

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5 Targeted Market

- Blind and visually impared people without ICT skills which want to access in a simply way to digital world
- 2 millions persons in Italy
- First domestic target: 1.250 users in 24 months, thus 0,06%

mediavoice Speaky

6 Competition

Speaky is the first solution in its niche: fully speech interaction systems for blind which do not require computer skills.

Some of our 'partial' competitors:

- http://www.oceanbluesoftware.com

solution with speech sinthesys only, without speech recognition

- http://www.winguido.it

solution needing user computer skills

mediavoice Speaky

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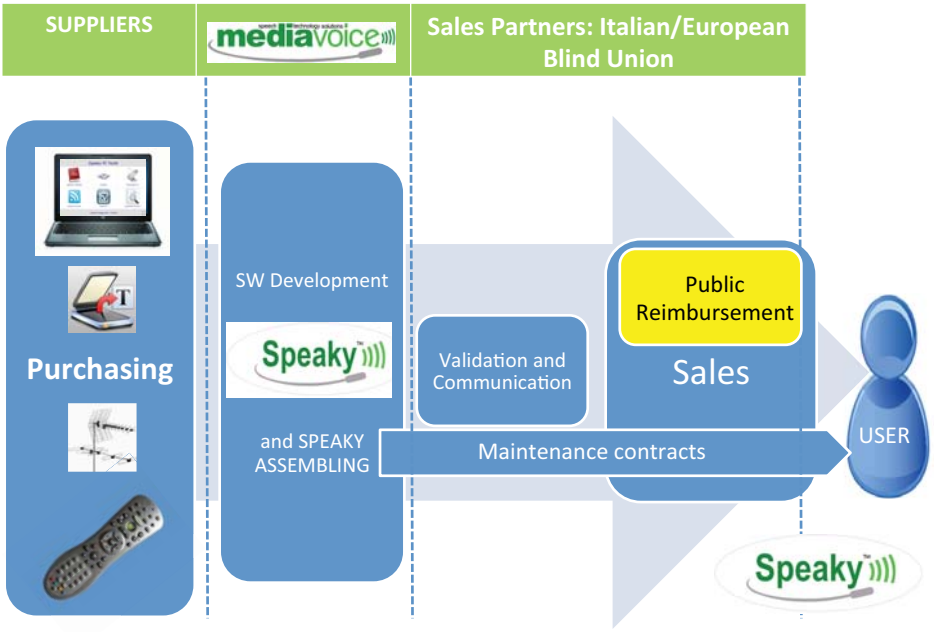
7 Simplified Business Model



8 Go to market strategy

- **Partnership, Communication and sales strategy**
  - UICI, Mediavoice partner, enables Mediavoice to call UICI subscribers
  - Final user can try the solution in any regional UICI center
  - The user can get the solution both paying directly to UICI either using the Helth Public Sector payment
- **Development strategy**
  - National market: we select Optics Shops and Pharmacies
  - International Market: we'll replicate the same business model by a partnership with European Blind Association (to which UICI belongs), starting from Spain, France, Great Britain and Germany

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9 The Team

- Fabrizio Giacomelli, CEO, graduated in computer engineering and in philosophy, is Microsoft Certified Systems Engineer, founded many companies working in the HCI field in which he holds 2 int.l patents
- Francesco Danza, CFO, graduated in physics, he has been financial responsible in large companies before to join Mediavoice.
- Nicolamaria Manes, CTO, graduated in computer science, is a senior developer in large companies with 20 years experience, he has also been Software Development Professor at University of Molise.

10 History of the project

- 2000: Mediavoice was born by 2 founders, now 11 shareholders (more than employees: 9!)
- 2001 was awarded by FIAT Group with the «best start up Award» between 400 young companies
- 2004 got first international patent
- 2007: Mediavoice and UICI decided to work joined to develop new solutions for blind people
- 2013: Speaky first version, without TV and Scanner
- 2015: Speaky Acutattile prototype ended, after a 7 milions € project funded with 11 partners by Italian Minister of Development
- 2015: Speaky 2.0

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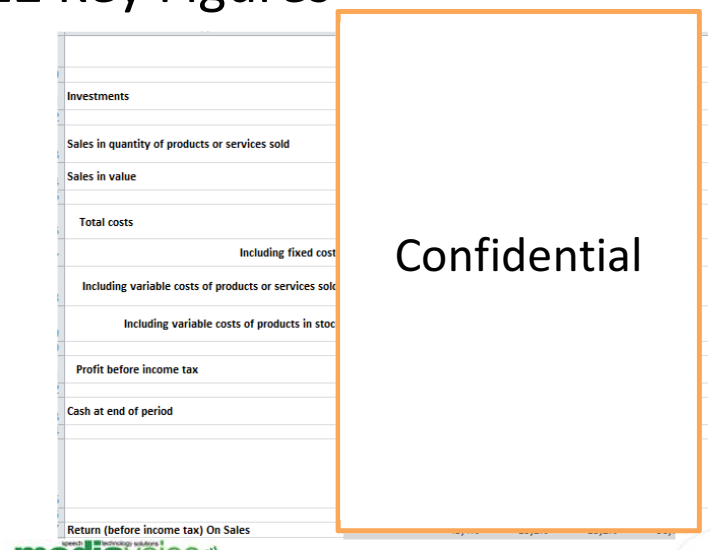
11 The next 18 months

- September 2015: Speaky 3.0
  - Voice mail
  - Facebook, Twitter (Social)
  - Dictation
- June 2016
  - First international market: Spain
  - Speaky Acutattile: a new patented haptic device for blind which becomes a new Speaky module
- January 2017
  - Second international market: Germany

12 Key Figures



Confidential

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13 Risks

- Competitor: Large company which may work in this niche
  - Continuous investment in intellectual property
- Regulations: Different kind of law systems concerning reimbursement of the Speaky cost in international markets
  - Before facing a new market country, a deep health public system analisys is needed

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14 Demand

- Capital contribution: 1.000.000 €
  - 500 k€ in 2015
  - 500 k€ in 2016

- Commercial support for Internationalization (UE and worldwide) to find local:
  - distributors
  - service developer
  - after sales activities provider

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