Impact Report for Europe

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The *ASTP Impact Report for Europe* showcases how technology transfer makes the world a better place.

Materials and support

The *ASTP Impact Report for Europe* is available in both print and electronic formats. Visit the ASTP website or headquarters for more details.

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About ASTP

The initiative of a multinational group of professionals to meet and share experiences on a regular basis resulted in the establishment of the non-profit Association of European Science and Technology Transfer Professionals. ASTP is practitioners and members-focused and is growing rapidly.

The association consists of more than 600 members, covering 41 European countries. The majority of its members are technology transfer professionals at public knowledge institutions. The ASTP wishes to professionalise and promote technology and knowledge transfer between the European science base and industry.

I wish to thank Ivan Dvorak, Fermin Lucena, Dirk Dantz, Primoz Kunaver, Mads Skjelstad and Richard Stokes for their work in reading through and scoring all the stories that were entered under the call. I also thank Olivier Lescroart from KU Leuven for teaming up with ASTP and making this publication possible and for his critical reading of the stories.

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Koen Verhoef, PhD, RTTP

As Vice President of the Association of European Science and Technology Transfer Professionals (ASTP), I am very proud to present to you the first edition of what I hope will become a regular ASTP publication: *the ASTP Impact Report for Europe*.

With this publication, we wish to highlight outstanding examples of products that have been successfully introduced in the marketplace and were made possible by research results obtained at a European public research institute. After all, helping make such successes possible is what the technology transfer profession is – and should be – all about.

This *Impact Report for Europe* also serves to underscore the importance of investment in research and innovation as it has the potential to dramatically alter the lives of people for the better.

The stories that you will read in this report have been selected after a call was put out by ASTP in late 2011 for submission of success stories. The call was distributed among our members and the national networks for Knowledge and Technology Transfer in Europe. We were thrilled to receive almost 50 entries in response to the call.

The stories were scored by a jury consisting – in good ASTP tradition – of volunteer members.

Four parameters were evaluated: (1) major step (i.e. how revolutionary is the product: disruptive versus incremental innovation), (2) economic impact, (3) societal impact and (4) whether the technology transfer office was instrumental in making the story a success.

The scores for each of the parameters were added up for each entry and the stories were subsequently ranked from highest to lowest total score. The societal impact parameter appeared to strongly favor health-related innovations over non-health-related stories so we reduced the relative weighting of this parameter in the overall score by 50%. The 14 highest-scoring stories were selected for inclusion in this first report.

I hope you will enjoy reading the stories as much as I have.

Koen Verhoef, PhD, RTTP
Vice President, ASTP

Europe has excellent universities and research institutions where state-of-the-art knowledge is available. In order to strengthen Europe's competitiveness further and create more jobs, we need to seize every opportunity to unlock knowledge, to use our research, to encourage innovators as well as entrepreneurs and develop innovative products and services. Continuous investments in R&D are therefore necessary and European universities and research institutions will need to develop this capacity further to share key knowledge and knowhow with those best placed to take it to the marketplace.

In fact, the EU's Framework Programmes for research have systematically supported knowledge and technology sharing since the early 1980s: the 7th Framework Programme is currently supporting over 4000 collaborative research projects. Over the years, increasing emphasis has also been placed on training including the development of business-oriented skills. The recently launched calls for proposals under the current FP7 Framework Programme earmarks €30m for European Industrial Doctorates, over €80m for Industry Academia Partnerships and Pathway and €10m for the new Proof of Concept Grants administered by the European Research Council to allow their existing grant holders to test potentially marketable concepts. The Commission is also promoting a set of "Principles for Innovative Doctoral Training" which recommends including exposure to industry and employment in other relevant sectors. But more must still be done to make it easier for industry and commerce to access the knowledge and knowhow that they need to remain competitive.

This is why the Commission's proposal for Horizon 2020, the next generation programme for research and innovation (2014-2020), will further support this approach. The Europe 2020 Strategy for smart, sustainable and inclusive growth, to pull Europe out of the current economic downturn, highlights the importance of a coherent approach towards research and innovation. Horizon 2020 will, therefore, focus on turning scientific breakthroughs into innovative products and services that will create new business opportunities. It will provide increased support for frontier research, from which so many unforeseen spin-offs and innovations arise and will concentrate collaborative research on key societal challenges that can be best tackled at the EU level such as better and cleaner transport, food and energy security, health and dealing with our ageing societies.

Participants in Horizon 2020 will benefit from greatly simplified and harmonised procedures that will reduce administrative overheads and allow for more flexibility in reclaiming direct costs. This will be of particular benefit to SMEs who will also benefit from grant support and debt and equity funding covering the whole innovation cycle.

The mission statement of the Association of European Science and Technology Transfer Professionals makes it clear that transfer is a two-way process between the European science base and industry: an exchange and sharing of experience. The examples highlighted in this book demonstrate that such cooperation leads to some really outstanding results.

Robert-Jan Smits,
General Director, DG Research and Innovation,
European Commission

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Sutent

Prolonging the life of cancer patients

For decades, research teams have been looking for ways to treat cancer. A pioneer in this field, Professor Axel Ullrich, developed Sutent, a drug that prolongs the lives of cancer patients by blocking the blood supply to the tumour. This drug originated in the laboratories of the Max Planck Institute and has become a blockbuster for Pfizer Oncology.

'The breakthrough is that Sutent is a drug for a disease that was not treatable before,' says Axel Ullrich, Director of the Department of Molecular Biology at the Max Planck Institute for Biochemistry in Martinsried, Germany. 'The approach is quite new: we have found a way to stop the tumour from growing by inhibiting the supply of blood, oxygen and nutrients that a fast growing tumour strongly depends on.'

- **Product:** Sunitinib (brand name Sutent), a cancer drug
- **Research institutes:** Max Planck Institute in Munich (Germany) and SUGEN
- **Marketed by:** Pfizer
- **On the market since:** 2006
- **Noteworthy:** New generation of cancer drug, delaying tumour growth

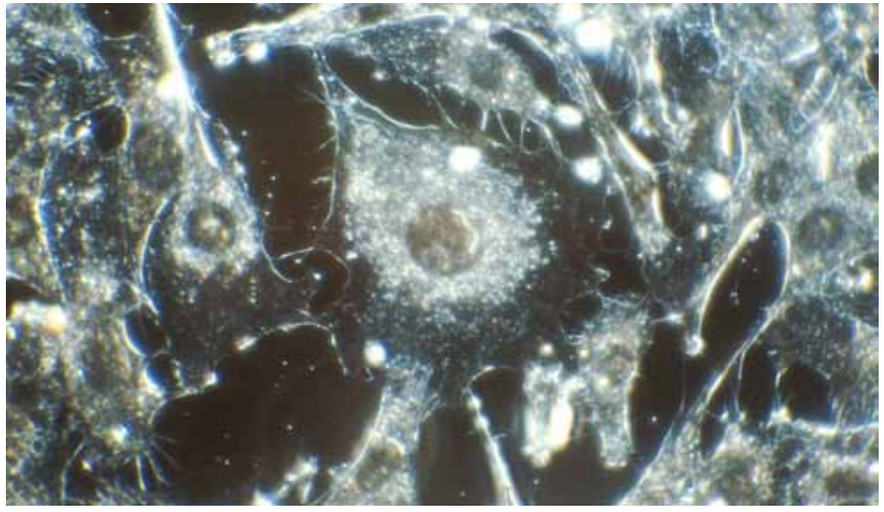
The active ingredient in Sutent is sunitinib, which leads to tumour shrinkage and therefore significantly delays tumour growth. Sunitinib shrinks the tumour by blocking the so-called tyrosine kinases which are enzymes that cancer cells need to grow and multiply. Due to this inhibition, sunitinib stops blood vessels from growing, reducing the supply of oxygen and nutrients to the tumour.
Sutent is now used daily by thousands of cancer patients. By using this drug, tumour growth is significantly delayed. It therefore improves their quality of life during the late phase of their disease. Unfortunately, like most present cancer medications, the drug is not able to completely cure the disease.
'A positive side is the fact that it works on several kinds of cancer,' Ullrich adds. The drug is indicated for patients suffering from advanced kidney cancer (advanced renal cell carcinoma or RCC), gastrointestinal stromal tumour (GIST, a rare cancer of the stomach bowel or oesophagus) and pancreatic neuroendocrine tumours that have advanced too far for surgery. Sutent was the first cancer drug that was simultaneously approved for two different indications in 2006. 'At Pfizer, they continue to investigate the use of this drug for other types of cancer. That is how they found it could also be used for patients with pancreatic neuroendocrine cancer', Ullrich says.

Pioneering with molecular cancer targets

Many years before Sutent hit the markets, Axel Ullrich and his team were studying proteins involved in cancer. 'When we started out, we did not know what we would find. We were looking for specific locations on the cell surface that certain stimulants used as a binding site, so-called receptors. Receptors are proteins that transfer signals from the outside to the inside of the cell finally resulting in growth and division. What we did was to collect information about the function of each of these receptors, demonstrate their function in a cellular model and finally validate their role as being relevant for tumour growth. Due to our findings, the receptor with the most promising effect in the end was VEGFR-2 (Vascular Endothelial Growth Factor Receptor 2). This receptor controls the tumour making its own blood vessels,' Ullrich explained.

'Several millions of euros a year in license fees can be used for more fundamental research'

Back then, we thought that all molecular cancer targets had their own specific binding site and that these sites would be sufficiently different for us to be addressed by a therapeutic agent. Surprisingly, the result was that a whole series of different small molecules bound to our target receptor but most of them were also interacting with other related



blockade Sunitinib deprives the tumour of oxygen by inhibiting the development of blood vessels. (Photo by NCI)

receptors. Most importantly, we identified a number of these molecules that could block the growth stimulating function. VEGFR-2 was our candidate for further development, eventually leading to the compound sunitinib, the active ingredient of Sutent.'

SUGEN

The fundamental research was carried out at the Max Planck Institute of Biochemistry in Munich, Germany. In 1991 Ullrich decided to launch a spin-off company where this basic research could be carried on to the next level, translating the science to actual, clinical applications. He founded SUGEN in Redwood City, California with fellow researcher Joseph Schlesinger of New York University. The company name was derived from the initials of Schlesinger and Ullrich with the addition of 'gen' for genetics. Pharmacia took over SUGEN in 1999 and became part of Pfizer in 2003.

SUGEN went public in 1994 and first started trials with another compound. This compound did not show enough potential after early tests in cancer patients. SUGEN continued screening several different enzymes and came up with the compound SU11248 (sunitinib) in the end.

Before Pharmacia took over SUGEN, the company worked closely with the Max Planck Institute. 'The whole project came out of my laboratory. My research partner Birgit Millauer and I had a personal connection to the project. Once SUGEN was taken over, we had nothing to do with it anymore. Big companies often think they can do things themselves and I must admit, in this case, they were right,' says Ullrich.

Licences

Together with Heinrich Kuhn, the former Managing Director of Max Planck Innovation, Jörn Erselius (current Managing Director) was closely involved in the developments. 'We set up SUGEN in 1991 and negotiated the licence and collaboration agreement. I can tell you that this kept us busy for quite a long time, even after SUGEN was bought by Pharmacia. The basic patents are owned by the Max Planck Institute, where the technology was developed. The patent for the compound is now the property of Pfizer, which has a licence to these patents as well as to basic know-how. Today several millions of euros per year in license fees provide the Max Planck Institute with an income that can be used to conduct more fundamental research.' The institute is no longer directly involved with Sutent. 'Max Planck does the fundamental science but as soon as our findings are licensed and used to develop actual applications and products, we are out. That is not our role anymore.'

In the spotlight: A new generation of drugs

Birgit Millauer was Ullrich's research partner and worked with him identifying the protein targeted by Sutent, resulting in the inhibition of tumour growth. Today she is a partner in a law firm based in California, practicing biotechnology patent law. She remembers the excitement of those pioneer years. 'Looking back, I now realise the enormous impact of our research, leading to a new generation of cancer therapeutics. Because of its specific mode of action, depriving the tumour of oxygen by inhibiting the development of blood vessels, Sutent detracts less from quality of life than conventional cancer drugs. For instance, conventional cancer drugs attack every growing cell in the body, leading to numerous side effects, such as a harmless but visible one like the loss of hair. In contrast, Sutent targets only dividing endothelial cells, the cells that form blood vessels, thereby avoiding many of the side effects associated with traditional cancer therapeutics.'

quality Sunitinib is not a cure, but improves the quality of life for cancer patients by delaying tumour growth. (Photo by NCI)

Blockbuster

To get the financial means for developing Sutent, SUGEN collected $2m from small investors to set up shop. Biotechnology investor Stephen Evans-Freke handled the financial side of SUGEN and was able to attract more investors, including large companies to support the research. SUGEN proved to be a good investment, according to Ullrich. 'Sutent sells a billion dollars a year, which is pretty good for a drug,' he says. 'This drug turned out to be a real blockbuster for Pfizer. They have done very well. Although the number of diagnosed patients is increasing, sales are stabilising due to the fact that new cancer medications that have recently been approved for treating the same types of cancer are now available,' Erselius adds.

Translating science into clinical success

Ullrich enjoyed working with SUGEN. In his academic career, this was the first of five start-up companies he founded. Others are Axxima, U3 Pharma, Kinaxo and Blackfield. Another start-up where he was one of the leading scientists was Genentech in San Francisco, California, the very first biotechnology company in the world. Genentech was taken over by the Swiss pharmaceutical group Roche for billions of dollars. 'I worked at Genentech for ten years before going back to Germany to work at the Max Planck Institute. I learned how to translate science into applications in medicine. For most of my life, I have been working in translational science. To see how your own research leads to results in the clinic is very satisfying.'

Cochlear implants

Better speech recognition with cochlear implants

Cochlear implants greatly improve the quality of life for severely hearing-impaired people. However, understanding speech in noisy conditions remains a challenge. Scientists from the University of Leuven in Belgium and market leader Cochlear are developing software that improves signal processing in cochlear implants, enabling better speech recognition.

Many of us do not even think about it – but our natural ability to hear is rather remarkable. When we talk to friends in a noisy bar, with music and chattering in the background, we are able to filter out sounds that we need in order to understand the conversation and ignore the noise. When listening to an orchestra, we can recognise the sounds of many different musical instruments playing at the same time and appreciate the richness of their combined timbre. For people with hearing loss, this skill is not so natural. Even when they use a hearing aid or a cochlear implant (CI) – a hearing device placed surgically into the inner ear – the fine nuances of sound perception lie beyond their reach.

'Some major technological improvements have been made over the past decade,' says Professor Jan Wouters of the University of Leuven (KU Leuven). His aim is to improve the performance of the implants. 'The first generation of CIs merely allowed people to hear basic sounds and only in a quiet environment. Today's implants are much more sophisticated, even allowing people to have phone conversations. Nevertheless, improvements are still dearly needed,' he stresses. The quality of "artificial sound" is still not approaching that of natural sound and people with cochlear implants still face severe limitations.

- **Product:** Software to improve sound processing of cochlear implants, enabling better speech recognition
- **Research institute:** Departments of Experimental Otorhinolaryngology and Electrical Engineering, KU Leuven (Belgium)
- **Marketed by:** Cochlear (Australia)
- **On the market since:** cochlear implants since early 1980s; KU Leuven's technology incorporated since 2005
- **Noteworthy:** Cochlear is developing implants that receive their signals directly from TV or cell phones via bluetooth

KU LEUVEN

Electric signals

Together with market leader Cochlear, Wouters and his colleagues are developing software that improves the processing of sound signals that are transmitted to the inner ear. A cochlear implant, Wouters indicates, will help a person who has a functional auditory nerve but has a problem with the hair cells that convert sound vibrations into neural signals. These hair cells are found in the cochlea, the spiral-shaped space in the inner ear. The cochlear implant directly stimulates the auditory nerve, thereby bypassing the middle ear and hair cells. The electrodes receive their information wirelessly from a processor with microphones, worn behind the ear.

'In this process,' says Wouters, ' much of the sound information is lost. Speech and music are incredibly complex. Certain cues in those signals are lost during signal processing in standard cochlear implants.' That is why speech sounds rather metallic to a person using a cochlear implant, he elaborates and why much of the magic of music is 'lost in translation'. 'Our challenge is to design mathematical models that describe acoustic signals in as much detail as possible,' says Wouters, 'and to apply these models in software that turns acoustic information into electric signals.'

Sound coding

Wouters and his colleagues had already been collaborating with Philips Hearing Implants for many years when this division was taken over by Cochlear twelve years ago. Cochlear is an Australian company with a research and development department in Belgium. It is responsible for around 70% of the cochlear implant market worldwide. The two institutions are cooperating closely to the benefit of both, according to Bas van Dijk, Global Research Coordinator "sound coding" at Cochlear.

widely used An algorithm originating at the KU Leuven now serves 26,000 new cochlear implant recipients each year.

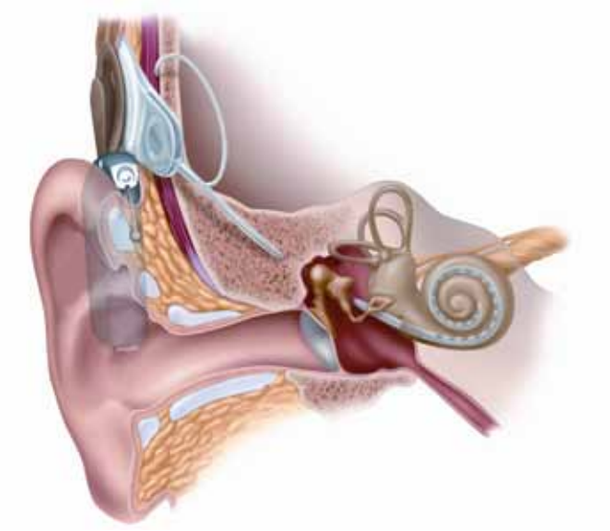
'The KU Leuven conducts its research at a much more fundamental level than a company would do,' he says. 'You never know which elements of the research will find their way into market applications but when they do, they lead to remarkable technological improvements.'

As an example, he names the main invention that originated at the KU Leuven which now serves 26,000 new cochlear implant recipients each year: a so-called beam-forming algorithm. This mathematical procedure selectively amplifies sounds coming from the direction in which the person is looking – which are likely to be the sounds that he or she wants to focus on. This is a major

improvement in everyday conversations. 'People who are using older systems can usually get an upgrade of the external part of their device,' says Van Dijk, 'which allows them to benefit from the new technology.' Worldwide, over 250,000 people are using Cochlear's devices and this number is increasing rapidly.
Wouters highlights another advantage of the collaboration between the KU Leuven and Cochlear. 'At the university, we bridge the gap between laboratory and clinic,' he says. 'First of all, due to our medical contacts here at the university, we are well aware of the relevant clinical questions. Secondly, once we have moved from mathematical models to signal processing to audiology, we need to test how a patient experiences these changes. We conduct so-called psychophysical tests with patients in our laboratory to establish which elements of signal transduction actually determine the quality of sound and the intelligibility of speech. Once we have tested these effects and adjusted the technology where needed, we can transfer it to the company to be further developed.'

Luxury position

Bruno Lambrecht, Legal Advisor at the KU Leuven, is the technology transfer officer involved in the collaboration. 'For the very first project, we negotiated the terms and conditions of the collaboration,' he says, 'and we have reused that frame for several subsequent projects which is somewhat of a luxury position.' This is possible, he adds, because the scientists have convincingly proven the value of their algorithm which creates a high level of mutual trust. 'This is absolutely crucial for any long-term collaboration.'
Cochlear, as Lambrecht explains, holds all patents and intellectual property rights associated with the shared inventions. 'A global market leader requires patent control in order to respond adequately to the market,' he explains. The company pays the university an agreed fee per shared project and a "fair compensation" when a concrete invention is applied in Cochlear's devices. In addition, the collaboration receives funding from the Flemish government because of its fundamental research component. 'Companies are usually not interested in fundamental research when outcomes are unclear. This is why the support from the Flemish government makes a difference. All parties benefit. We call it the "triple helix" – academia, business and government work together, paving the way for truly innovative technologies,' Lambrecht explains.



nerve stimulation A cochlear implant will help a person whose auditory hair cells do not convert sound vibrations into neural signals.

Children

Based on their main challenge of improving signal transduction, the KU Leuven and Cochlear are now collaborating in three-year projects that address separate areas of potential improvement.

> 'What we are doing touches directly upon people's quality of life'

'We continue to improve the suppression of background noise,' says Wouters, 'and are looking for ways to improve sound perception for people who use a cochlear implant on one side and an external hearing aid on the other.' Another ambition, as both Wouters and Van Dijk point out, is to develop objective ways to determine the correct settings for the device, for instance, in the case of children who are too young to describe what they are hearing. 'What we are doing touches directly upon people's quality of life. I have received many emails from patients all over the world, telling me how much better they can hear today. For me as a scientist, that is immensely satisfying,' Wouters says.

In the spotlight: Hearing loss

Hearing loss – also known as hearing impairment, or (partial) deafness – is quite common in the general population. An estimated 0.2 to 0.4% of babies are born hearing-impaired. Hearing loss can also occur later in life, because of ageing, exposure to noise, head trauma or disease. An estimated 20% of all adults experience some level of hearing loss and this percentage increases to 30-50% among people over 65.
Many hearing-impaired people benefit from conventional hearing aids that amplify sounds. However, if hair cells of the inner ear are lacking or damaged, these conventional hearing aids will not be helpful. Cochlear implants fill that gap. It directly stimulates the auditory nerve, thus bypassing hair cells. A variant is also available for people who lack a functional auditory nerve. This variant works much like a cochlear implant, only it transmits its electrical pulses directly to the auditory part of the brain itself.

one in five About 20% of all adults and 40% of senior citizens experience some level of hearing loss. (Photo by Terence McNally)

Mammaprint

Preventing unnecessary chemotherapy with Mammaprint

Up to half of all women suffering from breast cancer receive chemotherapy although they do not need it. Agendia's Mammaprint can reliably predict whether a tumour will return or not and thus, if a patient needs chemotherapy.

- **Product:** Mammaprint, a microarray breast cancer recurrence test
- **Research institute:** Netherlands Cancer Institute (The Netherlands)
- **Marketed by:** Agendia (The Netherlands/ United States)
- **On the market since:** 2004
- **Noteworthy:** The world's first diagnostic microarray test

Although medical science has improved over the years, cancer remains a terrible disease. It often requires demanding chemotherapy. This therapy is one of the most effective ways to treat cancer, despite the severe side effects it often causes. Yet, not all tumours have a malignant nature. Early-stage breast tumours, for instance, do not always require chemotherapy. Often, hormone therapy following removal of the tumour by surgery is enough to cure the disease. The crucial question remains: how does a doctor correctly identify such a tumour?

Presently, Amsterdam-based company Agendia sells Mammaprint, a molecular diagnostic test, based on microarray technology. With great certainty, the test classifies the prognosis of early stage breast tumours as good or bad, thus showing whether the tumour will ever return. If the risk of recurrence is high, chemotherapy will be required, but women with low-risk tumours can receive a less demanding therapy instead.

'Traditionally, we rely on a few coarse parameters to estimate the chance of a tumour's recurrence,' says internist-oncologist Peter Nieboer of the Wilhelmina Hospital in the Dutch city of Assen. Nieboer often requires Mammaprint for his patients. 'Even when traditional analysis shows low probability for a returning tumour, we are used to prescribe chemotherapy. This means that we unnecessarily treat a large group of women. By using Mammaprint, we can stop this unnecessary treatment.'

Good prognosis

Mammaprint is an invention of professor René Bernards and his colleague Laura van 't Veer of the Netherlands Cancer Institute at the Antoni van Leeuwenhoek hospital in Amsterdam. They both analysed the DNA in tumour cells in early-stage breast tumours and discovered differences in gene expression between tumours with a good prognosis and those with a bad prognosis. Bernards explains, 'The activity of its genes completely determines the behaviour of any type of cell. If you know the activity of all twenty thousand genes in a cell, you can understand the behaviour of that cell. A liver cell for instance, differs in its behaviour from a kidney cell. The pattern of gene activity in the liver cell thus differs from the pattern in the kidney cell. If you extrapolate this knowledge to cancer cells, you can assume that the gene activity in a tumour cell that does recur differs from the gene activity in a tumour cell that will not recur.'

Bernards and Van 't Veer analysed the activity of all genes in early stage breast tumours that they retrieved from the archives of the Netherlands Cancer Institute. The archive contained samples from breast tumours at the time of diagnosis. Moreover, Bernards and Van 't Veer retrieved patient data from the computer from the time of diagnosis until ten years later. Through this, both researchers knew if the tumours had returned or not. They found differences in gene expression between recurring and non-recurring tumours. These differences showed whether the tumour did or did not return.

This discovery paved the way for a molecular genetic test that differentiates early stage breast tumours in a group with low or high chance of recurrence. Bas van der Baan, Agendia's Vice President Clinical Affairs explains the success of Mammaprint using the results of a clinical study, 'Between 2004 and 2006, 427 women suffering from early stage breast cancer all received a Mammaprint test. Of all women whose tumour had a low risk of recurrence, 85% waived chemotherapy. Five years later, almost all women, 97% of them, lived free of cancer. In the group of women with breast tumour with high risk of recurrence, 80% chose to receive chemotherapy. Five years later, 91.2% of those women lived free

René Bernards

Laura van 't Veer

individual Mammaprint has paved the way for individual cancer therapy.

of cancer. Thanks to Mammaprint, chemotherapy can be used by women who really need it because our test showed that their tumour has a high risk of recurrence.'

'The use of Mammaprint can save €10,000 per patient'

Internist oncologist Nieboer agrees with Van der Baan. 'Now we can decrease the number of women who unnecessarily receive chemotherapy and just give it to women who really need it. Mammaprint enables us to use chemotherapy very effectively.' Mammaprint also has major implications for the costs of healthcare. A test costs almost €2,700 while chemotherapy costs about €13,000. So every time Mammaprint shows that a patient does not need chemotherapy, over €10,000 is saved.

Licence agreement

The development of Mammaprint started around year 2000 in the laboratories of the Netherlands Cancer Institute. Bernards and his colleagues received funds from the Dutch government and the charity Dutch Cancer Society. In 2003 Bernards and van 't Veer founded Agendia. They asked the British technology transfer company Cancer Research Technology to help. 'According to Dutch law, our employer, the Netherlands Cancer Institute owns the intellectual property and the patents of Mammaprint. So we had to negotiate the terms before setting-up Agendia and the use of our own invention with our own employer. We considered this quite awkward. Therefore, we asked Cancer Research Technology to hammer out a licence agreement for us,' Bernards explains of the process. Agendia was financed by venture capitalists at the beginning. It started with an initial financing of around €5.5m in 2003. Eight years later, it tried to go public at

Netherlands Cancer Institute Mammaprint was conceived in the laboratories of the Netherlands Cancer Institute.

Mammaprint

the Amsterdam Stock Exchange – a plan that it had to abandon due to market conditions. Shortly thereafter, Agendia raised €50m from private investors.
'We want Agendia to remain an independent company,' Van der Baan says of the future of Agendia. 'Because we know that Agendia is just at the beginning of its possibilities, we want to keep control of our growing company ourselves. We acquired a lot of expertise in the field of molecular diagnostics. Expertise that we use to develop other diagnostic tests.'

Intelligent process

Along with Mammaprint, Agendia, together with the Netherlands Cancer Institute, also developed complementary tests in the field of breast cancer. These tests determine the molecular subtype of a tumour or its sensitivity to hormone therapy. 'These complementary tests, based upon differences in gene activity, turn the diagnosis of breast cancer into a much more intelligent process. With these tests, we give information about the prognosis of the disease and the best therapeutic course to follow – for each individual patient,' says van der Baan.
After breast cancer, Agendia points its arrows at colon and lung cancer. Bernards is developing a test for mutation analyses of oncogenes. 'Our laboratory has acquired the world's most advanced machinery for high throughput DNA sequencing of tumour samples. The profile of mutations in oncogenes will become an increasingly more important diagnostic criterion for colon and lung cancer. It will inevitably lead to more individual treatment plans for cancer patients.'
The new research at Agendia is partially financed by several millions worth of grants issued by the European Union. Meanwhile, some 120 people work at Agendia's laboratories in Amsterdam and Irvine, California. Most of them received higher education in the field of science and technology. Van der Baan points out that more and more cancer patients will benefit from an individual diagnostic approach in the future. 'During the next few years, we will further extend our menu of oncology tests. These tests will answer the patient's most urgent questions: What is the prognosis of my disease and what therapy is the best option for me?'

In the spotlight: Laboratory on top of a glass slide

Mammaprint works by measuring the working orders the active parts of DNA (genes) produces in the tumour cell. These orders are made of RNA, a molecule that highly resembles DNA. The more active the gene becomes, the more RNA it will produce. In order to measure the activity of a gene, it suffices to measure the amount of gene-specific RNA. This is simultaneously possible for all 20, 000 human genes. The technique scientists use is called the microarray technology. A microarray is a genetic laboratory on top of a glass slide. Small pieces of genetic material that very specifically bind to RNA of a single gene are attached to the glass. When RNA, isolated from a tumour, is applied to the glass, it will bind to its specific location on the microarray. After binding, it will cause a fluorescent signal. Patterns of fluorescent spots on the microarray represent the gene activity. Such a pattern is specific for a type of cell, like a liver or kidney cell or a recurrent or non-recurrent breast tumour cell.

Beneforté Broccoli

Super broccoli with cancer-fighting nutrients

Many people know that broccoli is a healthy vegetable. Thanks to British scientists, a healthier variety of broccoli is available in the the United Kingdom and the United States. This broccoli contains up to three times more of the nutrient glucoraphanin than normal broccoli. Scientific studies indicate that this nutrient may offer protection against cancer and cardiovascular diseases.

'Producers and retailers in Great Britain are enthusiastic about super broccoli and want to continue selling it,' says Jan Chojecki, Managing Director of Plant Bioscience Limited (PBL). PBL is the technology transfer company that helped in protecting and commercialising the new broccoli variety. The Beneforté Broccoli, as the super broccoli is called, was launched in British supermarkets in October 2012. 'In the United States, Walmart daughter, Sam's Club, stock this broccoli as their only kind of floreted broccoli,' says Chojecki. 'Probably this summer, the Beneforté Broccoli will become available in Scandinavia and other European countries.'

Wild brassicas

The Beneforté Broccoli project emerged from the research of Professor Richard Mithen. He went to the south of Italy to collect wild brassica species as a PhD student in the early 1980s at the University of East Anglia. Then he began analysing chemicals in these wild brassicas which were thought to protect the plants from pathogen and insect attack. Mithen found that the levels of these 'glucosinolates' in wild plants were elevated compared to the cultivated brassica species like broccoli.

- **Product name:** Beneforté Broccoli, broccoli with extra nutrients
- **Research institutes:** John Innes Centre and the Institute of Food Research Norwich (United Kingdom). Both institutes are funded by the Biotechnology and Biological Sciences Research Council.
- **Marketed by:** Plant Bioscience Limited, Norwich (United Kingdom), Monsanto Vegetable Seeds (United States)
- **On the market since:** June 2011 (United States), October 2012 (United Kingdom)

John Innes Centre · Institute of Food Research · PBL

Later, various research projects around the world showed that a particular compound sulforaphane, derived from the glucosinolate glucoraphanin, could prove beneficial to human health. It was associated with certain anti-cancer effects. Glucoraphanin is converted in the gut into the bioactive compound sulphoraphane, which circulates in the bloodstream. In 1990 Mithen was appointed as a research leader at the John Innes Centre (JIC), Norwich, the United Kingdom. 'I wanted to investigate the genetics of the wild brassicas to understand how these plants boost their levels of glucosinolates,' says Mithen. 'By finding the answer, we would be able to boost the levels of glucoraphanin in cultivated brassica species.'

Partnership

To discuss his idea of developing broccoli with a high content of glucosinolates, Mithen went to Plant Bioscience Limited (PBL) also located on the Norwich Research Park. This technology transfer company was established by JIC and others in 1994 and specialises in plant, food and microbial science. 'It is always difficult to predict whether there is chance of success or not with every new idea but the broccoli project looked promising,' says Chojecki.

In 1996 one of Mithen's PhD students, Kathy Faulkner, started exploring the genetics of glucosinolates with funding from a Biotechnology and Biological Sciences Research Council studentship award. She also started developing broccoli breeding lines with high levels of these compounds.

'After we filed a patent on high glucosinolate broccoli in 1998, we started talking to seed companies. We also gauged the opinion of experts in the field about the end product – the fresh vegetable. Developing a fresh vegetable for the market containing an elevated amount of a health-related nutrient was unprecedented at that time and still is,' says Chojecki.

decade The intensive breeding programme to develop commercially acceptable varieties took ten years.

form When designing new crops, even the shape of the head of the broccoli is important.

In the spotlight: A high-profile patent case

The stakes in the field of plant/vegetable development are very high for plant breeding companies. Patents can sometimes be challenged by competitive companies. This also happened with PBL's granted European patent on Beneforté Broccoli. In 2003 plant breeding companies Syngenta and Limagrain opposed this patent. 'The patent consists of two sets of claims. One is the high glucosinolate broccoli itself. The other is the method of breeding it. In European patent law "essentially biological processes" are excluded from patenting. Syngenta and Limagrain want clarity about why our method of breeding is not excluded from patenting. The matter is still with the European Patent Office,' Chojecki explains.

'We needed a partner with the means, experience and commitment to develop our broccoli ready for the market. It had to be a major partner because the development of exactly the right broccoli types to guarantee year-round supply and meet all the needs of growers, retailers and consumers takes many years.'

Chojecki explains, 'You need at least two or three varieties to supply produce of reliable quality in every month of the year in different growing areas. In addition, a feature such as the shape of the head of the broccoli is important. This determines how produce fits in a crate. You have to get all these things right. Otherwise, your product will have little chance to make it to the market. This is simply how the food industry works.'

In 2000 PBL teamed up with Seminis, one of the major vegetable seed companies, which at the time accounted for almost half of the global broccoli seed market. Seminis did the intensive breeding programme to develop commercially-acceptable varieties – a process that took another ten years. Looking back, the collaboration with PBL was crucial to the success, Mithen says. 'I could not have managed without PBL. They secured the IP, found a major partner, stayed critical in all discussions and are still helping in the ongoing patent discussions, as well as assisting current interactions with growers and retailers.'

> 'A fresh vegetable with a high amount of health-related nutrients is still unprecedented'

'Many academic innovations are at such an early stage that most companies do not want to take the risk of spending money on something that might never reach the market. To bridge that gap, you need a skilled technology transfer organisation (TTO) with the ability to invest in and develop immature innovations. It is still a tough job to decide which inventions could become a success and which will not. It is a kind of a lottery, but so far we are doing pretty well. In the last eight years about 40% of our projects makes some kind of revenue. Technology transfer has become more and more popular in the last decade and most funding agencies require that their projects should deliver something that creates revenues or has social impact.' Chojecki continues.

Beneforté Broccoli

Health effects

Apart from marketing the Beneforté Broccoli, Mithen has undertaken more research into the health effects of its nutrient glucoraphanin. 'I wanted to demonstrate that high-glucosinolate broccoli indeed has claimed health effects. It meant changing from research in plant science to research in human health and nutrition,' says Mithen, who now does his research at the Institute of Food Research in Norwich.

'This was a big step, because you don't see it often that scientists leave the comfort zone of their own discipline and experience. However, even in these completely new areas, he managed to continue publishing in top journals,' Chojecki adds.

Mithen and colleagues first showed that the high level of sulforaphane delivered by the new broccoli to the gut was indeed absorbed into the systemic circulation. This established that the body takes it up rather than just excreting it.

Collaborating with the Norfolk and Norwich University Hospital, Mithen showed that men with early signs of prostate cancer who were put on a broccoli-rich diet showed changes in gene expression metabolites consistent with reductions in the risk of cancer developing later.

A study is also being carried out by the Institute of Food Research to examine the effects of a broccoli-rich diet on cardiovascular disease. Differences between a diet of regular and Beneforté Broccoli will also be investigated. 'We hope to publish some of the results later this year. Moreover, we have recently commenced a further study on the effect of the super broccoli on prostate cancer with support from the United States Prostate Cancer Foundation,' adds Mithen.

Although Mithen and his team and also other researchers have accumulated more evidence about the positive health effects of broccoli, the possibilities of advertising these facts as claims on the product are still very limited. 'The regulations governing food health claims are new and very strict about this: product claims of health benefits require a substantial body of evidence and approval of the European Food Standards Agency, which takes time. Science is usually far ahead of legislation and approvals. Still, despite these limited statements currently made on the food product, the sale of Beneforté Broccoli is doing very well,' Chojecki explains.

health effects Professor Richard Mithen wanted to demonstrate that the high glucosinolate broccoli indeed has the claimed health effects.

Integranova

Computer programming made easy

The Spanish software company Integranova automatically writes computer programs, eliminating the need for manual programming and thus human error. Their conceptual modelling language is easy to understand, even for non-experts and reduces the time to create software by years to months or weeks.

rental car The Integranova modelling language makes programming a rental car site easier and cheaper.

If you want to build a new house, you ask an architect to design one for you. The architect asks you about your wishes and starts to work. After he has finished, he will show you the building plans so you can see what the house will look like. Now imagine that the architect puts his plans into a machine. He pushes a button and, like magic, your new house is being built in a matter of minutes instead of months. Researchers at the Universidad Politécnica de Valencia in Spain and the software company Integranova realised this for creating software.

'There's no magic behind it, we don't create computer code out of thin air,' says Juan Carlos Molina, Chief of Research and Development at the Valencia-based Integranova. 'Basically, we have made a modelling tool that introduces all the requirements of a company into a model and automatically creates an application. This is very simple and very fast,' Integranova's Director Jose Miguel Barberá adds. 'Developers need not worry for their jobs. They are still needed to make the program, only now, they use our modelling language instead of the usual programming language,' Molina says.

- **Product:** Conceptual modelling language, saves time and money in computer programming
- **Research institute:** Universidad Politécnica de Valencia (Spain)
- **Marketed by:** Integranova, Valencia (Spain)
- **On the market since:** 2005
- **Noteworthy:** The world's first automated programming system

The inventor Professor Óscar Pastor of the Departamento de Sistemas Informáticos y Computación from the Universidad Politécnica de Valencia explains how the conceptual modelling language works, 'Imagine that we create an information system for a rent-a-car company. Firstly, we will collect all the requirements for that system. We define classes, for instance a class named 'car' and a class named 'customer'. Next, we define relations between these classes. The relationship named 'rental' is an association between the class 'car' and the class 'customer'. This is the structural part of the system's architecture. After that, we bring life to the system. We define the behaviour of the classes. For instance, one customer can rent one car. The last component of the architecture is the interaction with the user. We define what the user interface will look like and what information, like the customer's name and the type of rental car, the user has to introduce into the system'.

This method describes the way all software manufacturers work when they build a software information system: first, they create a model. But as of now, Integranova's method differs drastically. 'Normally, you would program the application manually in let's say, Java. Our model transformation engine, that we call the conceptual model compiler, automatically generates the Java application, without the need for manual programming. The compiler can make computer codes for several systems like a desktop PC or a web-based application,' Pastor explains.

Sophisticated

'The model is our computer code,' Pastor says. This is a radical new way of working. 'Our conceptual modelling language is far more sophisticated and easier to understand than other computer languages not only by the developers but also by the customer. You cannot show the customer a computer code and discuss it with him. You can however, show him a model, in the same way an architect shows you the building plan of a house. Now, the customer can understand the system that we are creating, so we can discuss it.'

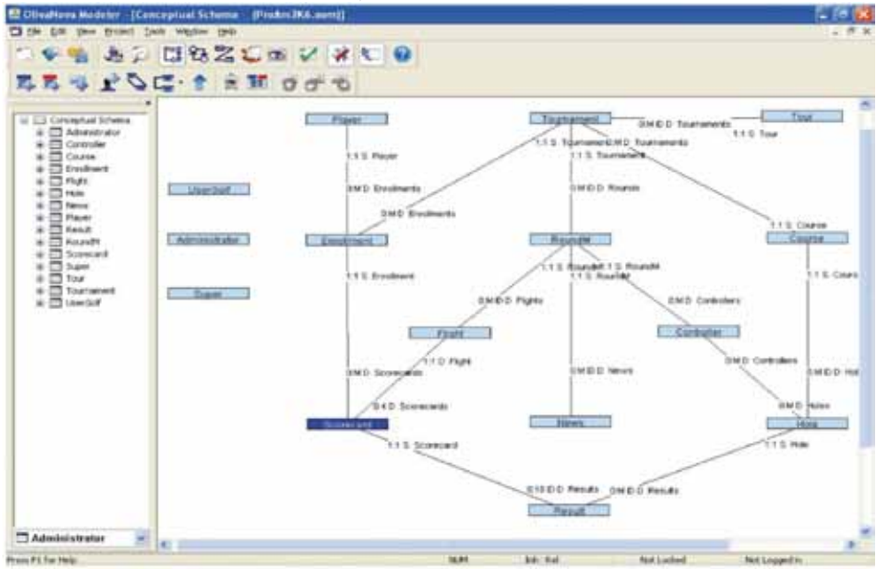
The conceptual modelling language mainly creates business software based on a relational database. 'We can build business software for many industries like the automotive industry. However, we cannot build software embedded in the hardware of their cars,' Molina adds. Some examples of Integranova's customers are the German Army (see box on p. 29),

pharmaceutical company Abbott, the government of Valencia and financial institutions like the Bank of Arabia and the German Bundesbank.
The result of Pastor's research is a fully functional automated software-creating tool that Integranova now commercialises. The main advantage above all competitors is that Integranova spectacularly reduces the time of software development because it no longer relies on tedious programming work. The acclaimed Gartner Group for information technology research compared the conceptual modelling language with conventional software production methods. On average, Integranova produces software in 22 days as compared to 794 days for established manufacturers. That is, on average, two years shorter. Because manual programming is no longer needed, the chances of human error are nearly zero, just like the maintenance costs. Overall, Integranova produces cheaper, more reliable and high-quality software. The advantages to software companies and their customers are obvious. But what about the man in the street? The rent-a-car company that we used as an example can cut down costs on software and thus lower its rental prices. Renting a car could become cheaper. 'However, we cannot influence our customer's decision,' says Molina. 'They could also choose to maintain their fees and make more profit.'

Successful

Integranova's success story began in 1992 when Pastor finished his PhD thesis on conceptual modelling. A few years later, the Spanish property development and construction company CHG-

software On average, Integranova produces software in 22 days as compared to two years for established manufacturers.



group contacted him, because it wanted more efficient ways to improve their information system. Pastor informed the CHG-group about the state of the art methods for creating software available around the world. After his lectures, the CHG-group was especially interested in his research on conceptual modelling. As of that moment, they funded his research. This finally resulted in the founding of Integranova in 2005. Initially, the project received some local and national grants in Spain. It was because of the university's technology transfer policies that the commercialisation of the conceptual modelling language was so successful. 'Since the end of the 1980s, our university has a Centre of Technology Transfer. We are proud of it because receiving help when transferring technology is not very common in Spain. Meanwhile, the centre evolved into the Innovation City, which is dedicated to the creation of spin-off companies and the interaction with the industry,' Pastor relates.
'With the help of the centre, at first we agreed with the CHG-group that the intellectual property remains with the creators, my team and me. The company got the rights for the industrialisation. We also agreed to preserve the participation of the researchers in the company,' Pastor continues.

'The university's technology transfer office made the conceptual modelling language a commercial success'

'Recently, we decided to transfer all the intellectual property to Integranova. The transfer makes our company more valuable because now we have IP-assets. Meanwhile, we protected the product with nine patents in the United States, Europe, Canada and Australia,' Molina adds.

In the spotlight: Integranova helps German army

One of the clients who experienced how much time, money and personnel Integranova's modelling language can save, is the German Army. Last year, the company created a new software system, which helps control its costs for all departments of the armed forces. This programme, named Kolibri, includes asset accounting, infrastructure, material, services and staff costs. Integranova's competitors expected that it would take them three years to build Kolibri. They calculated it would take 40 developers and cost €5m. Integranova pulled it off within three months, with only four developers, within a budget of only €1m. The army says that they are very impressed by the system's performance.

Partners

Pastor still works on improving his conceptual modelling language, 'We try to develop a business process model that directly transforms the requirements of a business to computer code without having to make the conceptual models.' The future looks bright for Integranova even when the economic climate in large parts of the world appears grim. 'We are establishing a network of partners and alliances worldwide. Now we focus on Latin America, because the crisis has hit this region less hard. They have more money to spend on IT,' Molina says. 'Although we are not as big as Microsoft or Oracle yet, after all these years of adventure, we are still around and strong,' Pastor concludes.

Tenofovir

Controlling HIV with a trojan horse

Being an HIV-infected person in the 1980s meant having a mostly lethal condition and taking up to twenty pills a day to postpone the inevitable death sentence. Thanks to research done in a collaboration between Belgian, Czech and United States researchers, an HIV infection is now rather a chronic disease for which only one pill a day is sufficient to lead a virtually normal life.

One of the most remarkable developments in medicine of the last decade is the transformation of the deadly disease AIDS to a bearable, chronic condition. The hero of this tale is tenofovir, a drug that kills the HIV virus that causes the disease at its most sensitive stage – when it tries to invade human cells. Professor Jan Balzarini from KU Leuven in Belgium was one of the leading scientists on the team who discovered the drug in the 1990s. He did this together with professor Erik De Clercq, also from KU Leuven and professors Antonin Holý and Hana Dvořáková from the Institute of Organic and Biochemistry (IOCB) of the Academy of Sciences in Prague, Czech Republic. 'This drug has become the cornerstone of HIV therapy. It is now taken by 80% of all treated HIV-infected people worldwide,' Balzarini says.

- **Product:** tenofovir disoproxil fumarate, (trade names: Viread, Atripla, Complera, Stribild, Truvada), a drug against HIV
- **Research institute:** KU Leuven (Belgium)
- **Marketed by:** Gilead Sciences (United States)
- **On the market since:** 2001
- **Noteworthy:** 4.4 million patients worldwide receive tenofovir disoproxil fumarate, the active ingredient in Viread, making it the most widely prescribed molecule in HIV therapy

KU LEUVEN RESEARCH & DEVELOPMENT

Dead end

After infection, the virus invades the human cell. It converts its own genetic material, stored in an RNA strand into DNA to allow incorporation in the human genetic material. If the virus achieves this conversion from RNA into DNA, the human cell will be able to produce new virus particles. This is where tenofovir comes into play. The drug resembles a trojan horse, posing as it does as a building block of DNA, but there is an important difference with

real building blocks that are threaded onto DNA like beads on a string. The tenofovir bead is a dead end. After addition by the virus of a tenofovir molecule on its growing viral DNA string, the string can grow no further. At the same time, the RNA of the virus is left with deadly damage. The result: the virus that came to replicate dies prematurely and the cells do not make any new viruses.
One dose of tenofovir is active for as long as a day. There is no need for the patient to take more than one dose of the drug per day. This is a great step forward, says Balzarini. 'Adherence to the medicine is a large problem in HIV control. You can imagine that patients sometimes forget to take a pill when they have to take twenty pills a day, or simply are fed up with it. However, when the medicine is not taken on time, the level of active drug in the cells drops that the virus survives. It can find a way around the inhibiting effect of the drug and become resistant to the therapy. However, patient adherence to tenofovir is very good. Additionally, tenofovir does not give many side effects,' says Balzarini.

developing When tenofovir was approved, Gilead established a treatment access program for developing countries.

Cure

After only a few weeks of taking the medicine, almost no virus can be found in the blood of HIV patients. This sounds as if the therapy with tenofovir could eventually cure patients by killing each and every HIV particle in the body. However, in the body of infected people, there are always cells where the genetic material is already invaded with viral DNA. Whereas new viruses that are produced by this cell will easily be cleaned up by tenofovir, the infected cell keeps producing them until the cell dies by itself, from natural causes. 'There is currently no technology available to efficiently clean up this so-called proviral DNA in an infected person,' explains Balzarini.

'Tenofovir is taken by 80% of all treated HIV-infected people worldwide'

In the spotlight: KU Leuven Research and Development

KU Leuven Research and Development (LRD) was created in 1972 to promote and support the transfer of knowledge and technology between the university and industry. LRD helps researchers valorise their research results. Some of the activities include assistance with research collaborations and agreements (over 1,300 new collaborations per year), the management of intellectual property and the creation of innovative spin-off companies. LRD is an independent department of the university with around 80 employees.
Since 2006 LRD has an investment fund and technology transfer platform in place, the Centre for Drug Design and Discovery (CD3). CD3 stimulates the discovery of innovative small molecule drugs by providing drug discovery expertise and financial resources. For this task, CD3 has €24m in funding available, partly from the European Investment Fund (EIF). Potential new therapies for HIV and Alzheimer's disease have already been discovered and are being further developed by pharmaceutical companies.

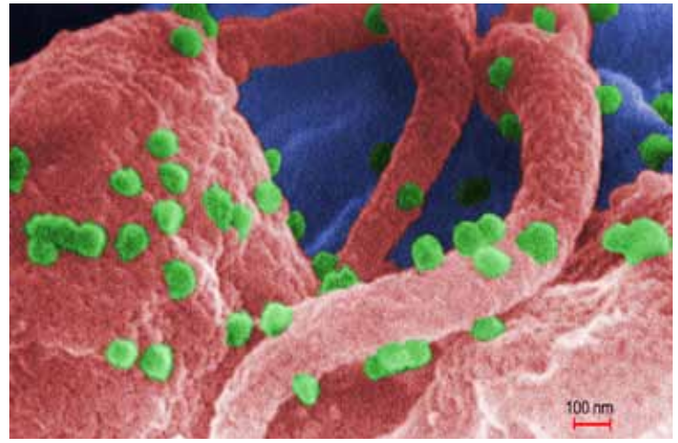
Therefore, this potential virus supply must die out by itself. Most human cells die within weeks or months and are replaced by new ones. Some live for years. 'We now have more than twelve years' experience with the drug,' says Balzarini. 'Whereas patients can take tenofovir without many problems for such a long time, it apparently takes more than that to eradicate the virus. Possibly longer than the life span of the patient.'

Costly

After the researchers did the first investigations, they filed a patent application on this class of products and their action. By publishing in scientific journals and giving presentations at conferences, the results were advertised. With the help of the Prague-based patent attorney firm Inventia, agreements were made with the pharmaceutical company Bristol-Myers (now Bristol-Myers Squibb) to invest in the further development of the products under a patent licence. However, the development of the product stopped when Bristol-Myers merged with the pharmaceutical company Squibb.
Dr. John Martin, working on this class of compounds, left Bristol-Myers Squibb and went to work with Gilead Sciences, a United States-based biopharmaceutical company. Bristol-Myers Squibb returned the licence for tenofovir to the universities because it did not fit in their new strategy. Martin, well aware of the great potential of the product, successfully approached De Clercq, Holý and colleagues to license the product to Gilead Sciences. The company now sells a number of drugs with tenofovir as one of the active ingredients, such as Viread, Atripla and Truvada. Additionally, tenofovir is a core component of a medicine, Truvada, that is approved for the prevention of HIV infection. In combination with the practice of safe sex, it reduces the risk by 75%, says Bischofberger. The total amount of sales of these products is estimated at several billion dollars per year.

Developing countries

'Viread, containing tenofovir, was Gilead's first HIV therapy. Early on, the company recognised the urgent need for HIV treatments in the developing world where the epidemic is most severe,' says Dr. Norbert Bischofberger, CSO for Gilead Sciences. 'When Viread was approved in 2001, only 240,000 people in low and middle-income countries had access to HIV therapy.'
The company established a treatment access program for developing countries, Bischofberger explains, which included the provision of tenofovir-containing medicines at steeply discounted prices in developing countries and allowed Indian manufacturers to produce and sell high-quality, low-cost generic versions of tenofovir in developing countries.
Today 8 million HIV patients are accessing therapy in the developing world and 3.5 million of them are receiving tenofovir-containing medicines.



HIV-virus Almost half of the developing world's HIV patients receive tenofovir-containing medicines.

Technology transfer

Clearly, the development, technology transfer and marketing of tenofovir have been very successful and the involvement of technology transfer professionals has been and still is important in this regard. Patrick Chaltin, a former senior IP Officer at KU Leuven Research and Development (LRD) and current Managing Director of the Centre for Drug Design and Discovery (CD3), explains how LRD can assist scientists at KU Leuven in the technology transfer process, 'We are able to help them analyse and describe the invention and protect it in a patent. We help with contacting commercial partners who may be interested in a licence on the product and negotiate the licensing agreements. In general, LRD helps to speed up and streamline the technology transfer process.'
'This process of transfer of knowledge to a commercial partner is essential for a product to reach the market,' says Jan Balzarini. 'The clinical studies are so costly that they cannot be performed by an academic institution. That is impossible, but it is also not our aim. In academia, we discover new antiviral leads and therapeutic concepts and explore and reveal the molecular mechanisms of drug action. Once we feel we have something important, we file a patent and offer it to an industrial partner to develop it into a commercial product.'

CEERAM

Virus detection kit prevents food poisoning outbreaks

Imported foods such as shellfish and soft fruits may be contaminated with harmful viruses. Until recently, there was no adequate technology for large-scale virus control of such imports. Together with the French company CEERAM, the University of Barcelona in Spain developed a user-friendly kit to detect hepatitis A in food, which prevents virus outbreaks.

Dozens of cargo ships enter European harbours to deliver shellfish from South America every day. Their loads are usually safe and thousands of Europeans enjoy their oyster dishes. There is always a small chance, however, that some of the oysters are contaminated with a virus such as hepatitis A.

This virus may wreak havoc among unsuspecting consumers. Just a few virus particles are enough to cause severe food poisoning. An outbreak may affect thousands of people, even killing some of them.

A hypothetical scenario? By no means, says Albert Bosch, microbiologist at the University of Barcelona. 'There have been several outbreaks of hepatitis A in Europe that were traced back to shellfish from Peru,' he says, 'with hundreds of people being affected. As a result, Europe banned all seafood imports from Peru for many years. This was disastrous for the Peruvian trade.' Similarly, in Germany, strawberry yoghurt cake turned out to be contaminated and was withdrawn from the market in 2012. Sun-dried tomatoes were also implicated in several virus outbreaks in Australia, the United Kingdom and the Netherlands over the past few years.

'Food-borne viruses are a real threat to public health,' states Bosch, 'but the problem is that the EU currently has no regulations in place to control imports of viruses.' The reason for this, as the scientist explains, is that until recently, there was no technology available that would allow for large-scale inspections of imported foods. 'Samples would have to be taken to specialised laboratories and the results of their tests would not be available for a few days or even weeks. Even apart from the fact that such measures would be expensive, they would hamper the trade in fresh and frozen foods.'

- **Product:** Kit for the detection of hepatitis A in food, environmental and clinical samples
- **Research institute:** Department of Microbiology, University of Barcelona (Spain)
- **Marketed by:** CEERAM (France)
- **On the market since:** 2009
- **Noteworthy:** Kits are also available for other viruses, including noroviruses and for various bacteria and parasites

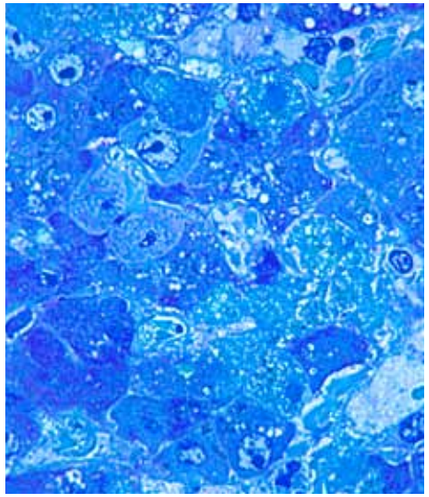
ceeram
ANTICIPATE TO BETTER PREVENT

versatile A fast detection of pathogens can be used in several sorts of foods.

Leading companies

Bosch and his colleague Rosa Pintó at the University of Barcelona knew that there was a solution within reach. Laboratories around the world are already working with fast and efficient kits to detect several kinds of viruses. 'What was needed,' says Bosch, 'was a simple to use, standard procedure that could be carried out by people without a scientific background. We decided to develop a kit for the detection of hepatitis A that would meet these demands and would be suitable to be used in the context of any future EU regulation. To do that, we needed a partner who could bring this technology to the market.'

Bosch and Pintó contacted Fabienne Loisy, microbiologist and co-founder of the French company CEERAM – the European Centre for Expertise and Research on Microbial Agents in Nantes, France. This company develops tools for the genetic detection of pathogens. 'CEERAM is one of



multiple The kit can detect as few as 10 virus particles in a sample.

the leading companies in this field,' says Bosch, 'so we knew that our ideas would be in excellent hands.' One of the main innovations, as Bosch explains, is that the newly developed kit uses a strong safety mechanism: all critical steps in the assay are separately controlled. The kit not only checks the sample for the presence of the target virus, in this case hepatitis A, but also for one other virus, which is added to each sample that is analysed. 'This is to make sure that the kit is working correctly,' Bosch explains, 'because if it does not detect the control virus, you know that something is wrong.'

High sensitivity

One of the patents that the university filed to protect its invention applies to the use of this extraction control. The second patent covers the specific technology for virus detection which is based on the polymerase chain reaction (PCR), a technique used to quickly amplify predetermined fragments of genetic material. The challenge, as Bosch explains, is to identify specific bits of genetic material that are characteristic for hepatitis A and to make sure that only those are amplified during the PCR.

'One of the main advantages of this invention is its high sensitivity,' Fabienne Loisy at CEERAM elaborates. 'This kit is able to detect as few as ten virus particles in a sample. Ten virus particles are enough to make a person sick and cause an outbreak. Our contribution is that we converted this invention into an application that can be used by local service laboratories. It is easy to use and ready to use, it is standardised and the technology has been validated by different laboratories.'

CEERAM introduced the kits in France in 2009. Business rapidly spread into Europe and now even stretches as far as the United States, Southeast Asia, South America and North Africa. 'There is an enormous demand for this application,' Loisy indicates. 'Last year, we had more than 200% growth in sales compared to 2011.' This demand is both market and policy driven. Companies are keen to prevent outbreaks due to the loss of reputation as well as the unnecessary destruction of food batches.

'Virus control in food will become part of the routine'

'The EU is currently working on regulations that will make virus control of imported foods compulsory,' she says. 'Of course the EU will not specify which particular kit will have to be used for this purpose but it will describe the minimum requirements. We are confident that our kit meets those requirements.'

CEERAM

Royalties

'This case is a great example of technology transfer,' says Lurdes Jordi. Jordi works at the Fundació Bosch i Gimpera, the Technology Transfer Office of the University of Barcelona and was involved in the kit's development. 'Our researchers and those at CEERAM have a shared background which makes their cooperation quite natural.' CEERAM is a relatively small company compared to multinationals that develop similar technologies, Jordi points out. 'This is actually an advantage. Smaller companies are much more flexible and efficient when it comes to acquiring new technologies and moving them from the planning phase to implementation and marketing. However it is much easier to reach an agreement with them.' The ownership patents of the technology lies with the University of Barcelona, she explains, which has granted an exclusive licence to CEERAM. 'Initial funding for this research came from the Spanish Government,' Jordi adds, 'but at this point, CEERAM is bearing the development costs.'

One step further

Expanding the market is not the only ambition of the partners involved. Both Bosch and Loisy have ambitions to take their technology one step further. 'We are still improving our kit to enable it to work with dry as well as wet reagents and make it even more sensitive,' Loisy says. 'We are also working on new applications to detect viruses in food, environmental and clinical samples.' Currently, CEERAM is also involved in a European project to detect viruses in drinking water.

Bosch is confident that virus detection will become much more common in the food sector than it is today. 'Virus control will become a routine activity,' he predicts, 'not just in the context of seafood, greens and soft fruits, but also for hard foods such as apples and hard surfaces such as kitchen desks.'

In the spotlight: Hepatitis A

Hepatitis A is a contagious liver infection caused by a virus. The virus spreads via faeces and is usually contracted by the consumption of faecally contaminated food or water. Symptoms include weakness, fatigue, headache, nausea, vomiting, fever and diarrhoea. These symptoms usually last for a period of around two months although some patients remain ill for over six months. The infection leaves no lasting symptoms.

In regions where adequate sanitation is lacking, in some developing countries for instance, the circulation of hepatitis A virus is high. However, 90% of the young children who contract the disease experience no symptoms after infection. The disease is more problematic for incidental visitors to these regions or when imported foods are contaminated causing outbreaks in industrialised nations.

human liver

DepthSense

Ingenious in gesturing

No more remote control, keyboard or mouse between you and your television or personal computer. Instead Belgian company SoftKinetic is working on a sensor that will allow you to interact with the digital world through gesturing. Their 3D DepthSense sensor and camera will change automotive engineering, consumer electronics, interactive digital entertainment and healthcare at a fundamental level.

Controlling machines, just by making gestures at a distance. Until recently, most people thought this idea was mere science fiction. In 2007, a Belgian company named SoftKinetic was the first in the world to show it was indeed possible, with early 3D cameras and specially developed gesture recognition software. Consumers experienced the futuristic concept for the first time in 2010 when the Kinect was launched, a controllerless system for the Xbox. Kinect made it possible for you to have an animated figure in a video game by dancing in front of your television. Somewhat like a Wii without the controller. The Belgian device, named DepthSense, is even better. Several large companies (such as Intel, Texas Instruments and Melexis) are investing heavily in it. Daniël Van Nieuwenhove, currently Chief Technology Officer at SoftKinetic, has been involved in the development of the sensor right from the start. 'It was 2002 and I had just graduated in microelectronics at the Vrije Universiteit Brussel. Professor Maarten Kuijk asked me if I would be interested in developing a 3D sensor and camera. At that time, most commercially available cameras only recorded in two dimensions: they could not measure depth. The main attempts to achieve 3D capturing had been based on stereo vision and had not been very successful. It took too many calculations to build up an image. Professor Kuijk proposed a totally different approach. He wanted to use the so-called time-of-flight principle to measure depth. That turned out to be the solution.'

- **Product:** DepthSense
- **Research Institute:** Vrije Universiteit Brussel (Belgium)
- **Marketed by:** Optrima, later merged with SoftKinetic
- **On the market since:** 2009
- **Noteworthy:** The DepthSense sensor, cameras and middleware play a prominent role in Intel's long-term Perceptual Computing Research Programme

gestures The Depthsense sensor can recognise movements in three dimensions, allowing you to control your computer without a keyboard or mouse.

Flight

Kuijk proposed sending an infrared light signal to the object and then measuring how long it takes for the light to come back. Since points at the front side of the object are closer, the light will return sooner than light reflected by points at the back of the object. By catching the returning light on a screen of pixels, DepthSense can calculate the distance between the reflecting feature and the sensor per pixel. Combining the information from all the pixels results in an accurate 3D image of the object. Since every pixel is in fact a sensor in its own right, including ultrafast electronics, moving targets can be imaged in real time. The system can capture a whole scene at once, using cheap LEDs and making use of complementary metal-oxide-semiconductor (CMOS) technology. Because CMOS technology is fully developed and well known, the Depthsense system is faster, more accurate and cheaper than the sensing principle the Kinect uses.

Van Nieuwenhove and his colleagues soon realised they had struck gold. 'In a very early stage, probably in 2004, we patented our findings. The Technology Transfer Office of the university played the leading role in that process. But it was not an easy step, he emphasises. 'European universities still feel a trade-off between patents and publications. For a researcher, publications count. Patents are perceived as less relevant, as peers do not scientifically evaluate them. I was the odd man out by wanting to patent first and publish later to keep innovations secret.'

Best

It was 2005. There was a patented prototype based on one pixel that could measure time-of-flight. Then the researchers met one of the people who later founded SoftKinetic: Eric Krzeslo, Chief Marketing Officer of the company and one of its co-founders. 'We had been working on software systems for gesture recognition for advertising purposes,' Krzeslo says. 'At the time, we had invested four years of research in prototypes based on stereoscopic cameras. We had already been working with a few companies in Germany, Switzerland and Israel when we found out about the system Daniël and Professor Kuijk were working on. In our experience, their approach was the best one.'

At the same time, Melexis, a semiconductor

In the spotlight: The power of ignorance

It was 2002. A group of people, led by Professor Maarten Kuijk, started working on a completely new concept for 3D sensing. Or so they thought. 'In our ignorance, we just assumed that no one else was working on this idea. We never bothered to conduct a literature study, we just took off. Only a year later, after having filed our first patents, did we discover that there was a German group working on this type of cameras since the late 1990s. Their technology was based on a very different concept though – they worked with charge-coupled device (CCD) cameras instead of complementary metal oxide semiconductor (CMOS) technology – and their solution was not nearly as advanced as ours was. Looking back, I think the fact that we just started, blissfully unaware of other ideas in the field, turned out to be our luck: it enabled us to come up with a totally new, innovative concept. Unbiased people can be key to achieving breakthrough innovations,' Daniël Van Nieuwenhove tells of the Depthsense story.

company in the automotive industry working on things like parking sensors, became interested and started to sponsor the research. A little later, Texas Instruments and Intel also became involved. Van Nieuwenhove and his colleagues decide to launch a start-up company: Optrima. It was founded in 2008, one year after SoftKinetic was born. 'At that time, we had a camera consisting of 120 by 90 pixels that we could sell. Meanwhile, we kept in touch with SoftKinetic. They invested in our company and we founded a joint venture. Later on, in 2010, we decided to merge both our companies into SoftKinetic,' Van Nieuwenhove says.

'Our system is in the heart of Intel's Perceptual Computing programme'

Today, DepthSense is the most advanced 3D time-of-flight camera on the market. SoftKinetic not only offers the hardware, but also covers the entire chain from the hardware that captures full body motion to software that translates this information to user experiences. 'A unique approach,' Van Nieuwenhove emphasises. Although the sensor and camera are available to consumers, the Belgian company primarily aims for Original Equipment Manufacturers (OEMs), such as today's major current partners Intel and Creative Labs. 'Our system is in the heart of Intel's Perceptual Computing programme. At the moment, they are reselling the cameras under the brand of Creative Labs, challenging developers to come up with applications,' Van Nieuwenhove comments proudly. 'At the San Francisco game developing conference, Intel will demonstrate the first wave of applications,' Krzeslo adds.

Existing

It was a deliberate choice to aim for OEMs, Krzeslo says. 'This is a game-changing technology. We take advantage of our strategic partners' strengths such as marketing and distribution channels to bring our products to the consumers.' This does not mean SoftKinetic is not selling any cameras at all. 'Anybody interested can buy it through our website. We are not really pushing that business though, as we are not competing with Creative Labs.'

Before DepthSense penetrates households, content and applications will have to be developed, Krzeslo explains. 'We need a critical mass of content before consumers really start to get interested. Game developers and the video game industry adopt and push new technology fast. It is the best sector to launch something as groundbreaking as our system. But we are also working on user interfaces for PC and TV and augmented reality experiences.'

'Furthermore, we are constantly improving the system – reducing the size and price and improving the performance by working on the resolution, the field of view, the speed and precision of tracking. We are able to track the full body skeleton of several users up to four metres and individual fingers up to one metre, but we also want to be able to track finger movements at a large distance.'

Roots

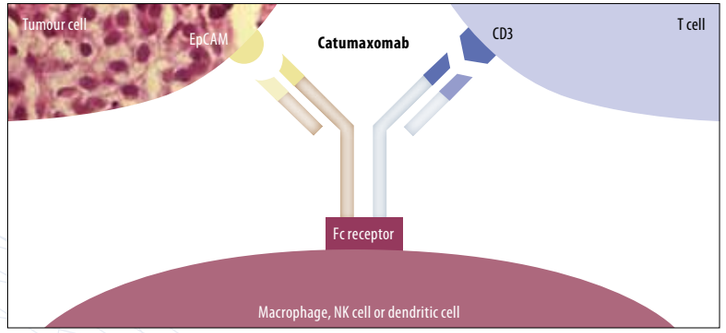
The company is doing well. 'We doubled our revenue each year since 2007 and I expect that we will be profitable this year,' Krzeslo states. 'Although taking just a decade to come from an academic fundamental finding to a profitable company might be very fast, it was a long time to sustain a start-up company,' he adds. But although the timelines in business differ greatly from those in academia, SoftKinetic still has strong links with the Vrije Universiteit Brussel. 'We still cooperate with Kuijk's group at the university,' says Van Nieuwenhove. 'You should never forget your roots.'

tracking The Depthsense camera can track the full body skeleton of several users up to four metres and individual fingers up to one metre.

Removab

New drug relieves cancer patients

When Horst Lindhofer started research on bispecific antibodies in cancer treatment, he could not have expected that many years later, the drug developed from this research would be so beneficial to cancer patients. The drug, called Removab, inhibits painful fluid build-up in the abdomen.



trifold By leading two immune cells to the tumour cell, Catumaxomab is effective against fluid build-up in the abdomen.

'Bispecific antibodies fascinated me because they could become a promising anti-cancer therapy,' says Horst Lindhofer. Antibodies are small Y-shaped proteins that detect foreign objects in the body, such as bacteria, viruses and cancer cells. As early as 1985, bispecific antibodies that are artificially made for medical purposes were described as an effective anti-cancer therapy *in vitro*.

While normal antibodies bind to only one target, bispecific antibodies can bind to two targets simultaneously. These bispecific antibodies were engineered to bind simultaneously to a T-lymphocyte (important cell in immune system) and a tumour cell. In 1992 Lindhofer started research on this topic during his postdoctoral years at the Forschungszentrum für Umwelt und Gesundheit (GSF, now Helmholtz Zentrum München). He devised a method to yield a much higher percentage of correctly formed bispecific antibodies. 'My method worked and my boss, Stefan Thierfelder, suggested talking to a patent lawyer of the Helmholtz Institute. We filed for a patent on the production method in 1994. We continued to build up a solid patent portfolio in the following years.'

- **Product:** Catumaxomab (tradename Removab), a therapeutic antibody for metastasised tumours
- **Research institute:** Helmholtz Zentrum München (Germany)
- **Technology transfer partner:** Ascenion (Germany)
- **Marketed by:** TRION, Fresenius Biotech (Germany)
- **On the market since:** April 2009
- **Noteworthy:** First approved multispecific antibody worldwide, first approved antibody from a German research institute

Alliance

Lindhofer wanted to continue research on his bispecific antibodies but it was very difficult to attract public funding for the continuation of the project. Since the technology was still in its early stages, it was too early for business partners to become interested. Supported by the institute's technology transfer specialists, Lindhofer attracted the attention of venture capitalists when he won a business plan competition. In March 1998 he founded a spin-off company, TRION Pharma. Soon after, TRION entered into a strategic alliance with Fresenius Biotech which belongs to the large German Healthcare company Fresenius.

'TRION Pharma obtained an exclusive licence to the patent portfolio held by the Helmholtz Institute. Fresenius provided money for the further development of the bispecific antibodies in cancer therapy.'

In this research, Lindhofer further optimised the Y-shaped antibody. He developed bispecific antibodies where one of the two arms binds to a protein present on the membranes of many cancer cells (EpCAM) and the other attaches to immune cells that could destroy the cancer cell (T-lymphocytes). This way, the antibody connects the cancer cell with its killer.

But the innovation did not end there. Lindhofer discovered that the subtype of bispecific antibodies he constructed also make a third bond through the "foot" of the Y-shaped molecule. This foot binds to the accessory cells of the immune system, like macrophages, which can also destroy the tumour cells. By binding these three cells together, the antibody gives off an extra signal to the immune system for destroying the tumour cells.

'We created trifunctional antibodies which appeared to work much better than the bispecific antibodies,' says Lindhofer. 'Experiments in mice showed that the trifunctional antibodies were able to kill tumour cells very efficiently and also induce a long-lasting protective immunity against the tumour.'

Compassionate

'The development of the first clinical application, antibodies against malignant ascites, was a coincidental choice,' says Lindhofer. 'One of our technicians had ovarian cancer and developed malignant ascites, a condition in which fluids containing cancer cells build up in the abdomen. This caused her severe discomfort and the only treatment at that time was to puncture the peritoneum to let the accumulated fluid drain out regularly. She asked if it was possible to be treated with the experimental medicine, called

Catumaxomab. After careful discussions with ethical committees over compassionate use, she was treated. Although she could no longer be cured, the experimental medicine helped in the disappearance of ascites accumulation which made her feel better. She lived for another five months.'
Clinical tests conducted by Fresenius Biotech showed that patients who are treated with Catumaxomab (tradename Removab) do not need punctures for an average of 77 days. Patients who did not receive Removab required punctures after 13 days. Most of them also live longer. In general, the quality of life of patients is improved by controlling ascites.

Technology transfer
Removab received market approval for Europe in April 2009 for the treatment of malignant ascites. It is the first bispecific, trifunctional antibody on the market.
'This is a great success,' says Christian Stein, CEO of Ascenion, technology transfer partner of numerous life science institutes, among which the Helmholtz Zentrum München (former GSF).
Stein points out that the prudent patent strategy pursued by the technology transfer team at the Helmholtz Zentrum München at the time of the Removab invention was fundamental to today's success. 'A solid IP position is a precondition for industry partners to get on board.' The strategy of endorsing the foundation of TRION and licensing relevant patents in return for equity and royalties also paid off. 'This enabled TRION to continue product development as an independent, entrepreneurial entity while the Helmholtz Zentrum could be sure of adequate financial participation in the event of product success. 'However, as technology transfer professionals, many success factors lie beyond our control,' Stein admits. The Removab project is exceptional in a couple of aspects: Lindhofer managed to attract biotechnology company Fresenius, to form an alliance and finance his research. In addition, he became CEO of the spin-off company, which is not the rule.

Revenues
Through Ascenion, the institutes of the Helmholtz Association not only get the assistance they need to scout for new inventions, protect ideas and improve the exploitation of research results. They also reap financial rewards if their ideas find commercial applications in the market. Licensing revenues, from the sale of Removab for example, go to the originating institution. Surplus profits from Ascenion's operative business activities and from the sale of equity in spin-offs flow to the foundation and are made available as grants to public research.

In the spotlight: Antibodies

Catumaxomab was made in the laboratory in special cells that can be cultured in plastic bottles containing a special feeder medium. These cells, called hybridomas, are a crossing of antibody-producing cells with myeloma-cells (B cell cancer).
A normal antibody is a Y-shaped protein. The tips of the "Y" together can bind to one specific target (bacteria, virus or toxin). When scientists need antibodies that bind to two targets (A and B), they fuse two different hybridomas. However, these fused cells generate various mixtures of antibodies. Only a small percentage will have the right combination of binding properties.
Lindhofer used a new trick to get a larger percentage of correct antibodies: by fusing a mouse hybridoma with specificity A to a rat hybridoma with specificity B, this leads to a higher amount of correct combinations.

relief Cancer patients who receive Catumaxomab do not have to undergo a puncture to release fluid for 77 days.

> 'The drug's revenues of around €40m allow for new research projects to be pursued'

Thanks to success stories such as Removab, Ascenion has achieved a positive total balance across all its current 23 partners. Taken together, their revenues from the commercialisation of their IP outperform their investments into technology transfer, including the fees for Ascenion's services. 'These revenues have cumulated to around €40m over the last decade and allow for new research projects to be pursued,' Stein says. 'They pave the way for the creation of powerful technology transfer instruments that enable us to fund and support today's spin-offs much more comprehensively. Ultimately, this pays off for all – in the form of sustainable companies, jobs and products that enhance people's lives.'

New applications
In the meantime, TRION Pharma also develops trifunctional antibodies as a therapy for other diseases. Currently, the company is involved in a European research project to find a therapy against shistosoma, which is considered by the World Health Organisation to be the second most socio-economically devastating parasitic disease.
Moreover, TRION also continues the search for new applications for Removab. 'Malignant ascites is a niche market, trifunctional antibodies can be used for many more applications,' says Lindhofer. Clinical studies on treatment of peritoneal carcinoma and gastric cancer are now being performed. In addition, a new method of treatment of ovarian cancer is investigated. 'Right after surgery to remove cancer tissue, patients received Removab in the abdominal cavity to destroy residual disseminated tumour cells. After a three-year follow up period, this new method of Removab treatment shows promising results,' Lindhofer explains.

Diopma

Collaborating for cleaner copper

When the Spanish copper refining company La Farga Lacambra (LFL) needed a technological boost for their process, the DIOPMA Research Centre of the University of Barcelona in Spain stepped in. The innovative recycling process they developed allows the production of high quality copper from scraps in a faster, cleaner process, helping LFL to grow and increase its production almost sevenfold.

Copper is all around us. If it was not for copper, we would not have electrical wiring for light or computers, no water would flow from the tap and an orchestra would sound rather dull without the brass section. We use no less than 20 million metric tons of copper per year worldwide. Most of this is freshly mined, in countries like Chili, Peru and the United States. However, this easily accessible copper stock may run out in as little as 25 years. Besides, mining delivers only about 16 million tons of copper per year, not enough to fulfil our needs.
This dilemma can be solved by recycling the copper from discarded appliances such as electrical wiring, tubing and electronics. The company which developed the process of recycling copper was the Spanish holding La Farga Lacambra (LFL) with a more than 200-year history of copper production. It started producing copper pots for the Catalan fleet in 1808.

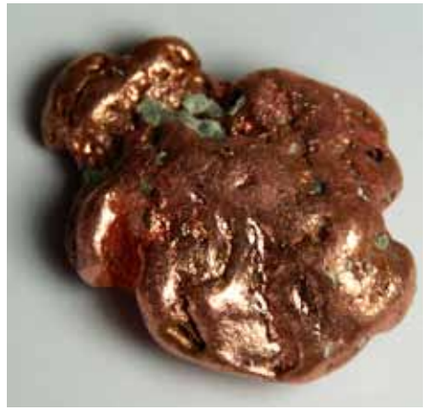
- **Product:** Ecocopper, innovative recycling process for copper
- **Research Institute:** DIOPMA, University of Barcelona (Spain)
- **Marketed by:** La Farga Lacambra (Spain)
- **On the market with the recycling process since:** 1984

Golden solution

In the mid-'90s, business was very slow for LFL, the division specialised in production and sales of semi-finished copper products from recycled materials. On the verge of bankruptcy, LFL needed a serious boost and decided to ask for the services of the DIOPMA Research Centre from the Department of Materials Sciences and Metallurgical Engineering from the University of Barcelona. A research contract paid by LFL was taken out for a study into possible improvements in the production process.
This proved to be a golden (or more accurately, a copper) solution for LFL. Oriol Guixà (Managing Director of LFL) and scientists at DIOPMA developed an innovative recycling technology that allowed LFL to produce high quality copper from used materials without using the energy-consuming electrolytic step that many others utilise. With this process, LFL became the first company to achieve this quality of copper while using recycled or secondary copper as raw material.

Environment

Professor Mercè Segarra from DIOPMA is one of the main scientists in the project. She explains, 'Our first contribution was to develop a process allowing the production of copper with a high quality and high electrical conductivity. The main innovation of this technology is that different processes take place in a single and continuous refining furnace. The process is called continuous casting and creates a closed cycle. The introduction of this technology helped to reduce not only the production process by 14 days but the consumption of energy, water, CO_2 and SO_2 emissions as well. It also minimised waste and liquid effluents.'
The classic process of copper production from ore or scrap includes fusion and a further electrolytic processing, which involves the immobilisation of a large amount of material in the electrolytic cells for a long time in order to obtain the purest copper possible, explains Segarra. The process that is presently applied at LFL comprises a huge improvement, she says. 'It allows obtaining a metal of similar purity, but with better properties, both electrical and mechanical, in a shorter time. The process does not involve any kind of solution, which causes an environmental improvement of the whole process.'
Carme Sáez, Competitive Intelligence Manager at LFL, agrees, 'The key success factor of the new process is the ability to recycle copper scraps directly into final products without the electrolytic refining stages. The scrap is melted, refined and directly cast into copper wire rod. This means extra low consumption of energy and water, a very low waste generation and extremely low emission of greenhouse gases.'
Avoiding the mining of new copper is of course a big advantage of recycling. Copper is one of the few materials that can be recycled again and again without losing its original quality or characteristics, says Sáez. 'The valorisation of the copper scraps at the end of their life is a fact that everybody can easily understand. Additionally, electrolytic refining is a massive energy and water consuming process. It also generates a lot of waste.' Getting rid of this step resulted in a sustainable recycling process of which the product is aptly named "Ecocopper".



copper Worldwide, we use no less than 20 million metric tons of copper per year.

Growth

In addition to the environmental benefits, there is an economical benefit. A lot has been invested in the

recycling Ecocopper is recycled by melting the scrap, refining it, and directly casting it into copper wire rod. (photos by Giovanni Dall 'Orto)

development of the recycling process, says Sáez. Since the first development in 1984, almost €6m was invested in the development. The research and development of the innovative new recycling technique by DIOPMA has cost approximately €675 000. 'When we started to collaborate in 1996, the company produced nearly 30 thousand tons of copper with 132 employees. LFL produced about 200 thousand in 2012, with a consortium of companies employing more than 300 workers. Our research group has helped develop a technology introduced in 30 facilities around the world, from China to the United States,' Segarra explains of the economic benefits.

Teamwork and trust

'The main success factors in the collaboration have been teamwork, compromise and results orientation,' says Sáez. For Segarra, the key to this success is trust between both parts. 'On the one hand, the company has always trusted the research group to transfer a suitable technology for their production process. On the other hand, the group knows the process perfectly well and we are continuously looking for solutions, not only to daily production problems, but also to find possible applications of their products in order to extend the market. The company has always been sure of the objectives it wants to reach and the interaction with the research group has been constant.'

For DIOPMA, the benefit is first and foremost to train professionals, Segarra says. 'The financing for the projects has been mainly allocated to create doctoral grants and contracts for young researchers. This way, we provide the industrial sector and the university with PhDs, while providing new ideas for the company to bring them into practice. This interaction helps us to keep our feet on the ground, to focus our research towards solutions for society. Personally, the collaboration with the company has helped me understand that the research we developed at the university becomes useful to society as long as researchers and entrepreneurs speak the same language and have very clear and accessible common goals.'

Award

DIOPMA and LFL were even awarded the Antoni Caparrós Prize for the best knowledge and technology transfer project in 2012, for their constructive collaboration.

The Antoni Caparrós Prize is awarded yearly by the University of Barcelona (UB) Board of Trustees and the Bosch i Gimpera Foundation (FBG) for best project in knowledge and technology transfer. According to the University of Barcelona, the award seeks to 'encourage the transfer of knowledge acquired through studies and research; to appreciate the importance of technology, knowledge and innovation transfer projects; to enhance the creation of innovative knowledge-based companies; to recognise the innovative capacity generated, and to promote entrepreneurial culture at universities.'

'DIOPMA uses the revenues from Ecocopper for doctoral grants for young researchers'

Segarra is very pleased with the award. 'The award represents an important recognition for our group. Our collaboration has been considered as an example of success of technology transfer between university and industry on numerous occasions but this is the first prize we receive.'

Sáez adds that the still ongoing collaboration has benefited both the company and the academic researchers at DIOPMA. 'One of the objectives of the University of Barcelona is to help the public and private sectors improve competitiveness in a globalised context by supporting research projects that provide consultancy and scientific analysis to industrial companies and institutions. The cooperation with DIOPMA has helped us develop new alloys and innovate our production process. We are still collaborating on projects like new sustainable solutions for the transmission and distribution of electric power.'

hMPV

When a virus creates jobs

In 2001 virologists in Rotterdam, The Netherlands discovered a new virus that causes serious respiratory illnesses mainly in young children. The discovery was the beginning of a successful company that enabled the development and production of a range of diagnostic products. This led to substantial job creation and made a positive contribution to public health.

About 2500 Dutch children are diagnosed with the dangerous respiratory syncytial virus (RSV) and admitted in hospitals every year. However, in 2001 researchers at the Erasmus Medical Centre in Rotterdam, The Netherlands discovered that 20% of these children were not infected with RSV at all. There had to be another virus causing their symptoms. 'So we opened our laboratory methods toolbox, to find out what caused the disease in these children,' Professor Ab Osterhaus recounts. Osterhaus has been head of the Viroscience department at the Erasmus Medical Centre since 1993.
This research revealed that a new virus was responsible for the illnesses, ranging from mild respiratory problems to severe cough, bronchiolitis and pneumonia. The Erasmus group named the new virus human metapneumovirus (hMPV). That discovery was the start of the establishment of the successful company ViroNovative.
'When research leads to such important results, it is a logical next step to file a patent application to support the commercial development of the finding,' says Osterhaus. Fortunately, he had good contacts with Professor Eric Claassen, who was experienced in commercialising knowledge. Since, as stated by Osterhaus, a university is an excellent place to perform research but not the best setting to conduct business, Osterhaus and Claassen developed a business plan for a new company. Professor Claassen, a medical biologist, immunologist and entrepreneur, is co-founder and CEO of ViroNovative. Prior to the initiation of ViroNovative, Claassen had been working for seven years as Research Director at ID-DLO Institute for Animal Health and Science of The Netherlands, where viral infections in animals are studied. He also became the first Biopartner Professor Entrepreneurship in the Life Sciences, on behalf of the Ministry of Economic Affairs at the Athena Institute of the Vrije Universiteit in Amsterdam, The Netherlands.
'From my experience with businesses that I had already set up in the past and my knowledge of laboratory research, I appreciated the field from both sides,' Claassen remembers. 'I communicate well with the people in this type of research, because I have been trained as an immunologist.'

- **Product:** Out-licensing the hMPV patent, enabling diagnostic and therapeutic applications
- **Research institute:** Erasmus Medical Centre (Erasmus MC), Rotterdam (The Netherlands)
- **Marketed by:** ViroNovative BV (The Netherlands)
- **On the market:** since 2001
- **Noteworthy:** ViroNovative sells knowledge instead of a product

Sequence

ViroNovative and the Erasmus MC developed the patent strategy in close collaboration. Osterhaus and his research group were the first to discover the hMPV virus and determine its RNA sequence. Being the first to discover the virus also meant that there were no existing patents on these viral sequences that could hinder commercialisation. This enabled the company to create a solid IP basis supporting its commercial goals. It also meant that the researchers were able to obtain patent rights with a broad scope of protection themselves.
To be exact, it is not the entire virus that is patented, but the use of pieces. These pieces (epitopes and RNA sequences linked to specific function) of the virus can be utilised to make a vaccine or a diagnostic kit. Osterhaus makes clear that, in this way, ViroNovative is an essential partner in the commercial development of diagnostics, vaccines, therapeutic or prophylactic antibodies and anti-viral compounds. Consequently, ViroNovative makes an essential contribution to the detection, prevention and treatment of hMPV infection.
ViroNovative, still located on the Erasmus MC campus, was a commercial hit from the beginning. Although the spin-out was facilitated by Erasmus MC, it did not receive start-up money from the medical centre. 'It was our own commercial success, because we immediately turned to industry and have been working with disclosure fees. Before the patent was published, companies with an interest in the patent had to pay first, before we showed the patent.'

discovery In 2001 Dutch researchers identified a human paediatric virus, that causes respiratory illnesses and hospitalises 1% of all children. (Photo by Amanda Mills)

Royalty payments

Claassen analyses the immediate financial success of the company further. 'Our philosophy is that you need to generate money from industry in the

pieces ViroNovative is a commercial partner in the development of applications in diagnostics, vaccines, therapeutic or prophylactic antibodies and anti-viral compounds.

first 18 months that your patent application is still confidential. Because we had a strong patent and our technology was powerful, we could generate money in the first year. If industry is not interested in this first period, they will not be later on. In a way, that first period is a measure for future success.'

'By smartly licensing patents, ViroNovative created more than a hundred research jobs'

Claassen also explains that to attract industry, it is of most importance to show that your claimed invention works. Therefore, you need a strong virology laboratory, to prove that the patent is valid. 'We are fortunate to have received very good support from the Erasmus Medical Centre.'
Subdivision of the market is another point that adds to the ViroNovative success story. ViroNovative sublicensed 14 companies for diagnostics and antivirals in the United States and Europe. Several companies develop and produce diagnostic kits. These kits differ in the use of particular detection methods or in their sensitivity or specificity, but they all make use of the knowledge that ViroNovative provides. End-users make their own choice on which kit they want to purchase and ViroNovative receives royalty payments.

Furthermore, ViroNovative out-licensed the patent rights to develop vaccines and therapeutic antibody applications claimed in their patent to the biotech company MedImmune that had plans for developing a vaccine. Since then pharmaceutical company AstraZeneca has acquired MedImmune and decided to abandon the development of an hMPV vaccine. This was disappointing for Osterhaus, who is eager to progress. 'We are now talking with new partners for the vaccine development.'

Hand-in-glove

But what about publishing research results? There is this unwritten rule in scientific research that says: what is unpublished does not exist. Osterhaus and his group's deep-rooted goal is to publish in high-ranking journals. However, with ViroNovative, he also wanted to create a vehicle that allowed the university to financially benefit from the commercial development of his research. Osterhaus needed to take into account the requirements for obtaining patent protection, which necessitate the filing of a patent application before the first publication of an invention. By doing so, virology researchers at the Erasmus MC have been able to publish in high-impact papers while securing patent rights. Business developers, IP experts and scientists worked together hand-in-glove. Consequently, there was no interference of scientific output with IP protection.

Creating jobs

With the patent, ViroNovative was able to generate several millions of euros of free cash flow. This money flows back to the Viroscience department. In that way, the company created more than a hundred jobs at Erasmus MC, which allowed more research to be performed.
The main driver to work at ViroNovative for Claassen is that he wants to do good work for society. He wants to make his business an economic success. 'In the end, it all boils down to the fact that I want to create jobs.'
Osterhaus appreciates the job creation that IP valorisation can bring, but his main ambition is to improve public health. 'We do important work on a virus that hospitalises up to 1% of all children and is also dangerous to elderly people and transplantation patients. In countries with a less-developed medical infrastructure, infected patients may die from this virus. So I think ViroNovative is of great importance to society.'

In the spotlight: Selling knowledge awarded

ViroNovative has developed a technology transfer model for biotech-based scientific research. The model focuses on capturing the value of new findings in continuous collaboration between academia and industry and with a direct link to the relevant industries for a better transfer to the market and ultimately to the patient. In 2009 ViroNovative won the annual Valorisation Award of The Netherlands Genomics Initiative (NGI). ViroNovative received the award for excellence in structuring and managing technology transfer activities. According to the NGI jury, ViroNovative has demonstrated excellence in deal-making with industry. This way, valuable knowledge developed by scientists is utilised to provide benefits for society and industry.

Galloprotect

Keeping an eye on the beetles

In 1999, alarm bells went off throughout Europe when a devastating pest to pine trees, which was already rampaging Asian forests for years, was detected in Portugal. Quick action by Spanish scientists, government officials and a producer of insect attractants resulted in Galloprotect – a multi-compound attractant that helps forest managers monitor and control the threat to their precious pines.

tree killer The pine sawyer beetle transports the worm *Bursaphelenus xylophilus*, a real pine tree killer.

When we talk about health, we generally mean human health. When the conversation includes farmers and veterinarians, we could also be talking about animal health. But what about forest health? 'Compared to human or even animal health, forest health is considered a small war. A minor problem in the general opinion,' says Professor Juan Pajares of the Sustainable Forest Management Research Institute of the University of Valladolid in Spain. However, forests are essential for life on earth, they form the habitat of a wide variety of humans, plants, animals and microbial organisms. Forests provide food, medicinal compounds, building materials and act as the lungs of the planet. Therefore, it is worthwhile to shift our attention to the health of other living species now and then. To trees, for example. In this case, pine trees.

- **Product:** Galloprotect Pack and Galloprotect 2D, traps for nematodes that harm pine forests
- **Research institute:** Sustainable Forest Management Research Institute (IUGFS), University of Valladolid (Spain)
- **Marketed by:** SEDQ (Sociedad Española de Desarrollos Quimicos), Barcelona (Spain)
- **On the market since:** 2010

GALLOPROTECT PACK

Tiny worm

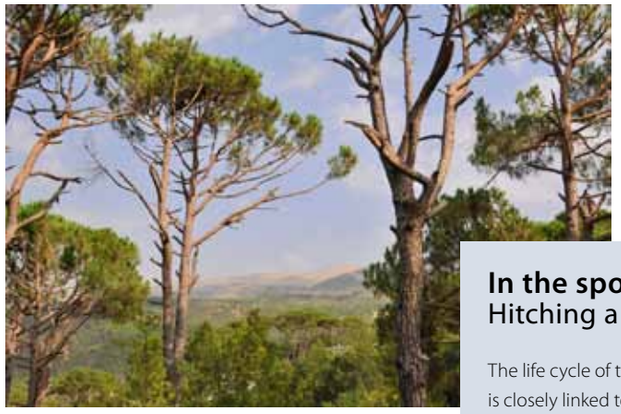
One of the health risks that pine trees are facing is infection with a very small worm, the pinewood nematode *Bursaphelenus xylophilus*. This one-millimeter long creature is a formidable adversary as it causes pine wilt disease, which affects the vascular system of the tree. In infected trees, water transport to the foliage fails and as a result, leaves and stems start to wilt, ultimately leading to the death of the tree. It is not exaggerated to state that the pinewood nematode is a real tree killer.
Originally from the United States, where native pine trees have developed a certain level of resistance, the pinewood nematode emerged in Japan in the early 20th century and developed into a serious pest. From Japan, the pest spread to China, Korea and Taiwan and is today a prominent threat to forest health throughout East Asia.
Besides the devastating ecological effects of massive tree loss, economic damages to the timber industry and related sectors are huge as well. No wonder that when the pinewood nematode was detected for the first time in Europe, scientists, forest managers and government officials started worrying. 'At first, we all hoped that this secluded location would help prevent the spread of the pest,' Pajares recalls. 'But that turned out to be idle hope. When the nematode was detected throughout Portugal, alarm bells went off in several European countries, particularly here in neighbouring Spain.'

Beetle turns bad guy

Pajares, who by that time had built a track record in studying the interactions between plant pathogens and their carriers got together with environmental officers from the Spanish government and scientists working in the same field to discuss the best approach to tackle this imminent threat.

> 'The key to the beetle trap is a smart combination of chemical attractants'

In 2003 a government-funded project was launched to find chemical compounds to attract the pine sawyer, a beetle that feeds on young twigs of healthy pine trees. A beetle? Didn't a nematode cause all the panic? This is where a new character enters the story. The threat is the pinewood nematode, but this tiny worm cannot move around on its own. It needs transportation and for this, it literally hitches a ride from the pine sawyer beetle. To fight the pinewood nematode, all eyes are on



protection State plant protection services all over Europe use Galloprotect products to guard their forests.

attracting the pine sawyer beetle *Monochamus galloprovincialis*. An impressive looking beetle with long horns that belongs to the *Cerambycidae* family of woodborer beetles, which feed on the bark and twigs of healthy trees.

Chemical communication

Although pine sawyers themselves cause damage to the trees, it is nothing compared to the impact of the pinewood nematode. 'Until that first detection in 1999, the *Monochamus* beetle family was hardly studied in Europe, because it is a secondary insect, meaning that it is considered a harmless beetle,' Pajares says.

'When looking for attractants for this particular beetle, we therefore started with compounds that were known as attractants for other species of beetle. For example, different types of terpenes, the characteristic pine scent and pheromones of other trunk borers such as bark beetles.' Pheromones are chemicals that insects use to communicate with other insects from their own species. These compounds can also have an effect on insects from a different species, in which case they are called kairomones. 'We quickly found out that we needed a mixture of different chemical compounds.'

In the spotlight: Hitching a ride

The life cycle of the pinewood nematode is closely linked to that of the pine sawyer beetle. This is how it works. The pinewood nematode lays its eggs in decaying pinewood, just as the pine sawyer beetle does. When the nematode larvae hatch and develop to a certain stage, they prepare to become airborne by entering the body of immature beetles also present in the decaying wood.

The mature beetles then emerge and move to the pine trees to feed on new shoots and that is when the young nematodes leave the beetle and enter the pine twigs through the bites. The nematodes then cause the death of the infected tree, leading to the arrival of new beetles to lay their eggs into the decaying wood. The infection cycle starts again when the nematodes enter the bodies of beetles present in the tree and hitch a ride back to healthy trees.

Pajares already collaborated with the Spanish company SEDQ on attractants for bark beetles and approached them to produce the three-compound lure for *M. galloprovincialis* made of a pine terpene and two bark beetle kairomones. SEDQ develops and produces a wide range of insect attractants and traps. 'SEDQ is a very scientific-minded company,' Pajares explains his choice. 'Their work is thorough and properly executed and they are very careful about what they do.'

Hitting the jackpot

The first mixture worked for monitoring, but the results were not sufficient for controlling the beetle. Pajares teamed up with David Hall of Greenwich University in the United Kingdom, an expert in pheromone research. They were able to identify the *M. galloprovincialis* pheromone that showed the same attractive effect as the three-compound kairomonal mixture. But when they combined these two approaches, they really hit the jackpot, says Pajares. 'The effect did not simply double, but quadrupled. Once we identified this mixture of pine attractants, bark beetle kairomones and pine sawyer pheromone, we quickly moved with government officials to get the mixture out to forest managers and enable them to monitor their grounds. We did this even before it was a commercial product, the need was that high.'

But commercialisation of the invention was not ignored. The University of Valladolid filed for a patent, which was subsequently licensed to SEDQ, where the invention was further developed into two commercial applications: Galloprotect Pack and Galloprotect 2D.

'Current users of the Galloprotect range are mainly public administrations and state plant protection services, but also research institutes and private individuals. All located in different parts of Europe,' says Patricia Acín, Agronomic Development Manager at SEDQ. 'The use of Galloprotect is increasing annually and in general, we can say that our users are satisfied with the performance of the product.'

Although GalloProtect does not prevent the spread of the nematode, it does allow monitoring forest health. This will give forest supervisors time to take measures against the spread of the disease, like removing dead wood, increasing surveillance and selectively cutting down trees.

What makes Galloprotect so special is the incorporation of the *M. galloprovincialis* pheromone and the formulation of the different compounds.' Pajares' group currently participates in REPHRAME, an EU research project on the development of applications of this attractant to be used in pine wilt disease management.

Respectful control

The collaboration with the group of Juan Pajares still continues. 'We are looking into improving traps for *M. galloprovincialis*. Moreover, we examine possibilities to develop related products for other species, because a different *Monochamus* beetle is responsible for the spread of the nematode in Asia. Collaborating with academic institutions is important for us to obtain a broader range of products', Acín says.

She foresees a growing market for products like Galloprotect. 'The use of pheromones and other attractants does not eliminate a pest, but enables us to control it to a level that large-scale economic damage can be prevented. To keep the pest below harmful levels, we need to monitor and control it continuously. That means an on-going market for this type of product, which control the pest but do so in a manner that is respectful to both environmental and human health.'

Ovizio

Expanding views with 3D microscopes

When scientists from the Belgian Université Libre de Bruxelles (ULB) met technology transfer professionals, they could not foresee how only a couple of years later they would be heading a firm developing and selling a full range of microscopes based on digital holography. The basic technology was developed at the university, the applications by the spin-off company Ovizio.

Studying liquids and making real-time images of cells in a flow, with a broader scope. These are just some of the advantages of 3D digital holographic microscopes, where the light source is a laser beam. These microscopes provide images that cannot be seen through a traditional lens. Instead, they are translated to the computer screen and can be transformed in quantitative actionable data. These holograms provide much more information than ordinary microscopes do. They can be used to count cells and determine cell viability in life science applications. Furthermore, it is not necessary to focus the lens on an object. The software refocuses all information. For classical microscopes, laboratory assistants have to prepare samples in a petri dish disturbing the culture under investigation. Using digital holographic microscopes means that the samples can be analysed directly without transferring them to a petri dish or treating them with a dye or other substance.

- **Product:** 3D holographic microscope
- **Research institute:** Vrije Universiteit Brussel (Belgium)
- **Marketed by:** Ovizio (Belgium)
- **On the market since:** 2010
- **Noteworthy:** Applications from cancer diagnostics to beer brewing

OVIZIO IMAGING SYSTEMS

Long road

The basic technology of digital holography in microscopes originates at the Université Libre de Bruxelles in Belgium, where Frank Dubois and Catherine Yourassowsky, worked on several research programs. Dubois, one of the pioneers in holographic technology, calls it a long and difficult road. Back in 1999 Dubois was busy finding an alternative light source to laser beams. 'Laser beams were commonly used as the main light source to produce holographic images. With my background, I knew laser beams tend to add a lot of noise to the picture. The images you get are disturbed.' To prevent this from happening, Dubois and his team tested different light sources and eventually found an advanced light source to produce images of the highest quality.

diagnostics Studying liquids and making real-time images of cells in a flow with a broader scope are just some of the advantages of 3D digital holographic microscopes. (Photos by NCI and Ovizio)

Space

One of the projects Dubois was involved in was the development of instruments meant for space experiments using holography. Two digital microscopes he designed and developed are now on board the International Space Station. In 2009 Dubois realised this technology would also be advantageous for applications in life sciences. He met Serge Jooris and Philip Mathuis and the idea to form a spin-off company was born. 'In the past Serge worked at the university as an assistant. He knew about the microscopes that Dubois developed for the ISS and went to talk to Dubois about another project we were working on. His plan was to develop an application for a webcam that would make perfect holographic measurements of the body to use in the fashion industry. Instead, he came back with this project and honestly, we both fell in love with the idea to develop applications for 3D holographic microscopes. We saw how many possibilities this technology offers, wrote a business plan and started Ovizio,' Mathuis, CEO of Ovizio, explained.

Intellectual property

Before the partnership could go ahead, the Technology Transfer Office (TTO) stepped in

In the spotlight: Food, water and beer

Not even the sky is the limit for applications for 3D holographic microscopes, since they already circle the Earth on board the ISS. Although Ovizio does not take on too many projects at once, the company is looking into various possibilities. Apart from obvious applications in life sciences, the technology can also be applied in fields like food and beverage, stem cell therapy research and water technology. Now, Ovizio is investigating the possibility to provide Belgian beer brewers with an application to count yeast cells during the brewing process.

beer Ovizio develops an application to count yeast cells during the brewing process. (Photo by Debora Cartagena)

to make sure all paperwork was done. At the beginning, the digital holographic microscopy technology was designed and dedicated to spatial instrumentations only. However, both the researchers and the TTO rapidly acknowledged the technology's potential, TTO Advisor Pierre Galland says. The TTO's first involvement was the protection of the intellectual property (IP). 'Thanks to the IP-dedicated fund of the university, it was possible to file several patent applications and maintain them during several years until the creation of the spin-off,' Galland says.
In all, the ULB filed three patent applications between 2001 and 2008. These patents, granted in several countries, cover different configurations of microscopes and the use of fluorescence. Ovizio obtained a worldwide licence to develop applications based on this technology. The patents they acquired for these applications are their own. The TTO also helped Ovizio to raise funds. Theodorus II, the venture capital fund of the ULB, invested in the first rounding fund of Ovizio. Finally, the TTO was involved in the licence agreement between the university and Ovizio to exploit the digital holographic microscopy (DHM) technology. 'We wrote the licence agreement, negotiated the terms: exclusivity, financial terms, first refusal right and so on. This licence agreement was the first requirement to enable Ovizio to raise funds,' Galland explains.

Finding partners

From the start, Jooris and Mathuis went out to find global, established partners who were interested in commercialising 3D holographic microscopes for specific applications. One of Ovizio's partners is Applikon Biotechnology. 'We signed an agreement for the use of our software platform to monitor cells in bioreactors used to develop vaccines and other cell-based therapies.' The technology is also well suited for cancer research, monitoring the migration of cancer cells in large samples. 'We have developed a device that analyses smears of patients visiting the gynaecologist. Today women have to wait at least four weeks for results. With our technology, the analysis can be done immediately,' Mathuis says. Another promising field is water technology. 'The university is involved in a research programme with several other universities and partners to adapt this technology to detect bacteria or other types of contamination in ballast water, drinking water and waste water. We have already identified dozens of possible markets for these applications.' All these projects give Ovizio the chance to grow. The company currently has 13 employees and more people will be needed before the end of the year. The company focuses on developing the platform technology, applications and software, leaving the commercial side of the work to a number of global partners and resellers.

Collaboration

Frank Dubois is very satisfied with the collaboration with Ovizio. 'I am a professor at the university not specialised in writing business plans. That is not my job. Working with people who know the business and how to promote products has been great so far. At the university, we develop new ideas, new improvements. We are still in close contact with Ovizio, sometimes daily, sometimes once a week. For them it is important to stay in touch so they have access to new ideas for their applications to evolve.' 'Ovizio is the perfect example that basic research can lead to industrial applications and the creation of a new business. Intellectual property is a crucial aspect of technology transfer and time is always against us. We are faced with deadlines and costs that could be very expensive for a university. Nevertheless, you have to take risks and in the case of Ovizio, it pays off,' Galland agrees.

> 'Ovizio is the perfect example that basic research can lead to industrial applications and the creation of a new business'

The university and Ovizio remain favourite partners for the development of the DHM technology: Ovizio has the right of first refusal, which means that new patent applications, new developments and improvements realised by the university on the DHM technology are first proposed to Ovizio for valorisation and industrial exploitation.

Beneficial

Dubois is convinced that holographic technology will benefit society in general. 'There is a huge market out there. Detecting cancer cells is relatively easy with these microscopes. That is already possible. We can provide faster answers and improve diagnostics in general. That will certainly have a big impact on the health of people. The same goes for applications in water technology, which will also be advantageous for people. I will be the first to admit that this new microscope is not a magical instrument solving every problem. However, what it will do is provide a range of breakthrough applications to be used in a wide variety of areas.'

Icon

Caries treatment without drilling

Drilling and filling is the usual dentist's approach to caries. In the early stages, however, caries progression can be halted with a new infiltrant fluid. This fast, painless technique leaves the healthy tooth tissue intact. The German company DMG has perfected the technology, which was invented at Charité-University Medicine in Berlin, Germany and brought it to the worldwide market.

- **Product:** Icon, a fluid that halts caries progression
- **Research institute:** Charité-University Medicine (Germany)
- **Marketed by:** DMG Dental Material Gesellschaft mbH (Germany)
- **On the market since:** 2009
- **Noteworthy:** DMG won the 2010 German Innovation Award in the category "medium-sized company" for Icon

Imagine a dentist who does not reach for his drill as soon as he identifies a caries lesion between two of your teeth. Imagine him sticking an ultrathin device between the teeth and applies a tiny bit of fluid instead, exactly in the right spot – and voilà, you are done. No anaesthetic, no drilling, no filling and no pain and sensitivity in the weeks to come. If you ask dental scientist Hendrik Meyer-Lückel, this will become the preferred routine in dental practices around the world. 'The technology's achievements are even better than we expected,' he says. 'Now the main challenge is to change the "drilling and filling" paradigm that still prevails among dentists.'

Together with his colleague Sebastian Paris, Meyer-Lückel developed this new caries treatment, called Icon, at Charité-University Medicine in Berlin, Germany. His research was funded in part by Deutsche Forschungs-gemeinschaft (DFG). 'Caries lesions are porous,' he explains. 'When left untreated, they will quite often progress due to acids secreted by bacteria in biofilms on the teeth. We are now able to halt this process by applying an infiltrant that penetrates into the porous structure of dental enamel. This fluid hardens and forms a protective layer that prevents further demineralisation.' The treatment is suitable for lesions in the early and medium stages, Meyer-Lückel clarifies, when there is no actual hole in the tooth yet. When the lesion is cavitated or has penetrated deep into the dentin, drilling will still be necessary.

Icon is applicable on all smooth surfaces of teeth but the technique offers most advantages for the so-called proximal surfaces: the sides of teeth that touch each other. 'These spaces are notoriously difficult to reach, both for everyday cleaning and for treatment,' says Meyer-Lückel. 'When dentists drill to treat an early lesion in this area, they will have to destroy a lot of healthy material to get to the affected tissue. This is obviously uncomfortable for the patient and shortens the lifetime of the tooth.'

Pore structure

Meyer-Lückel and his colleague Paris experimented with various combinations of etching gels and infiltrants and eventually found an ideal combination. 'We use hydrochloric acid to etch the surface of the lesion,' he elaborates, 'which opens up the pore structure. Then we apply a resin, consisting of low-viscous organic monomers, which flows into the capillaries of the lesion.' This resin only attaches itself to the affected tissue, he clarifies and hardens quickly. Clinical studies have shown the effectiveness of the treatment for up to five years but the scientist is optimistic that the benefits persist much longer. Product developer Hans-Dieter Höhnk at the German company Dental Material Gesellschaft (DMG) was enthusiastic about the Icon concept as soon as he heard about it.

> 'The challenge is to convince dentists not to drill and fill but use the Icon fluid instead'

'One of my colleagues, who is a dentist, told me about this invention,' he says, 'and said it was quite remarkable. We wanted to see this for ourselves and invited the scientists to present their technology to a team of experts at DMG. We immediately realised that this was what we have been looking for. It was new and inventive. It filled the gap between prevention and invasive treatment.'

Höhnk and his colleagues, however, identified some

dentist at work (Photo by Technical Sergeant Tony Tolley)

challenges in the application system. The scientists had been working with small strips similar to filter paper that contained the infiltrant. DMG developed a more advanced system: a pouch made out of very thin foil. The pouch is inserted between the teeth with the help of a special holder which resembles a simple floss tool. A syringe is then used to insert the liquid. The pouch has tiny holes on just one side, bringing the fluid into contact with the affected tooth only. 'This application system is completely new,' Höhnk emphasises. 'Our engineers at DMG developed it in close cooperation with the inventors at the university.'

Licence agreement

Although the initial contacts were made directly between the Charité-University and DMG, a third party was involved in negotiating the contracts: ipal, a German commercialisation agency for academic inventions.

microbes Caries is caused by bacteria that live on sugar residues.

In the spotlight: Caries

Dental caries is a very common phenomenon. An average person has around eight proximal (in-between teeth) caries lesions throughout his or her life. Caries, also known as tooth decay or dental cavity, is characterised by demineralisation of the hard tissues of the tooth: enamel, dentin and cementum. When left untreated, the decay can reach the underlying dental nerves, causing excessive pain and even loss of the tooth.
Caries is caused by acids released by bacteria situated in a biofilm on the tooth surface. These bacteria live on sugar residues. This is why adequate mouth care (i.e. biofilm removal) helps prevent caries. Tooth surfaces are constantly demineralised under the influence of acids, but remineralisation also takes place, promoted by substances in our saliva and fluoride in our toothpaste. Only when this balance is disturbed will caries get a chance to develop. Some people are more susceptible to caries than others, due to the composition of their saliva, oral hygiene, eating habits and even the shape of their teeth.

'Our technique can protect tooth decay for as much as a decade'

prevention Icon contains a fluid that hardens to form a protective layer on the tooth, preventing further damage. (Photo by David Shankbone)

'As the exclusive service provider, we are in charge of all inventions coming from the university,' says Janin Hofmann, Head of Acquisition and Commercialisation at ipal. 'The ownership of the patents on the technology still lies with the university. We acquired an exclusive license on the technology and we in turn have negotiated a sublicensing agreement with DMG.' Besides ipal's expertise in identifying an invention's potential, highlights Hofmann, the added value of this triangle construction is the fact that ipal can play a neutral part in the process of technology transfer. 'This allows us to serve the interests of the inventors as well as those of the licensee. We always keep the success of the future product in mind.'
Icon has been on the market since 2009 and is now available in many countries around the world, including Germany, the United States and Russia. 'Dentists often believe that if you do not drill and fill, bacteria will infiltrate the tooth and cause damage from within. This, however, is a misconception,' says inventor Meyer-Lückel. 'If there is no cavitation in the teeth, the bacterial film is limited to the outside of the tooth and the acids are blocked very effectively by our hardened resin.'
In addition, as both Höhnk and Meyer-Lückel point out, some dentists may be hesitant to employ a technique that protects a tooth for as much as a decade – fearing that this may hamper business. There is another side to this, though. Scientists have also developed a tool that allows dentists to identify the early stages of lesions much easier on X-rays. 'This should make dentists happy, because it allows them to find more lesions to treat,' laughs Meyer-Lückel. 'In any case, if they really want to act in their patient's best interest, dentists should opt for the preventive approach.'

White spots

Höhnk is optimistic. He too is convinced that the preventive approach will prevail. 'Although sales are not meeting our expectations yet,' he indicates, 'we definitely have a business case and sales are rising steadily. Surprisingly a new, aesthetic market has opened up: besides halting proximal caries, our product is also effective against certain discolorations of the teeth.' People with dental braces, for example, are often left with "white spots" on their teeth after brackets have been removed. Applying Icon will restore the tooth's original colour and protect from demineralisation. 'Clearly this is not what the infiltration method was originally developed for,' says Höhnk, 'but we are of course more than happy with this additional application.'

Colophon

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