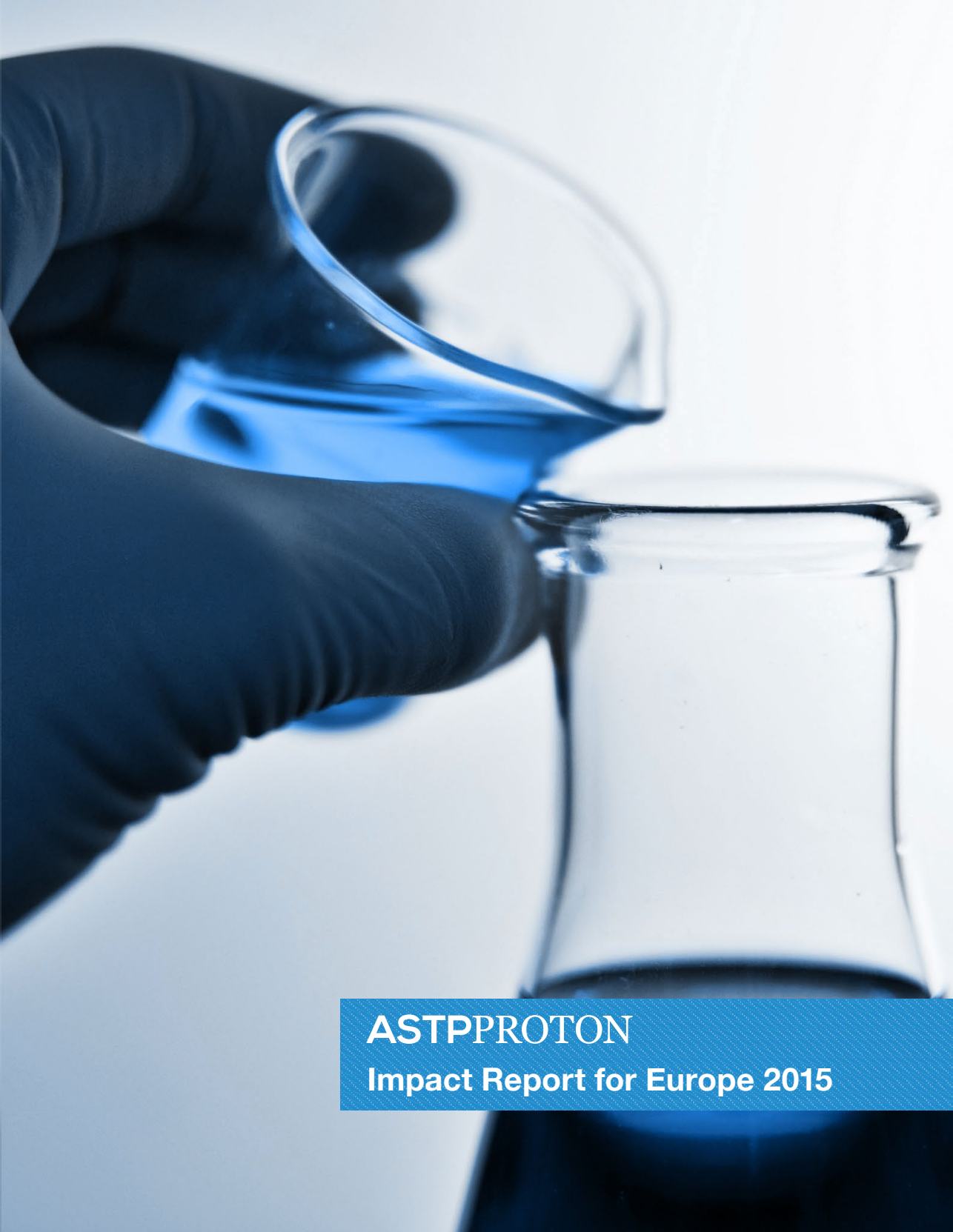

# ASTPPROTON

## Impact Report for Europe 2015

ASTPPROTON
KNOWLEDGE TRANSFER EUROPE

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

**About ASTP-Proton**

ASTP-Proton is the result of a merger of activities between ASTP and Proton Europe, the two pan-European associations that previously support the academic knowledge transfer base.

ASTP and Proton Europe decided to combine their activities in May 2013 to offer more and better services to knowledge transfer professionals with a broader scope, being more inclusive in the "innovation ecosystem".

We focus on knowledge transfer professionals and knowledge and technology transfer offices by establishing and exchanging best practices and training of professionals.

In addition, ASTP-Proton is a cooperative platform for the various national networks for knowledge transfer in Europe. We also represent the interests of our members at the European level in innovation and technology transfer policies and other relevant matters.

Last but not least, ASTP-Proton collects and publishes data, success stories and other information relevant to the knowledge transfer field and its stakeholders.

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entente
KNOWLEDGE TRANSFER IN HEALTH

*'Each of these stories is a convincing example of how academic health research can directly contribute to the successful development and market introduction of products and services addressing the needs of the patient.'*

Every year, a considerable amount of public money is invested into health research by public research organizations, research hospitals and universities. For instance, during 2014-15, the EU will have invested some €1200M in health research and innovation under the new Horizon 2020 framework programme.

In return for this investment, the general public reasonably expects that the results of the academic research effectively contributes to the improvement of the European health care. In view of this expectation, the European academic institutes have added to the traditional dissemination of research findings through publication and teaching an increasing involvement in technology transfer activities.

Supported by their technology transfer offices, the academic researchers more and more seek to convince the health industry and investment community that their research is a source of competitive innovation opportunities and that they are able to assist in the development of these technologies towards new, commercial health products and services.

The FP7 ENTENTE project aimed at contributing to strengthening the academic technology transfer offices and at promoting collaboration between industry and academia in the health sector, through networking and sharing between the European technology transfer stakeholders. Many different technology transfer organizations from both industry and academia supported the project by either sharing best practices, serving as hosts for the ENTENTE staff exchange programme or by delegating representatives to the ENTENTE Advisory Board.

In addition, the involvement of ASTP-Proton in ENTENTE and the kind participation of its membership allowed collecting the ENTENTE technology transfer success stories, which have been published in this document and the ASTP Impact Report 2013.

Each of these stories is a convincing example of how academic health research can directly contribute to the successful development and market introduction of products and services addressing the needs of the patient. We hope that this collection of stories will convince the readers of the relevance of academic research as a source of innovation for the health industry and may serve as an inspiration and motivator for both industry and academia to pursue and strengthen their collaboration.

**Olivier Lescroart**
**Technology Transfer Officer**
**KU Leuven Research & Development**
**Co-ordinator, WP3 ENTENTE**





*'This is what knowledge transfer is all about, ultimately: maximizing the chances that the results of academic endeavor find application in society.'*

Placed before you is the second edition of the 'Impact report for Europe'. The first report came out in 2013 and was published by ASTP. Having merged activities with Proton-Europe in that same year, this new edition is published by ASTP-Proton.

This new 2015 edition presents examples of the impact of European research on health through the translation of laboratory results into products and services that impact patients' lives. These are stories of products that have enjoyed success both in an economic and a societal sense and that originate from research performed at public research organizations in Europe.

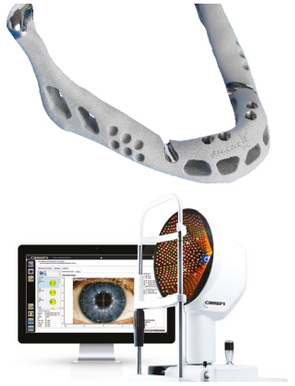
No matter what scientific discoveries tell us about the world around us, it is this practical application of scientific knowledge in daily life that for most people leaves the most important impression. This is what knowledge transfer is all about, ultimately: maximizing the chances that the results of academic endeavor find application in society.

The stories in this publication help make the case for public investment in academic research. They also put a face on the people who help bring about the transition from the laboratory bench to the patient's bedside: researchers, entrepreneurs, investors, physicians and knowledge transfer professionals.
Last but not least, the stories help create an image of innovation and leadership for those public research organizations that value not only scientific excellence, but that also take the necessary next steps to ensure that the fruits of their research programs do not stop at high profile academic publications.

While the odds that these activities will bring great financial rewards to the public research organization are small (especially in the short run), they contribute to a lively culture of entrepreneurship and help create high-end jobs. Before long, they will also help attract the most talented students and researchers and additional resources for research.

I would like to thank Chared Verschuur-Ballo, Olivier Lescroart, Erik Vane, Christian Stein and Maria Tavares for their contributions to the realization of this report and the ENTENTE consortium members for their support for this initiative. Last but not least, many thanks to those organizations who submitted their stories for review, helped with arranging interviews, collecting photo material and graphics and proofreading of the stories. Should your story not have been selected for inclusion in this year's report, I hope you will resubmit it (and others) for our next edition.

**Koen Verhoef, PhD, RTTP**
**Member, ASTP-Proton Impact Report Committee**
**Former Board member, ASTP and ASTP-Proton**







Contents


## abcdeSIM

# Simulation-based emergency training saves time and lives

Training in emergency medicine is a requirement for every doctor and nurse around the world. Naturally, expertise comes with practical experience. However, doctors and nurses must be prepared for all types of medical emergencies, even when they lack extensive experience. With abcdeSIM, health professionals can practice emergency training in different lifelike patient scenarios without putting patients at risk.

Simulation-based learning has long been used in aviation, space flights and the military as a tool to reproduce substantial aspects of the real world with guided elements. In medical education, simulation-based learning helps develop the knowledge and skills of health professionals while protecting patients from risks.

In the digital age, improved simulation platforms that are useful for medical education come in the form of video-gaming technology. Video-gaming creates a life-like visual tool for information that needs to be absorbed. Studies have also shown that video-gaming promotes problem-solving and thus resembles the required learning environment of a health professional. Dr. Stephanie Klein Nagelvoort-Schuit, Head of the Department of Emergency Medicine of Erasmus University Medical Center (Erasmus MC) in Rotterdam, explains gaming is, in fact, a good fit to medical learning, especially emergency medicine. They both feature stressful situations, she says, and both require quick decision-making while simulating real-life situations.

*'Gaming is, in fact, a good fit to medical learning, especially emergency medicine.'*

As an emergency medicine teacher, Klein Nagelvoort-Schuit explains that to learn emergency medical skills, hours of practical experience and training are essential for every doctor, nurse, or primary care provider. This takes up a significant amount of teaching time, which could be better spent at the bedside of a patient.

Klein Nagelvoort-Schuit turned to gaming technology for innovative medical training. 'At first, the idea was e-learning–to use a simulation game, to make a game to teach young doctors to treat patients,' she says.

**Product** abcdeSIM
**Research institute** Erasmus MC
**Marketed by** VirtualMedSchool
**On the market since** 2012

**Dr. Stephanie Klein Nagelvoort-Schuit (left) and Ronald Nanninga (right) use simulation to prepare doctors and nurses for all types of emergencies.**

### Serious game

Gaming is not only attractive as a platform but is also well-suited to emergency medicine. 'In emergency medicine, you work under stress and you make split-second decisions under pressure. So here we simulate the stress, the environment and the time constraints,' Klein Nagelvoort-Schuit explains.

E-learning and gaming, in this respect, are not mere ancillary forms of teaching but are maximised to their full didactic potential given the natural approximation of emergency situations.

The abcdeSIM is a combination of gaming and simulation technology that trains physicians to work in a medical emergency setting using the internationally adopted ABCDE method. Using the online realistic platform of gaming software design principles, abcdeSIM features medical and educational expertise, as well as an immersive emergency department environment to challenge doctors and nurses to respond to sick patients.

The concept is similar to flight simulation where student pilots learn the basic theories involved in flight maneuvers and develop instrument proficiency under controlled environments. 'The thinking was, if pilots use flight simulators to practice their skills, why do doctors not use similar tools?' says Ronald Nanninga, co-founder and CEO of Virtual Med School B.V.

Going a step further from other gaming software and regulator flight simulators, abcdeSIM made the simulation of the human patient more life-like and dynamic. Erasmus MC developed a mathematical model of human physiology, covering more than 200 parameters for respiration, blood pressure, circulation, consciousness, oxygen level, and breathing. With a model simulating human body response at 500 times per second, the patient reaction to the trainee's treatments is as real and immersive as it can be

'The simulation is totally new and based on physiology. The model will predict how the patient will react. The mathematical model reacts to what you do; it reacts to all the treatments you give. The model does it all by itself,' explains Klein Nagelvoort-Schuit. This enables doctors and nurses using abcdeSIM to recognise critical illnesses and injuries more accurately; they are then able to resuscitate and

stabilise accordingly. Doctors and nurses are given the opportunity to train in life-like situations without the accompanying risks. As in flight simulation, where missteps are not deadly, mistakes made in online simulation of emergency medical treatment in abcdeSIM are not fatal as in real life. Important learning points, especially towards the objective of keeping the patient alive, are learned given the accuracy of the treatment-reaction dynamic simulated by the game.

*With abcdeSIM, doctors and nurses are given the opportunity to train in life-like situations without the accompanying risks.*

**Raising skill levels and revenue**

From the development of the abcdeSIM for emergency doctors, four other versions of the abcdeSIM are now being used: abcdeSIM for emergency department nursing, for pre-hospital primary care, for severe burn victims, and for paediatrics.

Developing the abcdeSIM from concept to commercial roll-out required input from universities, medical institutions, and digital learning developers. According to Nanninga, the initial versions of abcdeSIM were developed and financed by Erasmus MC; SBOH, a Dutch foundation for the education of those training to be general practitioners; and Stichting Coolsingel, a foundation that supports the development of innovative medical solutions in the Rotterdam region.

Further development of the life-like physiological patient model was provided by the University of Twente while technical support for the game was provided by IJsfontein and Health-e-Solutions. abcdeSIM for the treatment of burns was co-created with the largest burn centre in The Netherlands, the Maasstad Hospital, while the version for paediatrics was made with the Sophia Children's Hospital in Rotterdam. From the beginning, Erasmus MC's Technology Transfer Office (TTO) was involved to facilitate abcdeSIM's shift from the realm of science to market release. The TTO arranged and negotiated all collaborative contracts, ensuring that the intellectual property for the content and the software were protected.

An Erasmuc MC spin-off company, VirtualMedSchool BV, was then founded to manage the commercial roll-out, headed by co-founder and CEO, Ronald Nanninga. 'We are direct-selling licenses, and work with partners and resellers with a strong link to the medical (educational) field, to resell our serious games and further develop or co-create new versions of abcdeSIM,' says Nanninga on how they market abcdeSIM.

The aim of developing a game to train doctors and nurses had been primarily to improve the services that health professionals give their patients; in the process of widening the technology's use and benefit, revenues were also earned. Raising revenues, Nanninga says, is a means to advance the technology as the income of VirtualMedSchool BV is largely re-invested in the development of new e-learning games.

**Quality time, quality research**

Balancing the need to provide more quality time for the bedside care of patients versus the need to teach or learn emergency medical skills to doctors and nurses had served as the impetus for the creation of the abcdeSIM game. And it ticked this objective. The serious gaming platform gave doctors and nurses more time to enhance their medical skills on their own even while off-duty. It freed up more time for doctors to care for patients and opened up more opportunities to conduct research. 'This training at Erasmus MC led to a 50% reduction in training time and cost. Also there was increased efficiency in scientific research in using abcdeSIM," says Nanninga. Since September 2012, abcdeSIM has been made mandatory in the training of residents and medical students at Erasmus MC, which receives up to 300 new residents a year.

Most recently, VirtualMedSchool BV, in partnership with the Royal College of Physicians, rolled out abcdeSIM in more than 60 hospitals in the UK as part of the hospitals' IMPACT (Ill Medical Patients' Acute Care & Treatment) course. In The Netherlands, more than 45 hospitals, including all University Medical Centers, use abcdeSIM.

The teaching software has become the first serious game to receive five hours of Continuing Medical Education credit in all medical specialist organizations in The Netherlands. It is expected to receive European accreditation soon.

The abcdeSIM's instructive framework and excellent graphics have also impressed some organizations as it won the Dutch National Smart E-learning Award, the Valid Game Award, and the Accenture Innovation Award.

Inspired by the effectiveness of abcdeSIM as a learning tool, Klein Nagelvoort-Schuit says her team is now collaborating with other departments in Erasmus University to use the technology applied to abcdeSIM to build a game that will teach cardio-pulmonary resuscitation to high school students. They are also working on an online course about serious gaming principles.

**In the spotlight:**
Remember your alphabet

The ABCDE approach stands for Airway, Breathing, Circulation, Disability, and Exposure. This simple mnemonic spells the widely accepted approach used by health care professionals in the immediate assessment and treatment of patients who are critically ill or injured. Because clinical situations are usually complex, the ABCDE approach helps break it down for better treatment.

First, the airway is assessed and treated for life-threatening problems. Airway obstruction often causes lack of consciousness, which may lead to cardiac arrest. Second, a breathing assessment involves checking if the respiration rate of the patient is enough and whether there is a need to assist with the patient's ventilation. Third, circulation can be assessed by, among other aspects, inspection of the skin and overall behavior. Color changes, sweating, and reduced consciousness offer clues for circulatory problems. Fourth, checking disability involves grading the level of consciousness: whether the patient is alert, voice responsive, pain responsive, or unresponsive. Last, assessing the patient's exposure involves judging what may have contributed to the patient's condition by looking out, for example, for signs of trauma, bleeding or needle marks.

The success of the ABCDE approach is anchored on the fact that it is applicable to all types of patients and all clinical emergencies, whether on the street or in a health facility.

## Blinatumomab

# Breakthrough drug emerges for B-cell ALL

After decades of research, scientists have discovered a drug that engages the immune system to fight B-precursor acute lymphoblastic leukemia, a rare and aggressive type of cancer. Blinatumomab, which has been approved by the FDA in the United States, is now awaiting the green light for its release in Europe.

How would you like to have a soldier at your disposal, programmed to attack specific enemies in your defense? Even more amazing, these soldiers can detect hostile elements masquerading as friends, and eliminate these threats to keep you safe.

Now imagine these soldiers inside your body.

This is what researchers found out more than 30 years ago—that the cure to some cancers can be found in the human body, and that antibodies can be engineered to attack and kill tumour cells. Their knowledge, however, did not translate to a clinically approved, commercially available treatment for cancer until December 2014, when Blinatumomab entered the United States.

**Product** Blinatumomab (brand name: BLINCYTO)
**Research institutes** Ludwig-Maximilian-Universität and Max Delbrück Center
**Marketed by** Amgen
**On the market since** 2014

Blinatumomab is the first and only bispecific CD19-directed CD3 T-cell engager (BiTE®) immunotherapy to be approved by the US Food and Drug Administration (FDA) for the treatment of adult patients with relapsed or refractory Philadelphia chromosome-negative precursor B-cell acute lymphoblastic leukemia (B-cell ALL), a rare and aggressive type of blood cancer. Blinatumomab is manufactured by Amgen and marketed in the United States under the brand name BLINCYTO.

B-cell ALL is a condition in which the bone marrow generates too many B-cell lymphoblasts, an immature type of white blood cell. It is estimated that approximately 6020 new ALL cases are diagnosed in the United States each year. Of these, roughly 2400 occur among adults. In the European Union, there are more than 7200 new diagnoses of ALL annually with approximately 40% or 3000 diagnoses occurring among adults.

With the FDA's approval for the commercial release of BLINCYTO in December 2014, there is hope that the mortality rate among B-cell ALL patients will drop. The availability of such a drug to treat a rare blood cancer is groundbreaking for B-cell ALL patients.





**Dr. Christian Stein of Ascenion (left) and Dr. Peter Kufer of Amgen (right).**

Christian Stein, Chief Executive Officer of Ascenion, the technology transfer partner in this discovery, said 'this is the first time the patients will receive proper treatment because before, chemotherapy was basically the option with all its terrible side effects and lack of specificity.'

### Ending deception

Blinatumomab is an investigational BiTE antibody construct that helps the body's immune system to detect and kill cancer cells, which have long been able to trick the immune system into thinking that they are normal healthy cells. Because the immune system is deceived, it has been unable to eliminate tumours.

With Blinatumomab, the T cells—a type of white blood cells known to be the immune system's most potent killer of cells perceived as threats—are able to recognize malignant B cells and work against CD19, a protein found on the surface of B cells that cause leukaemias and lymphomas. The drug connects these two cell types and stimulates the T cell to apply cytotoxic activity on the target cell.

'The development of Blinatumomab was quite an exciting journey,' says Dr. Peter Kufer, Executive Director of BiTE technology at Amgen Research Munich (formerly Micromet) and one of the pioneers that discovered the drug. 'I am really grateful to have had the opportunity over such a long period of time to substantially contribute to the development of a drug that made it to approval and now prolongs or even saves patient's lives.'

Various formats of T cell-recruiting bispecific antibody constructs have been in existence since the 1980s, but nobody knew how to best combine the anti-tumour cell with the anti-T cell binding arm. Hence, for more than two decades, there was no major progress in this approach. Meanwhile, Kufer's group at the Institute of Immunology at Ludwig-Maximilian-Universität in Munich had developed Blinatumomab, which as a single agent efficiently induces T cells to kill CD19 positive tumour cells. Kufer collaborated with the research group of Dr. Ralf Bargou from the Molecular Medicine in the Helmholtz Association (MDC) in Berlin, who provided the CD19 binding arm.

**Small partner, big partner**

In 1998, Micromet, a small pharmaceutical outfit founded in Munich, Germany acquired the intellectual property rights to Blinatumomab from the academic partners owning the IP. Micromet brought the biotechnology company MedImmune on board in 2003, granting the latter a licence to co-develop its lead drug candidate Blinatumomab, then labeled MT103. The partnership, however, was discontinued, and Micromet reacquired the complete rights to develop and market Blinatumomab.

The year 2004 was an important turning point for the clinical development of MT103. 'We started to treat patients continuously in our clinical trials to provide T cells with the help they required long enough for them to recognize and kill tumour cells,' says Kufer. A year later, developers of the drug observed the first objective clinical response in a patient with non-Hodgkin's lymphoma, a cancer that originates in the lymphatic system.

In 2008, an article was published in the peer-reviewed journal, SCIENCE, on MT103's high clinical response rate in non-Hodgkin's lymphoma patients. 'In the same year, we started to see molecular responses in adult ALL patients with minimal residual disease,' Kufer recalls. 'In 2010 we observed the first objective clinical responses in adult patients with relapsed/refractory ALL, which paved the way to the pivotal 211 study."

The Phase II study of Blinatumomab at Micromet caught the attention of pharmaceutical firm Amgen, which was headquartered in the United States. Amgen forged a US$1.2-billion deal to acquire Micromet in 2012. Following the acquisition, the pivotal '211 study' was conducted: 189 adults with B-cell ALL were enrolled and treated with Blinatumomab via infusion for at least four weeks. Of the patients assessed in the study, 81 achieved complete remission or complete remission with partial haematologic recovery within two cycles of Blinatumomab treatment.

The majority of the responses—in 64 out of the 81 patients—occurred within the first cycle of treatment. Among the patients who achieved complete remission with partial haematologic recovery, 32 proceeded to haematopoietic stem cell transplantation and 60 achieved minimal residual disease response, which was an important parameter in predicting relapse.

Armed with substantial clinical proof, Amgen announced on 22 September 2014 its submission of a Biologics License Application to the US FDA for Blinatumomab (trade name: BLINCYTO). On 3 December 2014, the FDA granted BLINCYTO breakthrough therapy designation, priority review and orphan product designation, five months ahead of its supposed application review completion. The orphan product designation of BLINCYTO highlights it as a drug that may offer a significant improvement in treatment over existing options.

'Blinatumomab is the first clinical and regulatory validation of the BiTE® platform, a new and innovative approach that helps the body's own immune system fight cancer. Where approved, BLINCYTO is a new option to help manage this serious disease,' Amgen says.

**Price tag**

Even if the drug was a niche indication with a relatively small patient population, BLINCYTO racked up US$15M in sales for the first quarter of 2015. The U.S. Wholesale Acquisition Cost price at which Amgen sells BLINCYTO to wholesalers, without taking into account discounts, rebates, and other price concessions, is $89000 per cycle. The median duration of treatment for patients who responded in clinical studies was two cycles.

Amgen says the price of BLINCYTO reflects the significant clinical, economic and humanistic value of the product to patients and the healthcare system, as well as the complexity of developing, manufacturing, and reliably supplying innovative biologic medicines.

In the United States, BLINCYTO is a breakthrough therapy for an ultra-orphan patient population. Approximately 900 patients have Philadelphia chromosome-negative relapsed/refractory ALL. 'These patients have a median overall survival of just three to five months and BLINCYTO is the first major treatment advance for these patients in more than two decades,' Amgen says.

Efforts are also underway to make the drug available in Europe in the near future. On 25 September 2015, Amgen announced that the Committee for Medicinal Products for Human Use (CHMP), the scientific committee of the European Medicines Agency adopted a positive opinion recommending a conditional marketing authorization for BLINCYTO for the treatment of adults with Philadelphia chromosome-negative relapsed or refractory B-precursor ALL. Conditional licence requires for it to be renewed every year and it will be converted to full standard licence once post-licensing commitments have been fulfilled. Amgen expects a decision on the conditional marketing authorization application from the European Commission in the coming months.

Looking back, Kufer says the determination to proceed with a completely new mode of action to obtain clinical proof would have been hardly possible under a big pharmaceutical company setting. He says the acquisition of Micromet by Amgen happened at the appropriate stage of the drug development. 'It was critical that the development chain from university via small biotechnology company to big pharmacy worked, and that the transitions from one phase to the next came at the right time points,' Kufer says.

## In the spotlight:
Bloody war

Blood cancers are keeping the field of biomedical research busy.

Leukaemia alone has four main types: acute myeloid leukaemia (AML), chronic myeloid leukaemia (CML), acute lymphocytic leukaemia (ALL), and chronic lymphocytic leukaemia. The key distinctions between these types of blood cancers are related to how fast they progress and where the tumour cells grow. Because of this, treatment is often complex; it is not limited to one kind of therapy. Thus, it is imperative that investigative and clinical studies on new forms of therapies are intensified to offer patients a cure. Worldwide, leukaemia is the 11th most common cancer, with roughly 352000 new cases diagnosed in 2012, according to Cancer Research UK. It is estimated that there are only close to 600 adults with Ph-relapsed or refractory B-precursor ALL in France, Germany, Italy, Spain, and the U.K.

## Cassini

# True corneal shape analysis aids corrective eye surgeries

A doctoral student finds a flaw in a method long used to diagnose astigmatism and comes up with a solution: the Cassini. This diagnostic tool provides images of both the front and back surfaces of the cornea for a more accurate picture to guide medical procedures.

Eyes diagnosed with astigmatism essentially have a refractive error, or problems focusing light. Thus, instead of having a single focus, light on the front or back (or both) of the retina focuses on multiple points.

A procedure to test the eye for astigmatism is called retinoscopy, or by shining a light into the eye while manually introducing a series of lenses between the light and the eye. To give a proper diagnosis of the cornea, a clinician must be able to understand the cornea's shape and optical performance; this is done through a process called corneal topography.

In the early 17th century, the earliest corneal topography was done using the reflection of marbles from the cornea. The current Placido-based topography came in the 19th century and used the same principle by assessing the reflection of circular mires or rings—called Placido's disc or keratoscope—from the front surface of the cornea.

Named after its inventor, Antonio Placido, Placido's disc is made up of equally spaced alternating black and white rings with a hole in the centre to observe the patient's cornea. That opening in the middle of the concentric circles houses a convex lens for magnification to aid the examiner.

Corneal topography analysis is commonly used in planning procedures to correct astigmatism, fit contact lenses, and enable the screening of candidates for refractive surgery. In post-operative situations, corneal topography can help evaluate the dioptric change created at the cornea. The dioptre measures the power of the lens needed to correct vision to normal.

Corneal topography, however, is limited to the central portion of the anterior corneal surface. The need to study not only the anterior but also the posterior and the peripheral parts of the cornea has given way to the creation of new devices that can provide faster and more accurate diagnosis. It is in this landscape that the Cassini was born.

**Product** Cassini
**Research institute** University Medical Center Amsterdam
**Marketed by** i-Optics
**On the market since** 2013

**The Cassini is a diagnostic tool that provides for a more accurate picture to guide medical procedures.**

### Cassini

The Cassini is a diagnostic device that offers 'true corneal shape analysis' for better outcomes in diagnosis and corrective procedures such as refractive surgery, cataract surgery, and corneal transplant. It is also used in examinations like pupillometry and color photography.

One of the inventors, Dr. Arni Sicam, was a Filipino studying for his doctorate at the VU University Medical Center Amsterdam (VUmc) in The Netherlands in 2002 when he started work on the Cassini. The medical physicist said it was not his purpose to invent anything, and that as a student, he was simply improving on the current method used in ophthalmology for corneal analysis.

He, however, found a flaw in the technique: the Placido rings appear as equally spaced symmetric reflections if the eye is perfectly spherical, and take an oval shape or become distorted if the cornea is irregularly shaped or deformed. Thus, if the patient has astigmatism, the Placido disc becomes less accurate as a diagnostic tool because the process assumes that the cornea is symmetrical.

Sicam set out to find a solution for this inaccuracy. The VUmc Department of Physical-Medical Technology (FMT) provided him with the laboratories and other assistance needed to develop what would become the Cassini technology.

### Points system

Instead of rings, the Cassini uses points–red, green, and yellow LEDs–positioned in a unique relationship to four of its neighbours. 'The advantage of this is you can use the points to be the three-dimensional marker in the cornea, like a GPS system. Also, any irregularity can be picked up,' Sicam explains.

Aside from providing a better understanding of the corneal surface, the Cassini also enabled the imaging and measurement of the back surface of the cornea, which the Placido disc cannot do. Sicam says the points system of the Cassini provides a second reflection—a faint but detectable image of the corneal back surface, which provides the clinician more accurate information on the cornea's refraction. 'Without [seeing] the back surface of the cornea, errors in cataract surgery might happen, and the error margin is a difference of about 1 dioptre.

Cassini

## In the spotlight
### Shedding light on the cornea

The cornea is the clear, transparent, dome-shaped surface that covers the front of the eye. As simple as it looks, it is formed by a highly organized group of cells and proteins. It has no blood vessels which may nourish it or protect it against infection. This is because the presence of blood vessels may cloud the cornea and prevent it from doing its main function of refracting, or bending light.

As the cornea is responsible for focusing most of the light that enters the eye, it must be free of any opacity to help the eye see better. The cornea acts like a window that focuses light entering the eye, contributing to 65% to 75% of the eye's total focusing power.

The cornea is made up of five layers: the epithelium, Bowman's Layer, stroma, Descemet's membrane, and endothelium. In 2013, it was announced that the sixth layer of the human cornea was discovered by Professor Harminder Dua of the University of Nottingham. The new 15-micron-thick layer—now called Dua's layer—was found between the stroma and Descemet's membrane, and is now the fourth of six layers.

That spells the difference between needing glasses and not needing it. If you have [images of] the back surface of the cornea, you reduce that uncertainty, and there's a higher chance that the surgery will successful,' Sicam says. The Cassini has brought changes to ophthalmology, particularly benefitting patients requiring eye treatment. Before the Cassini, people aimed to be able to wear eyeglasses following cataract surgery. With Cassini, Sicam says, cataract surgeries are conducted with a higher success rate.

'One of the things happening now is that the demand of patients towards accuracy is higher. Before, people were happy with diagnosis that is not optimal. Now, usually when people go for cataract surgery, they want to come out with no glasses,' said Sicam.

**From laboratory to market**

Following the initial technology development of the Cassini at the FMT, Bart Klijsen, Senior Technology Transfer Manager at IXA VU-VUmc (former Technology Transfer Office VU & VUmc) was approached in 2007 by the inventors to assess the potential and feasibility of patenting their new technology. The outcomes of the evaluation process were positive, and a patent was filed. Around the same time, contacts were established with i-Optics to probe the company's interest in the technology.

i-Optics develops smart tools for eye diagnosis to enable better care for patients, while at the same time increasing efficiency and decreasing costs. The company's interest was clearly there, and as a first step, VUmc and i-Optics engaged in research collaboration. The collaboration resulted in a second successful joint patent filing, with IXA again in a coordinating role.

'While discussing the terms of the commercial licensing agreement between VUmc and i-Optics on the two patents, we had to balance two interests: first, to estimate a realistic commercial value of the contribution of the patents to the end product; second, to enable successful valorization of the technology by creating an optimal starting position for i-Optics,' Klijsen says. Sicam later moved to i-Optics, which provided the company with an in-house expert on the licensed technology. In the end, it all worked out to the satisfaction of both parties: VUmc managed to find a good home for its technology, and i-Optics created a truly innovative and commercially successful product.

Thomas van Elzakker, i-Optics' Chief Operating Officer, says i-Optics has been working with universities for the development of products since the company started. The Cassini had been an obvious choice to license from the VUmc.

'We saw the potential of what it did. It is not only a machine for the highly accurate measurement of the front of the cornea, but it can also provide an image of the back surface of the cornea. That is rather unique. We know the challenges in that space. We understand the opportunity in serving that need,' says van Elzakker.

With the Cassini, van Elzakker says, the science-to-business collaboration had been smooth because each side had distinct roles in steering the Cassini technology from the realm of science to the market. i-Optics was responsible for the further development and commercial rollout of the Cassini, and interested in the opportunity to develop more applications for the product moving forward. On the other hand, VUmc and the inventors are responsible for the academic research and supportive in the valorization of the Cassini technology. 'We are all happy to license the product. Our goals in that respect are aligned,' says van Elzakker.

**Next frontier**

i-Optics counts the United States as its biggest market for the Cassini since it was introduced in 2013. The United States, van Elzakker says, is a market that is more adventurous when it comes to new technology.

The market entry strategy of i-Optics is to sell the product to well-respected doctors whose stature allows them to immediately try new technology. Cassini is also now beginning to get market traction in Germany, Spain, France, Switzerland, and the Scandinavian countries.

Sicam says that the next frontier for the Cassini is integration. i-Optics has connected the Cassini to the surgical suite of instruments that perform cataract surgery such as the LENSAR Laser System with Streamline.

The Cassini now automatically and wirelessly transfers pre-operative data to the LENSAR, providing ophthalmologists the specific treatment parameters to guide them in decision-making during surgery.

'The Cassini measures the shape change in the cornea, so you will get information on what the effect of that incision will be, and that can be recorded. Next time, you can consider that effect. Then you can close the loop because the Cassini also does post-operative measurements,' says Sicam. i-Optics is also gathering clinical data for presentations and scientific exhibitions to be able to share with more people more information on the Cassini's performance.

'We need to do this scientifically. The current customers understand the performance of the Cassini based on its technology, but the next tier [of customers] demand to have clinical proof of what it can do for them,' van Elzakker says.

## Clinell sporicidal Wipes

# Superwipe vs. superbug

UK's top supplier of disinfectant wipes partnered with Cardiff University to produce clinical proof that a sporicidal wipe can kill the resilient bacterium, *Clostridium Difficile*. Their award-winning partnership has yielded more positive outcomes than they hoped for.

It began as a bold marketing pitch: Clinell Sporicidal wipes are best at disinfecting hospitals from notorious bacteria. That pitch was backed by laboratory studies from no less than Cardiff University in Wales, but the market has grown skeptical.

Hospitals demanded clinical—not just laboratory—proof that the product could kill the problematic and resilient bacterium, *Clostridium Difficile* (*C. diff*), which has claimed thousands of lives around the world.

Clinell's manufacturer, GAMA Healthcare, moved quickly to put substance in its slogan. With a grant from Innovate UK, the government's innovation body, and the Department for Environment, Food and Rural Affairs UK (Defra UK), GAMA Healthcare entered a two-year Knowledge Transfer Partnership (KTP) with Cardiff University to establish the necessary proof GAMA's market required.

**Product** Clinell sporicidal wipes
**Research institute** Cardiff University
**Marketed by** GAMA Healthcare
**On the market since** 2005

Skepticism about the product was understandable, considering the *C. diff* outbreaks that health agencies all over the world had to manage in the past couple of years. About 25000 people die from serious resistant bacterial infections acquired in hospitals, according to the World Health Organization-Europe (WHO-Europe).

'Antibiotic resistance increases the costs of treatment because of longer hospital stays, more expensive antibiotic drug use and treatment, as well as indirect costs to families and society,' WHO-Europe said.

### Resilient

Two strains of *C. diff*—tagged as responsible for the global epidemic—have been found to be resistant to the antibiotic Fluoroquinolone, which until the early 2000s was being prescribed to fight the bacteria, research from the Wellcome Trust Sanger Institute revealed.

It also found that one of the two *C. diff* strains, called 027, produces spores that are highly infectious and resistant, allowing it to survive basic disinfection for weeks. Spores of the bacteria are usually passed out of the body through a person's stool, and once a person touches the surface of a contaminated object, the person could risk being a carrier of the bacteria or becoming infected.


**What began as a bold marketing pitch is now saving hospitals from the bacterium *Clostridium Difficile*.**

The interconnectedness of the global healthcare system was a contributing factor to the quick spread of the bacteria in healthcare facilities in North America, Australia and Europe.

In efforts to contain *C. diff,* few paid much attention to the possibility of using sporicidal wipes. One of them was GAMA Healthcare, a UK market leader in the antimicrobial wet wipe product industry and the largest disinfectant wet wipe supplier to the National Health Service (NHS).

GAMA Healthcare designed Clinell Sporicidal wipes to specifically target C. diff. Inactive when dry, the wipes produce peracetic acid as they are wet with water, killing C. diff spores and other known microorganisms. Its product description highlights how the wipes are 'a direct and safe alternative to chlorine products.' Despite its stature as the UK's top supplier and exporter of disinfectant wipes, GAMA Healthcare did not have an in-house laboratory. All related work, including product development and testing, had to be outsourced to Cardiff University's research group. Over time, the company saw the need to have its own facilities so that it could stay ahead of the competition.

The two-year KTP between GAMA Healthcare and Cardiff University filled this need. Aside from producing clinical proof, the KTP allowed GAMA to design its own research and development facility so it could create new products and validate their efficacy through an established protocol.

### Unexpected outcomes

With an in-house laboratory and a system in place,

## In the spotlight
Rise of the Superbugs

Antibiotics have been the key to treating bacterial infections, including fatal ones, but after its discovery over 70 years ago, the solution has become, in certain situations, a major problem.

The indiscriminate use of antibiotics on humans and animals has caused some bacteria, like *C. diff*, to become resistant to what was supposed to eliminate them. Antibiotic resistance can be transmitted between bacteria, particularly in the healthcare environment. Because of their constant exposure to pathogens in their workplace setting, healthcare workers face the possibility of being infected or becoming a carrier of antibiotic-resistant bacteria daily.

Thus, it is imperative to have effective disinfectants that when combined with effective cleaning, can reduce the number of pathogens from surfaces and equipment in hospitals.

'Infections from resistant bacteria can be difficult and sometimes impossible to cure, and they are increasing,' WHO-Europe wrote in a briefing paper.

'Meanwhile, research into the development of new antibiotics that will work is very costly and lengthy, and resistance often develops rapidly after new antibiotics are marketed.' The use of effective cleaning/disinfectant products offers a cost-effective preventive measure against AMR pathogens.

GAMA began providing scientific advising service to its clients.

'This aspect of knowledge transfer was not in the original project proposal but has proven to be a valuable resource as we are now able to offer scientific advice and support to existing customers as an additional service, i.e. how to use the wet wipe, further setting us apart from competitors,' says Professor Jean-Yves Maillard of Cardiff's School of Pharmacy and Pharmaceutical Sciences.

The partnership reinforced Cardiff University's reputation as a leading research institution and established its international reputation for infection control, particularly in the use of antimicrobial wipe products. The KTP received an outstanding rating from Innovate UK and, in June 2015, won Business Innovation Prize and People's Choice Award at Cardiff University's Innovation and Impact Awards.

'The Knowledge Transfer Partnership between Cardiff University and GAMA Healthcare has enabled the company to sustain its product development portfolio and remain at the forefront of innovation, whilst increasing the university's international reputation in infection control research,' Cardiff said in a news release.

'The award is wonderful recognition of the great support we received from Cardiff University, not just in terms of enhancing our knowledge but in terms of practically embedding capability that enables us to continue as a UK market leader," says Guy Braverman, Director and co-founder of GAMA Healthcare. 'Working with Cardiff University has enabled us to be an integral part of innovative research.'



Clinell sporicidal wipes

KTP Associate Harsha Siani played a critical role in ensuring the success of the knowledge transfer. Aside from training GAMA's people, Siani worked with Prof. Maillard to publish important data on the wipe's efficacy, which showed Clinell's superiority over competing brands.

*'Antibiotic resistance increases the costs of treatment because of longer hospital stays, more expensive antibiotic drug use and treatment, as well as indirect costs to families and society.'*

'Harsha's attendance at conferences and her direct interaction with existing and new customers has further raised GAMA's brand strength and scientific profile, as demonstrated by the repeated invitations for Harsha to present at infection control conferences,' Prof. Maillard says.

The dissemination of scientific data immediately produced results: Five major NHS trusts shifted to Clinell, generating sales of £200000 for GAMA Healthcare. Upon listening to Siani's presentation at a conference, one hospital administrator changed brands of their facility's wet wipe supply and opted for Clinell, an account worth £125000.

The benefits of the KTP did not end there. One of the unexpected outcomes was how the research design helped develop 16 new formulas, which later became three new products that were released within eight months. The company estimates that it saved £23000 in product testing alone. It expects the new products to generate sales of £1M in the next two years.

**Working with China**

The partnership's success crossed continents as well, as the company began working hand in hand with the Chinese government, which was contending with bacterial outbreaks in its country, too.

Siani, a microbiologist, flew to the world's most populous nation to teach microbiology techniques developed by Cardiff University. In the process, the Chinese learned about GAMA's ability to develop and market products that specifically address the need there. 'The project gave me lots of unique opportunities including traveling to China to educate staff at the Chinese Center for Disease Control and Prevention in Hangzhou, which has opened further opportunities for collaborative research between CDC, Cardiff University and GAMA Healthcare,' Siani says.

In retrospect, Prof. Maillard recognizes how valuable an opportunity the team had in the two-year partnership with GAMA Healthcare, saying such a break does not come every day. 'Research funding on "biocides' is and has always been really limited especially from RCUK. There are a few opportunities at present in the area of preventing/combating the rise of antimicrobial resistance,' he says. 'Having an industrial partner is essential.'

Prof. Maillard underscored the importance of continuous collaboration between industry and the academe, as seen in the KTP between GAMA and Cardiff.

'Interaction with industry is crucial to optimise research application "in the real world" and create impactful innovation—here, ensuring the product used as part of an infection control regimen in healthcare settings can make a difference and help infection control against troublesome pathogens,' he says.

## Digit Triplet Test

# Screening for hearing loss made swift and easy

Detecting hearing loss early on in a child's life allows for interventions to be put in place so that a child's development will not suffer. The University of Leuven has created a three-minute self-screening method for discovering hearing problems, which is now being used in schools and offices.

Hearing impairments have a significant effect on children's development. These could hamper their ability to understand school lessons and develop language skills, resulting in poor academic performance, derailed learning, and atypical general development. Hence, early detection of hearing loss is vital in determining interventions that would minimize, manage, or reverse the adverse effects of such a condition.

The Digit Triplet Test (DTT) is an automated speech-in-noise test created for self-screening of a person's hearing ability. The University of Leuven (KU Leuven) in Belgium developed the Dutch and French version of the test to screen children, as well as employees, for hearing problems in a fast, efficient, and effective manner that approximates situations of how a person hears in a regular environment. 'It comes closer to the real life performance of human beings listening to speech,' says Professor Jan Wouters of the KU Leuven Research Group of Experimental Oto-rhino-laryngology, who led the development of the DTT. 'It's more realistic, and that's what it's all about, measuring our ability to understand speech in difficult listening conditions.'

**Product** Digit Triplet Test
**Research institute** University of Leuven
**Marketed by** University of Leuven
**On the market since** 2013

### 3-minute test

The DTT is possibly the easiest and quickest relevant hearing test available today. It only requires a quiet room, a tablet computer with the software, and calibrated high-quality headphones.

To perform the test, the person being screened would be asked to recognize speech layered on background noise. The speech consists of random combinations of three digits. Numbers are used for the speech portion of the screening because these are among the first words that children learn, Wouters explains.

During the test, 27 triplets are presented. The background noise is set at 65 decibels (dB). At first, the speech in the test is at the same level as the noise. Next, the level of the speech is adjusted to be higher or lower by 2 dB, depending on the response of the test person. If the response is correct, the test is made more difficult by decreasing the speech level. If the response is incorrect, the test is made easier by increasing the speech level.


**The Digit Triplet Test, the three-minute self-screening method for discovering hearing problems, is now being used in schools and offices.**

The test is meant to determine at which level a person could still understand half of what is being said.

Within approximately 3 minutes, the person's speech reception threshold can be determined, and the results can be used to assess whether or not the person has to be referred to experts for further auditory diagnosis.

### Periodic screening

The starting point for the research for the DTT came from an intent to devise a test that would cover the way human beings receive sound in everyday life. The classic procedure in screening for hearing problems is based on detecting tones.

But recognizing tones does not necessarily translate to understanding speech, says Wouters. 'It does not cover the real communication channels that we as human beings are developing, and that's based on speech,' he says.

Universal neonatal hearing screening is already well-established in many countries, and has been conducted in Flanders since 1998. It is intended

Digit Triplet Test

## In the spotlight
Hear this

The World Health Organization estimates that 360 million people, or over 5% of the world's population, have disabling hearing loss.

Some 32 million of them are below 15 years old.

The prevalence of disabling hearing loss in children is highest in South Asia, Asia Pacific and Sub-Saharan Africa, and lowest in high-income regions, which include Western European countries, the United States, Canada, Australia, New Zealand, Brunei Darussalam, Japan, Republic of Korea, and Singapore.

The causes of hearing loss in children could be acquired or congenital. Congenital causes include low birth weight, the lack of oxygen during birth, severe jaundice following birth, and maternal infections, such as Rubella. Acquired causes include chronic ear infections, noise, use of medicines with a toxic effect on the ears, and infectious diseases such as meningitis, measles, and mumps.

According to the WHO, majority of cases of hearing loss can be treated through early diagnosis and proven interventions.

to detect hearing deficiencies in the first weeks of a child's life. In Flanders, a hearing test is also one of the mandatory medical examinations for school-age children. It is conducted at the ages of 4, 10, and 14 years. The latter is internationally unique.

Wouters notes that the number of children who develop hearing loss later in life may be as high as the number of children with hearing problems detected during the neonatal screening. Since hearing problems do not always show up in the first few weeks after birth, periodic testing is important. Otherwise, normal development could be arrested by undetected hearing impairment.

'Although neonatal screening is very important, it is equally important to check later because some reports indicate that the number of children with hearing impairment doubles in the years after birth, let's say, the ages of 7, 8, 9 years,' Wouters says. 'Those children are in their full educational exploration in school and if they do not hear well, that means they are not developing as they should develop.'

**Flemish funding**

KU Leuven was working on the development and implementation of the DTT when funding came in from the Flemish government through the Flemish Scientific Association for Youth Healthcare at the end of 2013. While not covering the cost of the entire research and development process, the fund was used for the final evaluation of the project and the application of the software in tablet computers.

Under the agreement, the association would get a non-exclusive licence for the DTT software, according to Joke Willems, legal counsel at KU Leuven who was the technology transfer officer for the project. The association uses the DDT software to screen pupils for hearing problems.

*The DTT is possibly the easiest and quickest relevant hearing test available today. It only requires a quiet room, a tablet computer with the software, and calibrated high-quality headphones.*

Since KU Leuven has retained ownership of the copyright for the software, it was possible to address additional groups of potential beneficiaries, such as employees and elderly people.

Companies that focus on hearing problems and occupational health services already showed their interest in licensing the DDT software on a non-exclusive basis, explains Willems.

With thousands of students needing to be screened for hearing problems, the DTT presents an advantage because of the simplicity of the setup, the ease of use, and the swift availability of results, without sacrificing accuracy.

Unlike the classical hearing tests, it does not require a special acoustically treated room or sophisticated testing equipment. It is also less costly, and could be set up at a cost of about €1000. The test can be completed in a short time. 'At the moment, we're down to about three minutes per child, so that's very efficient and with the precision of about one dB,' says Wouters.

A change by 1 dB is about the smallest change a human being can detect. The results of the test in schools can be immediately uploaded using wireless connection to a central database so that the medical team can monitor these at any time and any place, and take the necessary action. Data collected from the test, especially on older children and teenagers exposed to loud recreational sounds, can be used to set up schemes to prevent further hearing loss.

At the moment, the DTT is being used to test children between 8 and 15 years old, as well as employees, says Wouters. The university is developing the test to make it suitable for younger children also.

Medical advisory services who monitor the health of employees have also expressed interest in the test, and KU Leuven has issued non-exclusive licences to several of them, says Willems. The university charges a fee for the licence, but it is a minimal amount that just covers the cost.

As a research organization, KU Leuven does not intend to profit from it, Wouters says. It is looking for a third party partner to commercialize and distribute the test and handle related details of such a venture.

KU Leuven has been talking with local distributors, but Wouters believes that the test could also be marketed internationally to reach a bigger consumer base. He explains that it would be easy to adjust the test for other markets in other countries by changing, say, the language and the reference values.

If the DTT reaches a wider audience, more children, who are still developing into their full potential, could be saved from the adverse effects of hearing problems.

'We need to seek out those children that are hearing impaired as soon as possible so that we can help their hearing by giving them hearing aids or training,' says Wouters.

## Glybera

# uniQure launches first gene therapy product for LPL deficiency

Gene therapy used to be a far-off idea in the medical world, but with the trailblazing approval of the world's first gene therapy product, Glybera, a normal life may no longer be a dream for patients with genetic illnesses.

In 1972, gene therapy pioneers Dr. Theodore Friedmann and Dr. Richard Roblin made the bold prediction that altering defective DNA could someday treat human diseases.

'In our view, gene therapy may ameliorate some human genetic diseases in the future. For this reason, we believe that research directed at the development of techniques for gene therapy should continue,' they wrote in their paper, 'Gene therapy for human genetic disease?'

For a Netherlands-based medical company, this 'future' has finally come.

UniQure, a pioneer in developing gene therapy treatments, has dispelled concerns about the safety, efficacy and reproducibility of the technique with its groundbreaking treatment Glybera, the first gene therapy product approved in the world.

**Product** Glybera
**Research institute** Academic Medical Center at the University of Amsterdam
**Marketed by** UniQure
**On the market since** 2015

Glybera or alipogene tiparvovec is an AAV serotype 1-based gene therapy vector that is composed of a CMV immediate early promoter driving expression of a lipoprotein lipase cDNA, mutated at the last amino acid (S447X); a Woodchuck Post-transcriptional Regulatory Element; and a bovine growth factor poly A nucleic acid sequence flanked by AAV2 inverted terminal repeats.

Simply put, Glybera consists of an engineered copy of the human LPL gene packaged with a constitutive promoter in a non-replicating AAV1 vector, which has a particular affinity for muscle cells, uniQure explains. The composition of Glybera was designed by uniQure, but several third-party inventors discovered certain individual components of the product.

### Treating LPL deficiency

According to uniQure, Glybera was developed to help patients suffering from a very rare disease: lipoprotein lipase deficiency or LPLD. This particular gene mutation results in hyper-chylomicronemia, or dramatic and potentially life-threatening increases in the level of large fat-carrying particles (chylomicrons) in the blood after eating. Glybera restores and even improves the LPL enzyme activity needed to process fat-carrying chylomicron particles formed in the intestine after a meal. This is possible because Glybera uses a naturally occurring variant of the LPL gene that has 'higher enzyme activity than the normal version of the gene that encodes the protein.'


**With Glybera, a normal life may no longer be a dream for patients with genetic illnesses.**

Before Glybera was given the green light in Europe, there had been no approved therapy for the treatment of LPLD. Patients suffering from the disease were advised to adhere to a rigid diet restricting fat to less than 20% of their daily calorie intake.

Despite their supreme efforts, however, patients found it very hard to comply with this severe diet regimen, which often proved to be ineffective in reducing chylomicronemia. LPLD patients remained at increased risk for severe pains and pancreatitis, which can be fatal in some cases. With gene therapy, LPLD patients are given hope that they can finally live normal lives. According to uniQure, this type of treatment entails the one-time administration of a drug that can replace a patient's malfunctioning gene with a functioning one, either significantly improving the gene or potentially 'curing' the disease.

The drug used in gene therapy is characterised by its long-term, and possibly even lifelong, effect on patients. 'Helping improve the lives of patients who previously had no other treatment option, and reducing the need of these patients to spend time in hospitals and intensive care units are important achievements,' uniQure says.

Glybera was granted regulatory approval by the European Medicines Agency on 2 November 2012.

### Fixing faulty genes

While only 300 patients in the European Union suffer from LPLD, the significance of this invention extends to other conditions caused by gene mutation. With the success of Glybera, healthcare regulators now have proof that gene therapy can help patients

suffering from other ailments as rare and as difficult to treat as LPLD, such as haemophilia.

'A lifelong treatment for a disease like haemophilia B would have a huge impact on both patients and the worldwide healthcare system,' uniQure says. Like other genetic disorders, haemophilia involves a malfunctioning gene that inhibits a patient's ability to produce the protein that allows blood to clot. If a drug could 'fix' that faulty gene, uniQure surmises, haemophilia patients would no longer need constant and long-term infusions of the replacement protein. They would no longer be at risk of severe blood loss from something as simple as losing a tooth.

*'If a drug could 'fix' that faulty gene, haemophilia patients would no longer need constant and long-term infusions of the replacement protein.'*

Therapies that hope to address haemophilia and other diseases such as Sanfilippo B Syndrome, Parkinson's Disease, and congestive heart failure are currently under development. uniQure has signed a potential US$2-billion partnership with global pharmaceutical company Bristol-Myers Squibb to develop novel gene therapies that will help heart failure patients.

**Collaborations in Canada**

The story of uniQure began almost three decades ago in a laboratory at the University of British Columbia (UBC) in Vancouver, Canada. UBC's Dr. Michael Hayden and Dr. John J.P. Kastelein, a Dutch physician from the Academic Medical Center (AMC) of the University of Amsterdam in The Netherlands, had then begun collaborating to diagnose and treat metabolic lipid disorders.

After meeting a young patient with LPLD, Hayden and Kastelein conducted investigations that eventually revealed that gene defect was the cause of the debilitating disease. The physicians then decided to think of new therapeutic options for LPL-deficient patients that were based on the LPL gene itself. Their efforts, together with the work of then postdoctoral research fellow Dr. Colin J.D. Ross and the rest of their team, led to the development of Glybera.

Along with outstanding research, Glybera's successful roll-out can be traced to a well-oiled technology transfer process.

In 1997, the University of Amsterdam's AMC realised that it was not maximising the value of its research and scientists. The AMC Board then decided to implement a program that would stimulate researchers with promising and innovative products to start a spin-off company. AMC hired an experienced technology transfer professional to evaluate and report on interesting projects with commercialization potential. In 1998, Kastelein's LPLD gene therapy project was developed into a spin-off company named Amsterdam Molecular Therapeutics (AMT).

**From lab to market**

According to Dr. Willem van Oort, who in 2003 helped establish and joined AMC's first technology transfer office (TTO), AMC had acknowledged that the gene therapy project focused on a technique that was 'largely unknown' at the time.' 'For that reason, the Board preferred to remain the dominant shareholder, and initially did not invite venture capital,' explains Van Oort, who provided expertise on the establishment of AMT, and the ensuing licensing agreement between AMC and the spin-off company.





An umbrella agreement was made between AMC and AMT: AMC expressed willingness to invest in and fund AMT's programs during its initial years of operation, in exchange for 100% of the shares, while the researchers obtained option rights to eventually buy minority certificates.

The agreement also included the exclusive licensing of the patent applications, in addition to certain licensing rights for the company on future patent application on subsequent innovations in the same field made by the AMC researchers.

AMC and AMT also conducted discussions with the University of British Columbia, which owned a dominant patent on the product with pharmaceutical company Aventis. A licensing contract was successfully arranged between the parties under the guidance of the technology transfer expert.

While AMC maintained control of the company in the beginning, it eventually invited venture capitalists to invest in AMT when the development of the LPL gene therapy product began to show promise. This investment allowed AMT, which later became uniQure, to develop Glybera.

'The majority of new products, certainly in the area of medicine, are based on new insights obtained in scientific projects,' explains Joris Heus, Director and Business Development Manager of the AMC's Office of the Innovation Exchange Amsterdam, a collaboration of the TTOs in the region.

The results of such projects are screened by TTOs in knowledge institutes for commercial applicability, and subsequently offered and licensed to existing companies or new spin-off companies, as uniQure once was. 'This way, new technologies find their way to the market, to the benefit of patients and society in general,' Heus says.

With Glybera's launch in 2015, uniQure has undoubtedly broken new ground in medicine. 'UniQure has made the concept of gene therapy a reality and will continue to develop new gene therapies to help patients suffering from disease," the pioneering medical company says.

**In the spotlight**
The human gene

A gene is an essential unit of hereditary information. Genes, which are made up of DNA, carry the information that determines the traits, characteristics, function, and physical development of living organisms. An individual has around 20000 genes present in 23 chromosomes.

Each person has two copies of each gene, one inherited from each parent. Most genes are the same in all humans, but a small number of genes slightly differ between people. Forms of the same gene with small differences in their sequence of DNA bases are called alleles. The combined effect of alleles results in the physical differences in appearance among people, such as the colour of their eyes or the shape of their nose.

Dysfunctional gene behaviour is commonly referred to as a mutation. According to the World Health Organization, these mutations are responsible for causing illnesses. If the gene mutations exist in the egg or sperm cell, children can inherit the defective gene from their parents.

## Immunodiagnostic Systems

# Blood test products using vitamin D antibodies improve diagnosis, management of chronic kidney disease

Low concentrations of 1,25-dihydroxy vitamin D, a major hormone that regulates calcium and phosphate metabolism, are common in patients with chronic kidney disease due to loss of kidney function. With the 1,25-dihydroxy vitamin D blood tests manufactured by IDS, doctors and patients have an additional tool to diagnose and manage CKD.

Due largely to the prevalence of lifestyle diseases, chronic kidney disease (CKD), or the gradual loss of kidney function, has become an emerging public health issue affecting 8% to 16% of the world's population.

This translates to at least 560 million people whose kidneys can no longer work properly, resulting in the build-up of fluids, minerals and wastes in the body.

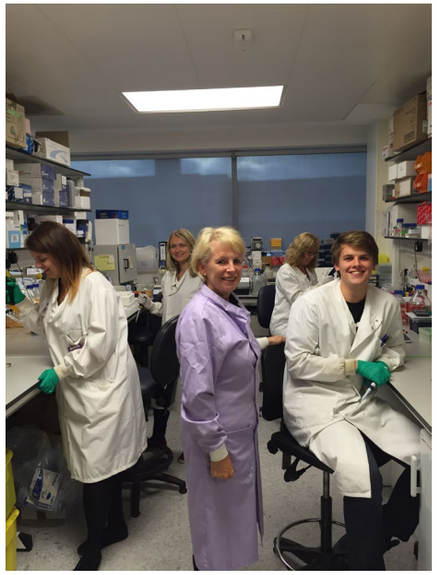
CKD can lead to an increased risk of heart and blood vessel diseases, as well as complications such as hypertension, anaemia, and weak bones. Patients with CKD have a high rate of severe deficiency in 1,25-dihydroxy vitamin D, a steroid hormone that maintains calcium and phosphate homeostasis.

This deficiency is further aggravated by the CKD patients' reduced kidney functions to turn 25-hydroxy vitamin D from diet and other sources into 1,25-dihydroxy vitamin D, the active form that the body can use.

'It's not something you need to take as a classical vitamin. It has a very specific structure with hydroxyl groups which distinguish it from other steroid hormones,' says Professor Anne White, a leading UK endocrinologist from the Faculty of Medical and Human Sciences at the University of Manchester.

She explains: 'The active form of vitamin D that is measured is 1,25-dihydroxy vitamin D. In order to develop a way of measuring it in the presence of the inactive 25-hydroxy vitamin D, we developed monoclonal antibodies that are very specific to that form of vitamin D. Before this development, it had always been difficult to produce very specific antibodies in sufficient quantities for diagnostic

**Product** Immunodiagnostic Systems
**Research institute** University of Manchester
**Marketed by** Immunodiagnostic Systems PLC
**On the market since** 1981



**Professor Anne White, leading UK endocrinologist, with her research group at the University of Manchester.**

companies to use them in diagnostic kits.' When vitamin D levels in the body get too low, the parathyroid glands, which modulate calcium metabolism, secrete more parathyroid hormone that can lead to secondary hyperparathyroidism (SHPT). Early identification and treatment of SHPT is crucial as SHTP can also cause the parathyroid glands to enlarge, which can result in permanent damage.

To slow the progression of SHPT, active vitamin D (calcitriol) therapeutic regimens are recommended. Doctors order several blood tests–also known as immunoassays–including the 1,25-dihydroxy vitamin D test. This particular test is of interest to CKD patients because the main enzyme converting 25-hydroxy vitamin D to the active form is located in the kidney. Immunodiagnostic Systems PLC (IDS) manufactures several blood test products to measure the 1,25-dihydroxy vitamin D levels of CKD patients and help them manage their condition. IDS does this using a monoclonal antibody developed by White and the late Professor Barbara Mawer at the University of Manchester.

### Three decades of partnership

IDS was the first to market the 1,25-dihydroxy vitamin D immunoassay in 1981. The development of IDS's 1,25-dihydroxy vitamin D immunoassay was carried out at IDS's own laboratory, after gaining the licence to manufacture and sell diagnostic products incorporating the unique monoclonal antibody based on research by White and Mawer at the University of Manchester. The partnership with the university has continued for more than three decades now.

White recalls: 'A head of research at IDS, Dr. Roger Duggan, used to come to conferences that we were at and would talk with us about what we were doing.' Unlike others who have approached her and Mawer with unrealistic views, Duggan was 'very interested and very realistic,' she says.

White and Mawer agreed to collaborate with IDS to try to develop the kit to measure 1,25-dihydroxy vitamin D. 'We used to produce all the monoclonal antibodies for the kits in our lab, but then as they sold more and more kits, it became absolutely impossible to do that, and they had to take that on as well,' White says. She credits their successful collaboration to the fact that IDS was a company that worked in a very specialised area and made decisions quickly.

UMIP, The University of Manchester's agent for intellectual property commercialization, worked closely with White to negotiate licence terms.

## In the spotlight
CKD and diabetes

Diabetes is a disease in which the body does not make enough insulin or is unable to properly use normal amounts of insulin, a hormone that regulates the amount of sugar in the blood. It is one of the two main causes of CKD, the other being hypertension. Around 30% of patients with juvenile onset or Type 1 diabetes and 10% to 40% of people with adult onset or Type 2 diabetes will eventually suffer from kidney failure.

Diabetes causes injury to the blood vessels, leading to diabetic kidney disease, also called diabetic nephropathy. When the blood vessels in the kidneys are damaged, the kidneys lose their ability to filter the blood, resulting in higher levels of water, minerals and waste in the body. The nerves can also be damaged, causing difficulty in emptying the bladder. The pressure from a full bladder can injure the kidneys.

There are five stages of CKD, mainly based on measured or estimated glomerular filtration rate. The earliest sign of diabetic kidney disease is a higher level of albumin in the urine. Blood urea nitrogen and creatinine levels will increase as the kidneys fail. Patients with Stage 1 CKD have normal kidney function, while those with Stage 5 suffer from end-stage renal failure.

Treatment options for kidney failure are kidney transplant, haemodialysis, and peritoneal dialysis. Diabetic kidney disease is expected to account for about 30% of the projected $1.1 trillion global cost of dialysis in the current decade.

Assisted by the deep understanding of the technology at IDS and White's commercial insight, the negotiation process served to strengthen the relationship between all parties and provide a solid platform for commercial impact.

**Robust and reliable products**

The concentration of 1,25-dihydroxy vitamin D in the body is very low, so it is important to ensure that it is actually the hormone being measured in tests.

Avoiding the need for complex specimen purification, as well as the use of tritium, a radioactive component, were the main challenges in developing a robust and reliable blood test product. It was fortuitous that White, who is trained as a cell biologist, had made hybrids between normal and malignant cells for her doctorate. When Georges Kohler and Cesar Milstein came up with a method to make monoclonal antibodies by producing hybrid cells, White was one of the people who knew the technique. At that time, White had a postdoctoral post in a university endocrinology laboratory where they wanted to develop new methods for the diagnostic assays of hormones.

'I was the cell biologist and I quickly learnt how to measure the hormones,' White says. She worked alongside clinical biochemists who measured patient samples and told her the problems they were encountering with the assays they were using. White's job was to develop monoclonal antibodies that improved their assays for patients. Making monoclonal antibodies, particularly for 1,25 dihydroxy vitamin D, is no mean feat. White explains that to make monoclonal antibodies, a form of the hormone (as an immunogen) must be injected into a mouse. The mouse would then make the antibody producing plasma cells, and these lymphocytes would be taken from the mouse. The plasma cells are then fused with myeloma cells to make hybridomas which are then cloned so they secrete monoclonal antibodies.

'We had to have an organic chemist who could make the structures that we injected into the mice. These structures would hold the vitamin D molecule in a way that presented it to the lymphocytes in the mice,' White says. 'So there were three different specialties: I was knowledgeable in making monoclonal antibodies; we had somebody who was knowledgeable on making these chemical structures to make the immunogens; and then there was an expert on vitamin D assays, Barbara Mawer.'

She explains that the difficulty in producing monoclonal antibodies for vitamin D is that in order to determine the concentration of the active form, the antibodies must only recognise that form, and not the inactive form. A good antibody must also be able to bind very tightly to the hormone. On top of that, the process must be done quickly because the hybrid cells must be cloned repeatedly and stabilised.

'The one thing that's quite tricky with making good monoclonal antibodies to steroid hormones is it's like trying to find a needle in a haystack,' White says. Using the monoclonal antibodies produced by the University of Manchester, IDS then went on to develop a novel immuno-extraction method that addressed the problem of sample purification. IDS has applied for a patent for the method they developed.

*'The one thing that's quite tricky with making good monoclonal antibodies to steroid hormones is it's like trying to find a needle in a haystack.'*

**Commercial success**

There are currently four products available from IDS. Three of them – 1,25-Dihydroxy Vitamin D RIA, 1,25-Dihydroxy Vitamin D EIA, and the automated IDS-iSYS 1,25-Dihydroxy Vitamin D – are being sold worldwide. Another product, the fully automated IDS iSYS 1,25 VitD$^{Xo}$, is available only in the European Union and Brazil.

Vitamin D has received increased attention in the last 5 to 10 years due to growing knowledge of its importance. In fact, IDS acknowledges that Vitamin D has been a substantial part of its positioning and success as a company. IDS was among the first in the market with 25-hydroxy and 1,25-dixydroxy vitamin D immunoassays. After only a few years, IDS reported a market share of 80% and revenues of some £50M.

Technology has come a long way since the launch of the 1,25-dihydroxy vitamin D immunoassay some 30 years ago. IDS has developed a fully automated instrument for the vitamin D test, called IDS-iSYS, which reduces the pressure of increasing volumes of testing on small and mid-sized laboratories. From an overnight manual assay done by two to three people using a lot of equipment, IDS-iSYS brings that down to 90 minutes' testing and up to 500 results a day. The goal, IDS says, is to keep improving its products according to its customers' needs.

## LayerWise

# Additive manufacturing (AM) aids world's first patient-specific jaw implant

Additive manufacturing technology has opened up possibilities for the production of medical products that can change the way reconstructive medicine is done all over the world.

It was the stuff of science fiction and comic book superheroes. That is, until a senior patient received the world's first custom-made, 3D printed, titanium full jaw implant in a surgical operation that restored the patient's facial aesthetics and allowed her to regain her speech in a matter of hours. With the success of the replacement/reconstructive surgery, the technology that produced this premier patient-specific metal mandible could very well be the shape of things to come.

Created layer by layer using the technology more popularly known as 3D printing, the titanium jaw implant was not only highly personalized but highly biocompatible as well. 'Such implants have excellent form and function; they speed up surgery and patient recovery, and reduce the risk of medical complications,' KU Leuven Research & Development (LRD) states in an impact report it prepared about the technology. Post-processed with ceramic coating, the titanium jaw also integrated multiple functions, and true to form, restored the elderly patient's facial aesthetics, allowing her to regain her speech within hours, the report adds.

As the four-hour reconstructive surgery was undoubtedly painstaking, LayerWise, one of the companies behind the operation, also took great pains in bringing to life the type of technology that made the metal implant conceivable. The company manufactures revolutionary orthopedic, maxillofacial and dental implants, as overseen by its medical and dental divisions. It also has an active industrial division with applications not only in the biomedical field but also in aerospace, marine, and several other industries.

Founded as a spin-off company from the Department of Mechanical Engineering at the Belgian university KU Leuven, LayerWise, is the first of its kind in Belgium to exclusively focus on metal additive manufacturing (AM) or 'the industrial version of 3-D printing,' as MIT Technology Review calls it.

**Product** LayerWise
**Research institute** University of Leuven
**Marketed by** LayerWise
**On the market since** 2008

### Revolutionary manufacturing

MIT Technology Review explains: additive manufacturing (AM) is 'additive' for the simple reason that 'it builds an object by adding ultra-thin layers of material one by one.' Fully computer-aided, additive manufacturing uses high-power lasers to rapidly melt industrial materials, such as polymers, metals, composites, and biomaterials, and just as easily spread, dry, and fuse together one ultra-thin layer of material onto the next. The meticulous layering is repeated until the desired object is created.

**LayerWise manufactures revolutionary orthopedic, maxillofacial and dental implants.**

LayerWise co-founder Jonas Van Vaerenbergh takes pride in the fact that the company's technology is additive rather than subtractive. He explains how their core business is 'to build up material in layers instead of removing it in different steps.'

Because the AM approach is capable of simultaneously producing functional metal parts of different shapes in series of up to 50000 pieces, the high-speed production allows LayerWise to drive down production costs for its clients, Van Vaerenbergh says. On top of production efficiency and cost-effectiveness, AM is hardly constrained by the geometry of an object that needs to be produced. LRD General Manager Paul Van Dun calls additive manufacturing 'a disruptive technology.'

Professor Jean-Pierre Kruth, a member of the Faculty of Engineering Science at KU Leuven and now promoter of LayerWise, agrees with Van Dun, saying the biggest impact of the AM technology is that it is a real 'revolution in manufacturing.'

Citing the medical applications of AM, Kruth explains that because no two persons are alike, many of the implants have to be made dedicated to the person. He says AM offers 'the freedom to make components that are totally customized, especially those that are so complex in geometry that they cannot be made by other manufacturing techniques.' Kruth says titanium is preferred and used as an AM material in dental and medical applications because because it is biocompatible and allows to make implants lighter. He explains that titanium, typically used in the manufacture of aircraft, spacecraft and other vehicles, is also favored for its palliative, non-aggravating effects.

### 3D designs

Today, LayerWise is one of the latest and most important acquisitions of the US technology giant, 3D Systems (3DS). Acquired by the 3D digital designs and fabrications company in 2014, LayerWise has no doubt seamlessly added a new dimension to the portfolio of 3DS. That the Belgian company has become part of the US company is only fitting as it was rapid prototyping, developed by 3DS in the 1980s, that laid the very foundation for LayerWise's AM technology. Kruth still remembers how this groundbreaking technology first made its way to

the Belgian academic community. 'The very first machines from 3D Systems were demonstrated in 1988, and the very first installations of the machines occurred in 1990,' the professor recounts. 'We at the University of Leuven were among the first to acquire that kind of machine called the stereolithography machine. And that's where it all started.'


**LayerWise CEO Dr. Peter Mercelis (left) with Professor Jean-Pierre Kruth (right).**

Indeed, 3DS paved the way for LayerWise's AM technology with the US company's invention of the stereolithography apparatus (SLA), first commercialized in 1989. Coined by its inventor and patentor Charles W. Hull, stereolithography involves the three-dimensional 'printing' of liquid plastic. That is, an SLA instantaneously draws out, spreads, and hardens ultra-thin layers of liquid photopolymer using ultraviolet (UV) rays.

The UV-curable liquid is also drawn out and laid to dry one layer at a time until a three-dimensional image is created, giving rise to 3D printing as we know it. Having invented the machine a few years prior, Hull successfully went on to found 3D Systems Inc. in 1986. LayerWise's AM technology is, in fact, a type of 3D printing, the latter originally developed under the name 'rapid prototyping' because, despite being a quick process, it was mainly feasible to produce plastic objects and components that could not be tapped as real functional products, and were mainly used as visual prototypes. Who would have known that from printing plastic 3D models of objects, rapid prototyping would evolve into AM technology using metals such as titanium to make the world's first functioning mandibular implant?

**Layer by layer**

Unlike rapid prototyping, the establishment of LayerWise was anything but instantaneous, although it did seem to have mimicked the layer-by-layer process of 3D-imaging. Kruth, who has been involved in manufacturing engineering for many years, chronicles the technological developments that led to the spin-off company's establishment, especially as they coincide with his own career.

In fact, for nearly three decades, the professor needed to acquire expertise in the trifecta of technological advancements that preceded AM, and by extension, LayerWise: non-conventional machining, computer-aided design systems, and plastic injection molding.

Kruth refers to these processes as the 'three drives' that pushed him to look into additive manufacturing. AM, he says, is a kind of non-conventional machining because it has had to use an uncommon method, as opposed to milling, boring, grinding, and similar traditional metal-cutting processes. AM mainly uses lasers and therefore qualifies as non-conventional or non-traditional machining.

Added to the laser technology that makes AM possible is computer-aided design (CAD) on which, Kruth says, AM is predicated from the time of CAD's development in the 1980s. 'Before that, you could not think of additive manufacturing,' he says. Completing the trio of technology that shaped AM is plastic injection molding, the technology that antedated 3D's stereolithography for the production of plastic objects. LayerWise founders Jonas Van Vaerenbergh and Peter Mercelis were both completing their doctoral thesis on Selective Laser Melting, a type of additive manufacturing that allows one to create solid objects from metal powders, when they first realized the potential industrial applications of the technology.

Mentored by Kruth at KU Leuven, Van Vaerenbergh and Mercelis sought and received seed funding from LRD, KU Leuven's technology transfer office, and went on to found LayerWise in 2008.


**Dr. Peter Mercelis (left) and Dr. Jonas Van Vaerenbergh (right) founded LayerWise in 2008.**

Van Dun describes the technology transfer of the metal AM technology from the university to a company as 'fortunate from both sides.' As a technology transfer office (TTO), LRD is fortunate to be working with Kruth and his students because the professor has prior experience, having created two other university spin-off companies before LayerWise, says Van Dun. As for LayerWise, the existence of LRD since 1972 means they can tap into a solid experience in setting-up and growing high-tech companies. 'Setting up a company is always about team work,' Van Dun says. 'If that is not possible, forget it.'

## In the spotlight
### Metals in medicine

Some metals have been instrumental in developments in the medical field. Among those with groundbreaking medical applications are stainless steel, titanium, silicon and zinc, cobalt-chrome, and tantalum.

Discovered in the 1920s, stainless steel is one of the oldest metals that have aided medical practitioners. It was first used to create implants to repair bone fractures due to wartime injuries. Later, stainless steel was used in the production of stents and artificial valves, orthodontic wires, and artificial eardrums.

Known for being lightweight, titanium is a biocompatible metal hardly rejected by the human body. It is commonly used to make dental implants that can last for over 30 years.

Silicon and zinc, together with calcium phosphate, are used to create new bones. In this process, the compound is printed and used to stimulate bone growth. The compound later dissolves, leaving only the new bone.

Because of its high wear-resistance and biocompatibility, cobalt-chrome has been used in the creation of artificial joints like knees and hips. This alloy is also corrosion-resistant, minimizing irritation, allergic reaction, and immune response.

## Smart Inhalation Technologies

# Targeted inhalation improves aerosol therapy efficiency

The efficiency of drug delivery to the lungs depends on various parameters, some of which are influenced by the inhalation system being utilised. The smart nebulisation technologies developed by Activaero targets drug delivery to specific areas of a patient's lungs by providing optimised inhalation flow, volume and timing.

For millions in the world, breathing is not an exercise that can be taken for granted.

According to the World Health Organization's latest estimates, 235 million people suffer from asthma, 64 million have chronic obstructive pulmonary disease (COPD), and millions more have under-diagnosed chronic respiratory diseases. These account for a significant population that, every now and then, requires assistance to perform the most necessary act of living: breathing.

Inhalation of aerosols is the preferred method of drug delivery in the treatment of respiratory diseases such as asthma and COPD, as well as cystic fibrosis, a genetic disease of the lungs and the digestive system that affect about 70000 people globally.

**Product** Smart Inhalation Technologies
**Research institute** Helmholtz Center Munich
**Marketed by** Vectura
**On the market since** 2005

However, unlike oral and intravenous administration of medication, the efficiency of inhalation therapy is affected by various factors.

Dr. Gerhard Scheuch, founder of Activaero and former head of the aerosol research team at the Helmholtz Center Munich, says many of the companies that conducted aerosol research thought that the aerosol particle size is the most efficient predictor to get the aerosol particle into the patient's lungs. Hence, these companies only manipulated or varied the aerosol particle size.

Scheuch, a physicist who has spent 18 years studying the behaviour of aerosols, knew that this principle was 'physically not absolutely correct.' He explains: 'The aerosol delivery systems in the pharmaceutical industry were all not very efficient. We talked about efficiencies between 5% and the maximum 20% of what you filled in a delivery device and what went into the lungs.'

What most researchers did not take into account at that time was the patient's breathing pattern. 'It's very simple. If you don't inhale at all, you will not get anything into the lungs,' Scheuch says. 'You can make the particles as small as you want but they will not go into the lungs if you don't inhale, and so the breathing pattern–how patients inhale–predicts the amount of particles that go into different regions of the lungs.'


**The AKITA® JET Inhalation System establishes a completely new quality of inhalation therapy with the FAVORITE technology.**

That was the original idea on which Activaero was founded. Today, the inhalation devices developed by Activaero solve some of the biggest problems in inhalation therapy, including the correct dosage and accurate delivery of medicines to the specific area in the lungs of patients with severe asthma or cystic fibrosis.

### Close cooperation

The beginning of Activaero can be traced to a few encouraging words and a lot of encouraging research results.

Scheuch had been working for the Helmholtz Zentrum München and for 18 years had been conducting fundamental research on aerosol particles and their behaviour–how they enter, are deposited into, and are eliminated out of the lungs. The institute's director, noting the practicality of his study, remarked: 'What you're doing here would surely be exciting for the pharmaceutical industry.'

This, and the success of his initial studies, emboldened Scheuch to bring his research out to the industry. In 1998, he entered and won a business plan competition, and invested the prize money, along with his own funds, to launch Inamed GmbH. From this start-up, he would carve out Activaero seven years later.

Ascenion, as technology transfer partner of Helmholtz Center Munich, negotiated licences that the institute granted to Inamed. From 1998 until 2001, Scheuch and his team, including a few engineers, used the same labs and enjoyed all the available technology at the Helmholtz Center, which was a shareholder of Activaero. 'Our idea was to develop a device that takes the breathing pattern of the patient into account,' he says.

## In the spotlight
### The FAVORITE principle

The unique therapy concept behind Activaero's smart nebulisation technologies—AKITA® JET, AKITA®2 APIXNEB and FOX—is called Flow and Volume Regulated Inhalation Technology (FAVORITE).

FAVORITE actively regulates inspiration flow and inhalation volume, making it possible to guide and control inhalation patterns according to each patient's specific condition and therapeutic requirements, thereby delivering the drug to the patient's lungs in an optimal manner and minimising unwanted deposition in the throat.

To provide targeted inhalation therapy for applications where precise drug delivery to the lungs is required, the AKITA Jet, AKITA 2 APIXNEB and FOX smart nebuliser delivery systems create a liquid aerosol and coordinate delivery after the patient has inhaled. Controlled application of branded and generic drugs is achieved through a modified nebuliser unit that delivers the nebulised aerosol tailored to the individual patient's breathing capacity.

FAVORITE is currently utilised in multiple clinical and several preclinical stage programmes, and thus contributes to the development of drugs.

For over two years, they studied different patient populations – COPD, asthma, and cystic fibrosis – to find out the breathing pattern of these patients and discover a way to use this breathing pattern to get as much drug as possible into the specific lung areas that require it. 'From this research, we found different breathing patterns which are optimal for the different diseases and to deposit particles deep in the lung,' Scheuch says.

**SMART devices**

According to Scheuch, in 1999, a large international pharmaceutical company wanted to be able to deliver a protein deep into the lungs of COPD patients. The pharmaceutical company, however, halted the project because in a study, it could only get 4% of the protein into the deep lungs of the patients. Given the cost and rarity of the protein, which was made out of blood plasma, the company said it could not work with such bad efficiency.

This provided an opening for Scheuch and his team. 'We told them we had an idea to increase this efficiency,' he recalls telling the pharmaceutical firm. 'We could show that when we worked within an optimal breathing pattern of these patients, we could easily get about 60% of the drug through the deep lungs of the patients.'

The increased efficiency promised by Scheuch's proposal made the project possible and brought the first contract to Activaero.

Activaero went on to develop the first AKITA device, a breath-actuated nebuliser that controls the patient's breathing pattern, for the German pharmaceutical company. Later, realising that the breathing pattern has to be adapted to each patient's lung function, Scheuch and his team developed the SMART CARD technology and introduced it into the AKITA system to optimise the device for a specific patient.



Smart Inhalation Technologies

Working with different lung function parameters, Scheuch's team categorised the patients depending on their breathing pattern and programmed a specific card for each pattern. This concept improved lung deposition even more. 'At the moment, we can realize 75% to 85% efficiency, which is very high,' Scheuch says.

'If you had one drug, for example, corticosteroid for asthma, you need it in the deep lung, in the airway. So we know the target and we know that these are asthma patients. We just need the information, e.g. how big is the lung of the patient? Is it a child, which has a lung volume of say, 1 litre, or is it a big athlete who has a lung volume of 8 litres?' Scheuch explains. This information allows them to program the SMART CARD for a certain category of patients.

**Big benefits**

Patients with severe cases of pulmonary diseases benefit most from the smart nebulisation technologies, as they are able to get the drug very deep into the patients' lungs. According to Scheuch, more efficient drug delivery not only means lower costs for patients, health insurers and pharmaceutical companies, but also less treatment time for patients.

*'More efficient drug delivery not only means lower costs for patients, health insurers and pharmaceutical companies, but also less treatment time.'*

One of the problems with inhalation therapy for patients with cystic fibrosis is the inhalation time. 'Some patients inhale for two-and-a-half hours every day because they need a high dose of antibiotic in the lungs,' Scheuch says. 'With our technology, you can reduce treatment times very significantly.'

A study published earlier this year also showed that patients with severe asthma were able to reduce oral corticosteroid use through the smart inhalation technologies.

'This was a very helpful study and we are continuously working on this,' Scheuch says. 'What we could demonstrate was that we significantly reduced the hospitalization and exacerbations of these patients when they use this technology. That is really positive.'

**Partnering with pharmaceuticals**

In its first years of development, Activaero conducted studies and investigations with pharmaceutical companies, from which it derived its income. When the company needed larger proof of concept studies, Activaero turned to venture capital and from 2009 to 2012, raised a total of €17M.

The company used part of the money to develop FOX, a handheld device that allows rapid drug delivery and enables the wireless transmission of inhalation parameters and compliance data.

It also developed other smart inhalation technologies such as the AKITA® JET, AKITA®2, and APIXNEB. Because of the success of these smart inhalation technologies, which are marketed in Germany, Activaero had revenues of €6M to €10M per year, says Scheuch.

In March 2014, Vectura acquired Activaero. Ascenion's proceeds from the sale of its equity in Activaero flowed to the Life Science Foundation for the Promotion of Science and Research, which funds various research projects of the endowing institutes, including the Helmholtz Zentrum München.

## STORM® Skills Training

# Science steps in to prevent suicides

Suicide is the quiet killer that gets national attention only when a celebrity dies of overdose or some form of self-injury. For decades, the issue has been taboo and therefore, largely unaddressed. Finally, a research programme at the University of Manchester put together evidence-based skills training to equip people to detect and address suicidal tendencies.

By the time you finish reading this—if you are an average reader—10 people would have died by suicide. In that same time, about 200 more would have tried to kill themselves.

This is how alarming the world's suicide rate is, according to Dr. Gill Green, co-founder and Chief Executive Officer of STORM® Skills Training Community Interest Company, a social enterprise that trains frontline workers like nurses and teachers to detect and manage suicidal tendencies at first sight.

'One death is one too many,' says Green. 'With one person dying by suicide, there are probably about 20 or so people who have attempted suicide, and many more have thought of it.' Unfortunately, she says, frontline workers who come face to face with these people have always found it difficult to ask sensitive questions such as, 'Are you feeling suicidal?' and 'Do you want to kill yourself?'

**Product** STORM® Skills Training
**Research institute** University of Manchester
**Marketed by** STORM® Skills Training CIC
**On the market since** 2003

### Bridging the gap

Since moving into research at the University of Manchester, Green has been specializing on studies concerning mental health and suicide prevention. Her interest in these subjects stemmed from her interaction with both patients and health workers when she was a nurse. For 12 years, she observed how hospital staff was unable to handle the suicidal tendencies of people they engaged.

'When I was a clinician, I nursed a lot of people who had depression and who were suicidal. Even though I knew about suicide, I really didn't know what I should be doing and how I should do it,' Green says. 'The only training that I had in suicide prevention was a lecture on what suicide is and how to help one that is suicidal. But that actually did not help me find the confidence and competence to do that well.'

This gap in what could be life-saving intervention sparked Green's interest in finding a science-based methodology to train people, especially frontline staff, to detect and respond to a suicidal crisis. Frontline staff is defined as anybody who is working in a role that engages with another person.

**With STORM®, there is now a science-based methodology to equip people to detect and address suicidal tendencies.**

Teaming up with Professor Linda Gask of the University of Manchester's Institute of Population Health and other researchers, Green reviewed extensive literature on suicide prevention and risk assessment. From this, the team created a skills-based training model that builds on adult education theories. 'We put together in a package all the methods that are known to develop the required skills for suicide and self-harm assessment and intervention, and worked out a study to determine if it actually works,' she says.

Thus STORM® began. From being a research programme in the 1990s, it evolved into The STORM® Project in 2003, a not-for-profit venture within the University of Manchester that was set up to make the STORM® training commercially available. STORM® training is a flexible programme designed to reach many audiences including those in healthcare, social care, education, criminal justice, defence forces, veterans services, human resources, occupational health, and personnel responsible for mental health and well-being in the workplace. The programme is delivered either via a Cascade model (Train the Trainer) or Direct-to-Participants model. It can be adapted to meet a particular group's needs.

'The training is very adaptable. Teachers work in a slightly different environment compared to, say, health workers in a hospital, so the training has been adapted to their culture of working,' Green says.

Since 2003, The STORM® Project has provided suicide prevention training to organizations in the United Kingdom, Republic of Ireland, Malta, Australia, and the Channel Isles. STORM® training

is recommended by the National Health Services, and the English and Scottish governments. STORM® facilitators have also brought the training to psychiatrists and mental health workers in Russia, Pakistan and Bangladesh, free of charge.

**Compassionate chat**

In the last decade, STORM® has created ripples in communities where suicide has been a problem.

With its pool of 1200 trained facilitators, the project offers evidence-based training on suicide prevention, postvention and self-injury mitigation. Suicide prevention focuses on skills needed to help a person at risk of suicide or self-injury; postvention training works with closed communities, such as the workplace and schools, to create a responsive strategy that would help those affected by a person's death by suicide. 'The impact of suicide is felt across the community. It is not just those close to the person but where that person went to school, works, shops, and involves himself,' Green says.

*'The impact of suicide is felt across the community. It is not just those close to the person but where that person went to school, works, shops, and involves himself.'*

She describes the STORM® approach as compassionate, emphatic, and collaborative while being evidence-based. 'We are not the only suicide prevention training provider but we are the first one that has been researched within the university,' Green says.

STORM® uses interactive methods such as role rehearsal, filmed role rehearsal, and discussions to engage its training participants and build their confidence in asking difficult questions.

Green shares a story of a woman who attended one of the STORM® courses and ended up saving the life of a colleague with suicidal thoughts. The colleague at risk has been off work for weeks, and the woman could see that she was not looking good. 'How about we go for a cup of coffee and a chat?' the woman asked. During their conversation, she asked her colleague if she was thinking of suicide. When the colleague said yes, she convinced her to see a general practitioner about it.

Another STORM® attendee shared how he sensed something wrong when he saw his neighbour taking out the rubbish one morning. The guy said 'Hi' and engaged the neighbour in conversation. Using strategies he learned in STORM® training, the guy asked his neighbour if he was thinking about suicide. The man said he was, and he agreed to see a doctor.

**Social business**

With the STORM® training a success—having earned over £1M—Green sought the help of Dr. Sonia Nikolovski of the University of Manchester Intellectual Property (UMIP) xto develop a sustainable business model that would allow the project to operate independently of the university.

In 2012, the STORM® Skills Training Community Interest Company (STORM® CIC) was established. It was important for the team to remain a non-profit venture so its business model and legal framework adopted the philosophy of the STORM® project: 'No one should profit from another person's distress.'

Despite its success, STORM® CIC has no specific marketing strategy. It relies heavily on word of mouth. As it has been running as a social enterprise, its community engagements have helped the business reach a wider audience. STORM® CIC also maximizes the use of social media to inform the public about its work and advocacies. 'We are getting a lot of interest through that platform,' Green says.

Green has won three awards for STORM® training: two HEFCE/UnLtD Social Enterprise awards in 2010 and 2011, and the UnLtD Fast Growth Award in 2015, all of which have helped the company in terms of business management support, mentorship, and pro bono expertise.

STORM® CIC uses part of its income to fund community projects with the aim of reducing the number of suicide cases and changing society's attitude towards suicide.

An example of its community work is #HeyAreYouOK?, an educational campaign raising awareness of distress, which is considered the main precursor of suicidal thinking.

'This is a big campaign on the back of STORM®. We want to help people identify distress before someone becomes distressed. This is so that you will ask for help before suicide becomes an option,' Green says.

The company is also hoping to develop an online version of the STORM® training packages so the training can reach remote and rural communities. That step is proving to be a challenge. 'The thing that stops me is the technology to replicate this in an online setting. We have to do it much the same as what we do face to face. That is tricky,' Green says.

STORM® CIC's ultimate goal is to make STORM® training available worldwide. The company plans to expand to the United States, China, and India soon. The easiest thing to do, according to Green, is to establish a presence in English-speaking countries first before they move into countries with different cultures and languages.

## In the spotlight
### Popular places to die

Some of the world's top tourist attractions are also popular spots for committing suicide. The Golden Gate Bridge, which spans the strait connecting San Francisco Bay and the Pacific Ocean, draws its share of people who want to end their lives in a beautiful place.

A person jumps to death from the Golden Gate every two weeks on the average. In 2014, 38 people died there.

Another popular suicide location is Japan's Aokigahara, the 3, 500 ha forest located at the base of the iconic Mt. Fuji. About a hundred suicides take place there every year, earning it the name 'Suicide Forest.' Since the 1970s, authorities have been conducting an annual body search in the area. Signs have also been posted along the trails to prevent more suicides. One of them in Japanese reads: 'Your life is a precious gift from your parents... Don't agonize over problems yourself—please seek counseling.'

## Tide Microfluidics

# Monodisperse microbubbles produce ultra-clear ultrasound images

Traditional imaging techniques used to be a bane to patients concerned about their long-term health and finances. With the patented microfluidic technique introduced by Tide Microfluidics in medical imaging, such issues may finally be a thing of the past.

Modern imaging techniques have propelled advancements in the medical field. Diagnosing the causes of symptomatic conditions, screening people for illnesses or injuries, and monitoring patients' response to treatments have become easier with medical images of the human anatomy.

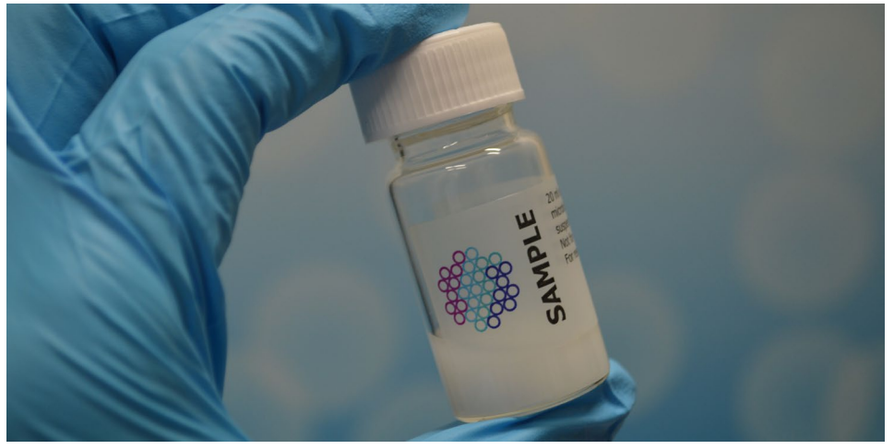
However, the advances made by these imaging techniques can be a double-edged sword for patients. X-rays, computed tomography (CT) scans, and positron emission tomography (PET) all involve exposure to ionising radiation that can increase a person's lifetime risk for cancer. While a fourth option—magnetic resonance imaging (MRI)—does not use radiation, the financial cost of availing it is still prohibitive for most patients.

Enter Tide Microfluidics, a Netherlands-based medical device company that is using a new microfluidic technology to make ultrasound images 20 times better than they used to be. The technology, which is based on the efficient production of monodisperse medical microbubbles, is changing the market by providing a safer and cheaper option for medical imaging.

'The world population is ever increasing and people have longer life expectancies, meaning the demands on the healthcare sector continue to grow,' says Wim van Hoeve, Managing Director of Tide Microfluidics. 'Tide's microfluidic technology enables advanced manufacturing of much needed pharmaceutical products for both diagnostic and therapeutic imaging procedures.'

Tide Microfluidics was founded in 2011 as a spin-off of the MESA+ Institute of Nanotechnology of the University of Twente. It was established to develop, manufacture and commercialize the patented microfluidic technology that was developed within the University of Twente in The Netherlands and the University of Sevilla in Spain. 'Everybody should have access to high quality and affordable healthcare through easy-to-use and accurate medical imaging procedures,' Tide Microfluidics declares as its vision.

**Product** Microfluidic technology
**Research institutes** University of Twente, University of Sevilla
**Marketed by** Tide Microfluidics
**On the market since** 2015




**Tide Microfluidics' novel platform technology allows for the creation of monodisperse microbubbles.**

### Uniform bubbles

Making superior medical imaging more accessible and affordable is crucial in building a sustainable healthcare sector. According to the European Science Foundation, medical imaging contributes to improved outcomes for patients and cost-efficient healthcare for all major diseases, Van Hoeve says.

Of all the medical imaging techniques being used today, he says ultrasound is the safest because it is non-invasive; it is also the most-cost effective as it is available in almost every hospital in the world.

Furthermore, ultrasound is not subject to factors such as calcified body areas (bones and hardened arteries), body size, and the skill of the person performing the scan.

The only downside to ultrasound is the low contrast of the images produced, making medical diagnoses more difficult. Tide Microfluidics is changing this. The new technique used by the company can magnify the smallest structures and organs in the human body so that the quality of ultrasound images is improved by 20 times.

This allows ultrasound to compete with other imaging modalities, such as MRI or CT scan. 'With Tide's products, the diagnostic capabilities of ultrasound can be drastically improved, resulting in more accurate and earlier diagnosis,' Van Hoeve says.

Tide's microfluidic technology enhances ultrasound images by producing superior quality ultrasound contrast agents (UCA) in the form of microbubbles and microdroplets smaller than red blood cells.

These UCAs, composed of billions of microbubbles, are not even as big as the thickness of human hair. They can be safely injected in the body to improve image contrast and allow better visualization of the soft tissue structures of organs of interest within the

## In the spotlight
PhD thesis becomes a product

The microfluidic technology was discovered when Tide Microfluidics founder Wim van Hoeve investigated the principles underlying microbubble formation as part of his PhD-thesis at the University in Twente in The Netherlands.

The technology works by enabling the controlled creation of microparticles—either bubbles or droplets—in a highly controlled environment. Such an environment ensures that the UCA's gas bubbles are produced one at a time and in the same repeatable manner, giving same-sized bubbles each time.

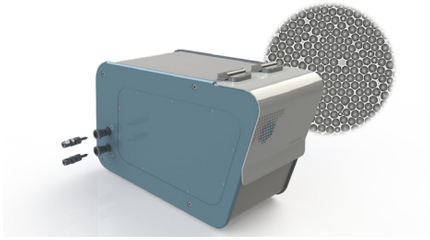
The University of Twente and the University of Sevilla jointly own the patent protecting this technology, with an exclusive license granted to Tide Microfluidics to develop such technology into commercial products.

human anatomy.

While commercially available UCAs are able to enhance ultrasound images in more than three million annual ultrasound procedures worldwide, they do so with limited success. At present, available UCAs are composed of microbubbles in different sizes which cannot guarantee the production of images that are optimal for ultrasound procedures. 'For the UCAs to provide a significant improvement to image quality, the microbubbles are required to be of a uniform size," Van Hoeve explains.

In order to work as contrast agents, microbubbles are made to resonate by the high frequency sound wave of the ultrasound equipment. The size of each microbubble plays a crucial role as resonance is only accomplished when the size precisely matches the operating frequency of the ultrasound equipment.

'This uniformity, or monodisperse nature, is something that our patented technology is able to produce,' says Van Hoeve. To efficiently apply the microfluidic technology, Tide Microfluidics created an innovative laboratory apparatus called the Microsphere Creator.



**The Microsphere Creator efficiently applies Tide's microfluidic technology.**

The apparatus, launched in January 2015, can manufacture UCAs at the bedside of patients. The Microsphere Creator enables ultrasound researchers to produce their own UCAs on demand. It also allows them to familiarise with microfluidic technology and develop new products based on monodisperse microbubbles.

### Awards and grants

Tide Microfluidics has received numerous accolades for its work. It proved to be the strongest contender during the Young Technology Award at the Commercialization of Micro- and Nanotechnology conference in Salt Lake City, Utah in the United States.





At the conference, young companies such as Tide Microfluidics presented a 3-minute pitch to an expert jury. Tide Microfluidics won both the first prize of US$5000 and the public prize of US$500. 'The jury was unanimous in its decision, stating that Tide not only showed an innovative technology but also had clear real world relevance in helping solve pressing needs within the healthcare system,' Van Hoeve says.

*'Tide showed an innovative technology with a clear real world relevance in helping solve pressing needs within the healthcare system.'*

Tide Microfluidics won another award in February 2015, the AXON Innovation for Health Award 2015. Innovation for Health is a premier Dutch healthcare innovation event held annually in Amsterdam. Tide Microfluidics received the €2500 AXON voucher for its pitch highlighting its innovative technology. The company has also received a European Union Horizon 2020 SME Instrument Phase 1 Grant, a subsidy consisting of a 70% contribution of €50000 from the EU.

According to Van Hoeve, the company will use this grant to further develop its business model for a bedside UCA production apparatus and continue to grow its company. Van Hoeve points out that the product is highly scalable, and can be used for targeted drug delivery by applying medicines to the microbubbles' outer shell.

The ultrasound is then used to monitor the patient until the contrast agent reaches the site being targeted, such as tumorous growths or lesions. Once the contrast agent reaches the site, the ultrasound field is used to burst the microbubbles, releasing the drug where it is most needed and where it can work most effectively.

### Food and drugs

The advantages of this technique include the continuous visualisation of the target area as the medicine is delivered; the reduction in the dose required as drugs are only released at the affected site; and the reduction in side effects, as drugs are not circulating and affecting other areas of the body but are focused on the site where they are needed.

'Ultimately, this leads to a next generation in medicine where treatments are personalised and the patient is treated as an individual (and not merely as a disease),' Tide Microfluidics explains in its company website.

Microfluidic technology can also be useful to the pharmaceutical, food and cosmetics industries by dramatically boosting the stability of dispersions and emulsions. By increasing monodispersity, the technology enables the creation of more uniform foams and emulsified structures. 'The uses of these emulsions and dispersions are varied from flavour and fragrance enhancers to food production and even solgels,' Tide says.

Van Hoeve says that Tide Microfluidics has been able to continue the development of the microfluidic technology into commercial products with the support of the University of Twente and the University of Sevilla. 'This successful transfer has also meant Tide is considered a valuable research and development partner to related research groups, with the continued exchange of students and ideas, which will hopefully lead to further IP transfer possibilities,' he adds.

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The *ASTP-Proton Impact Report for Europe 2015*, published by ASTP-Proton, celebrates the complex but very rewarding profession that is technology transfer. In this publication, you will read how excellent research is put to use to lengthen lives, thoroughly alter them or just make them a bit better.

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