
# MIRA in·sight

BIOMEDICAL TECHNOLOGY AND TECHNICAL MEDICINE

This publication introduces you to a young and ambitious research institute for biomedical technology and technical medicine: MIRA. Discover what MIRA aims for and what it has accomplished so far. Meet some of MIRA's researchers and find out what motivates them. Read about how science works when it mingles with an entrepreneurial spirit: through talent, cooperation, inspiration, hard work and even on occasions by chance. And most importantly: learn how patients profit from all of this, because our research provides better, less burdensome and affordable treatments and, ultimately, faster cure.

UNIVERSITY OF TWENTE.
WWW.UTWENTE.NL/MIRA

MIRA in·sight

UNIVERSITY OF TWENTE.

# MIRA in·sight

UNIVERSITY OF TWENTE.

MIRA
BIOMEDICAL TECHNOLOGY AND TECHNICAL MEDICINE

# MIRA
# in·sight

UNIVERSITY OF TWENTE.

MIRA
BIOMEDICAL TECHNOLOGY
AND TECHNICAL MEDICINE

[ table of contents ]

## 01 INTRODUCING MIRA



## 02 TISSUE REGENERATION

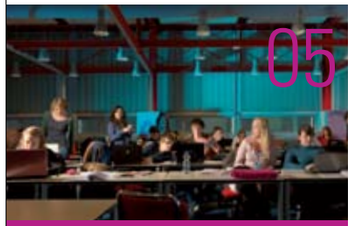


## 03 IMAGING & DIAGNOSTICS



## 04 NEURAL & MOTOR SYSTEMS



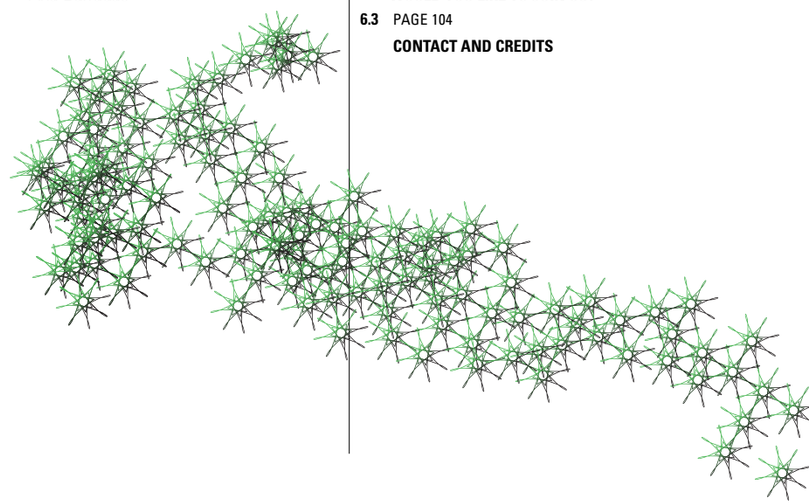


## 05 EDUCATION AT MIRA AND UNIVERSITY OF TWENTE



## 06 THERE'S MORE TO MIRA THAN MEETS THE EYE!





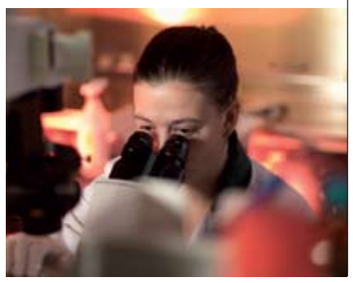
# INTRODUCING MIRA

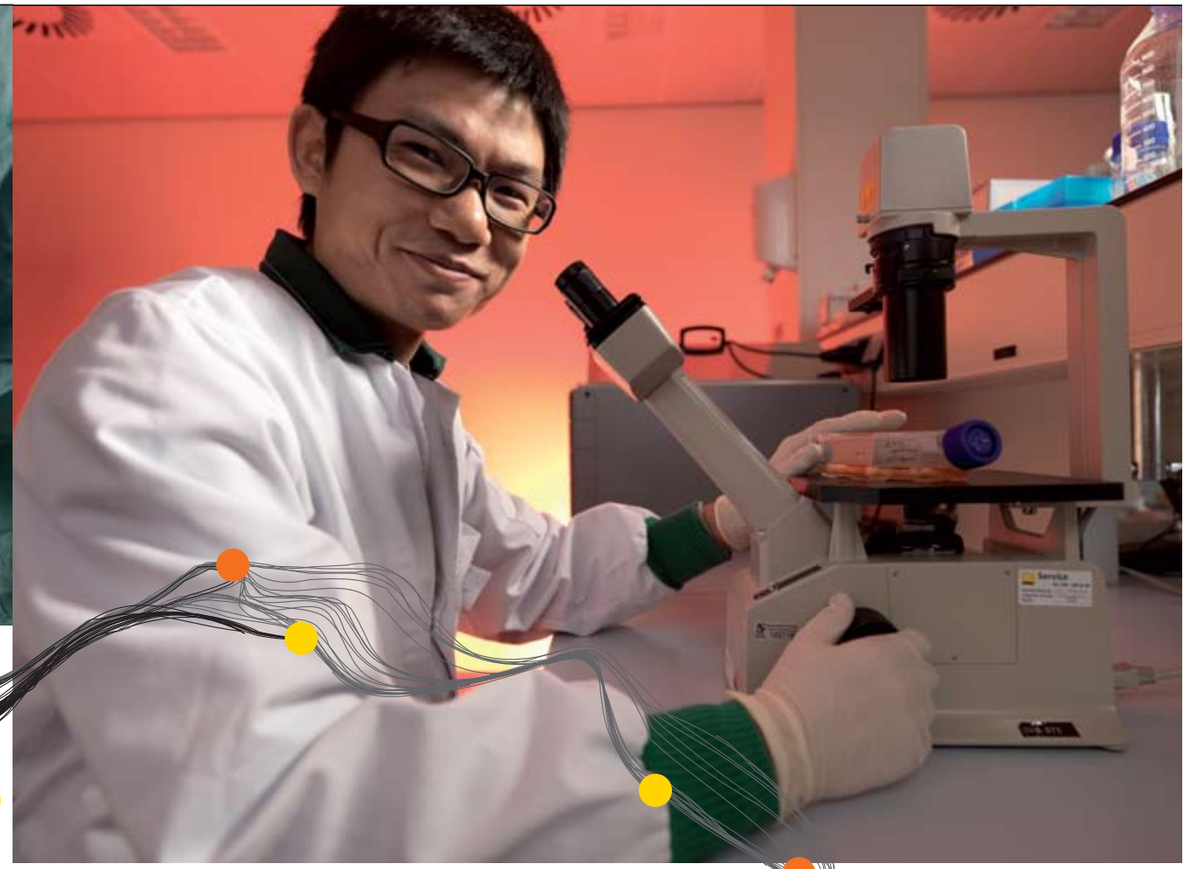
01

# dna of a young institute

# MIRA'S MISSION

In an era where technology is increasingly becoming a catalyst for innovation in healthcare, MIRA combines fundamental and applied research with clinical practice. MIRA encourages entrepreneurship and industrial collaboration so that its new technologies reach patients sooner and at an affordable price. MIRA's research will lead to new techniques to repair damaged tissue such as bone and cartilage. It enables doctors to make more effective diagnoses with the aid of improved imaging techniques, it helps to create drugs that are targeted in their effects, and it offers patient-focused solutions in rehabilitation technology. MIRA is also training a new generation of healthcare professionals and providing them with a unique focus.
Through close collaboration with hospitals, industry and government agencies MIRA aims to safeguard a leading position in Europe. ■





## making sure the technology reaches the market

We need companies to deliver technologies to patients at a favourable price. MIRA therefore tries to encourage entrepreneurship in various ways:

- create awareness
- scout and screen inventions
- assess market potential
- support spin-off company/business development
- negotiate licence agreements
- mentor licence performance

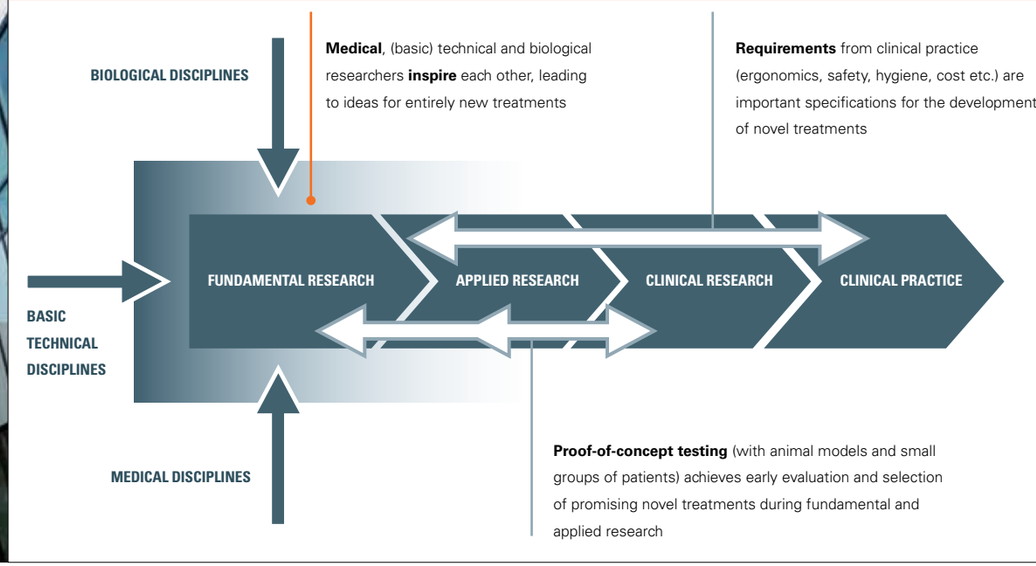
MIRA's entrepreneurial professors serve as role models. They ensure that researchers and students are aware of technologies with a high potential and know what needs to be done to commercialise these. The Programme Office of MIRA regularly talks with all researchers in its quest for pearls with business potential. If a patentable discovery is made then various options can be pursued. MIRA can try to sell the patent to a large company. Alternatively, the researcher can set up a limited company around the patent together with MIRA. In that case MIRA supports the researcher to make this business a success.

Biomedical technology and technical medicine research at Twente has already led to the founding of dozens of companies. MIRA wants to accelerate this trend. Its ambition is to spin off at least four companies per year and to have three companies that employ at least 15 people by 2014. ■

# filling the gap

In 2009, the institutes for biomedical technology and technical medicine at the University of Twente decided to join forces to form MIRA. The aim was, and is, to to fill the gap between fundamental research by biomedical technologists on the one hand and clinical applications from technical medics on the other. MIRA unites all the links in the chain: from fundamental concepts to innovative treatments that help patients to recover better.
MIRA has three research orientations: Tissue Regeneration, Imaging & Diagnostics, and Neural & Motor Systems. Each research orientation has its own full professorships to safeguard the value of the research. Two clinical professors are also attached to each research orientation. They work for one or two days per week at MIRA and spend the rest of the week working as medical specialists in a hospital. This puts them in an ideal position to formulate clinical research questions and to point out the needs in medical practice. The patients' welfare, during treatment and in health, is always the primary objective. The entrepreneurial professorships give MIRA a unique position in Europe. These professorships are filled by people with an academic background who have proven ability by successfully marketing a certain medical technology. Their specific skills, experience and network are vital for ensuring that new technology really does end up benefiting patients. Because that's MIRA's ultimate goal. ■

[ fig. a ] MIRA'S RESEARCH PIPELINE



1.4

[ extract from the schedule of... ]

MARTIJN KUIT

# ‘MIRA is growing fast!’

[ *intro* ] AS MANAGING DIRECTOR OF MIRA, MARTIJN KUIT IS SCIENTIFIC DIRECTOR CLEMENS VAN BLITTERSWIJK’S RIGHT HAND MAN. HE WORKS HARD ON REALISING AMBITIOUS PLANS FOR MIRA’S GROWTH AND SUCCESSFULLY COMBINES THIS WITH HIS FAMILY LIFE.


## 6.30 *Get up, check emails and bring the kids to school*

'My kids love it here. We used to live in the Randstad; due to a lack of space the playground was on the school's roof. Now we're in the middle of the woods. The school is in the woods, the after-school care centre is in the woods and when we step out of our front door we're in the woods in no time as well. The children play a lot outside and really enjoy that. There's also plenty to do in the city of Enschede. When I first came here I thought it might be a bit quiet, as Enschede is in a rural area. However, the city has recently grown and changed a lot; now there are loads of trendy neighbourhoods.'

## 9.00 *Consultation with venture capitalist about start-up*

'Tom Schwarz helps me with setting up entrepreneurial activities. The fantastic technology developed here must reach the patients and not sit collecting dust in the cellars of the University of Twente. But we don't want to be technology pushers. That's why we do everything possible to encourage entrepreneurship or to market our discoveries in other ways. For example, we're currently holding meetings with researchers who are busy with a start-up. They've asked us to transfer the patent to them and they would also like the university to become a shareholder in the new limited company. In principle, we're interested in that option. Finding capital and reaching agreements about who has the rights to what when the product becomes profitable in the future, is of course a complicated process. Tom advises us about the so-called capitalisation table.'

## Centre for Medical Imaging

**The Centre for Medical Imaging (CMI)** will provide new technologies to make even better images of the body than is currently possible by using MRI scans, CT scans, X-rays or ultrasound. We do that by combining signals such as light and sound and by developing innovative contrast media. In CMI, MIRA is collaborating with the University Medical Centre Groningen and with the German electronics giant Siemens. CMI is spread over two physical locations: from 2012 onwards the technological aspects will be worked on out at a refurbished building next to MIRA, while the technologies will be applied to patients at the hospital in Groningen.

## 10.00 *Interview with science journalist*

'MIRA is appearing in the news more often, with new discoveries or with "political" successes from the institute. This interview has been requested because we're involved in four of the eight centres that the Dutch science funding body NWO recently appointed as centres of research excellence with respect to innovative medical devices. For us this means growth as well as the recognition that we're on the right track as an institute. The initiatives chosen by the Netherlands Organisation for Scientific Research (NWO), fit in seamlessly with the research we're doing here.'

## 11.00 *First meeting with new colleague Christian Beckmann*

'MIRA is growing fast! Over the next few years we'll appoint some 150 new people. Christian is one of them. We've spent the past few months carefully thinking about the scientific focus we want to give to our new professorships. We've looked at how we can interconnect these and make sure they relate well to the consortia in which we're a partner, such as the Centre for Medical Imaging and LEO. Now we're looking for candidates. Christian is somebody who we're very happy to have found. He has previously worked at both the University of Oxford and Imperial College in London. He's impressed by what we're doing here and has decided to join us. It's nice to see that our visibility is increasing and that talent from abroad is now following what we do. That says something about the growing strength of our institute.'

## 13.00 *Lunch meeting with Joris Laarman, artist*

'We eat in our institute's restaurant, which is usually full of noisy students. Joris is an artist who we've already worked with on several occasions [see also page 098]. He's just back from New York, where he exhibited his Half Life, a lamp of living cells. Biochemistry meets interior design! Such ventures are also possible at MIRA. We're a young institute with a lot of young people; we work hard and a lot is expected

▶ CONTINUED ON NEXT PAGE

## [ *who is...* ]

**WHO IS MARTIJN KUIT?**

Martijn Kuit [1975] was appointed as the managing director of the fledging MIRA institute in May 2009. He was previously the director of the Centre for Entrepreneurship at Delft University of Technology as well as managing director of the research programme Next Generation Infrastructures at the same university. Up until 2002, Martijn was involved in research. He gained his doctorate with a thesis about strategic behaviour and regulatory styles in the energy sector. Martijn lives in Boekelo, just outside Enschede, with his wife and two sons.

CONTINUED FROM PAGE 013

from you. But that doesn't mean being serious all the time. Fun is also a part of our DNA. That can take the form of humorous projects with artists, an original competition or quite simply a fantastic party with good food, great music, dancing and

*'There's a clear professional ethos, but that goes hand in hand with a certain ease'*

a decent drink. The management team reflects that pleasure; it struck me from the moment I came here. There's a clear business and professional ethos but that goes hand in hand with a certain ease. Here, you're allowed to sit with your feet up on the table and I really like that!'

## 14.30 *Meeting with architect about the new location for the Centre for Medical Imaging*

'In 2012, the Centre for Medical Imaging will move to a building right next door to MIRA. The old chemical technology building will be completely stripped and refurbished for this purpose. Researchers will soon share that building with patients who will benefit from the most advanced equipment. The patients will then of course need to be separated from the people working on the equipment. And we'll need to keep sensitive equipment well away from lifts and cars as these

can cause disruptions. I need to discuss these requirements with the architect.'

## 16.00 *Meeting about the inaugural International Federation of Biomedical Institutes conference*

'The work we do at MIRA takes place in an international context as a matter of course. People from all four corners of the globe work here, English is our medium of communication, and we only publish in international journals. We want to collaborate more closely with other European institutes. So we're examining the option of setting up a federation of biomedical institutes. This has many advantages, For example, working together makes it easier for us to benefit from European grants. The University of Twente is an entrepreneurial university in every respect. I have considerable freedom, and we're going to set up a lot of new things. That's exciting.'

### Centres of Research Excellence

The Dutch science funding body Netherlands Organisation for Scientific Research (NWO) has made about 200 million euro available for collaborations between universities, industry and medical institutes that wish to develop healthcare by means of technological innovations. In 2010, eight national partnerships were selected, the so-called centres of research excellence. MIRA is involved in no less than half of these happy few: in two cases as the official technical scientific leader and in two others as a partner.
MIRA is the official technical scientific leader for the Centre for Medical Imaging [see page 012] and the Centre for Care Technology Research, a partnership that includes the University of Twente, Maastricht University and TNO, which will develop technology for an improved diagnosis, monitoring and treatment of patients outside the hospital. MIRA is a partner in NeuroControl, a consortium that works on improved rehabilitation techniques, and in SPRINT, which will develop smart prostheses to allow patients to move more easily.

## 17.00 *Off home, cook, eat and take the kids to bed*

'I really value being with my children in the evening and eating with them. From nine to five I'm at the

*'We don't want to be technology pushers.'*

institute and outside those hours I'm at home. However, this doesn't mean that I never work then. Early in the morning, late in the evening or sometimes even in the middle of the night, I'm often behind my computer. The same is true for many parents at MIRA. We're flexible as an employer: we're very clear about what we expect from you, how you do things is up to you. If you want to work for half the night so that you can play with your children in the sandpit in the afternoon, then, in principle, that's fine with us.'

## 19.30 *Reading the newspapers*

'I read the papers for myself, and for MIRA of course. We want to make connections with what's happening, also locally. The High Tech Health Farm is a superb example of that [see page 050].'

## 20.30 *Jogging*

'I go jogging for 30 to 45 minutes twice a week in the woods close to


The High Tech Health Farm [see page 050].

home, come rain or shine. I always feel really good afterwards.'

## 21.30 *Reading a book*

'Now I'm reading *Zoete Mond* [Sweet Mouth] by Thomas Rosenboom. It's a novel that's set in the 1960s and describes the rivalry between a vet and a village prankster. I read literature but also enjoy a popular American thriller once in a while. But I leave management books untouched these days. I read enough of those during my studies and my PhD research. Now I develop my management skills by simply getting on with the job. That's how you learn the most.' ■

### LEO, centre for Service Robotics

LEO is a broad consortium that works on intelligent service robots for a variety of purposes, including medical applications. Besides MIRA, partners include regional high-tech companies and Ontwikkelingsmaatschappij Oost-NV.
Robotics is the emerging technology in healthcare fields such as surgery and rehabilitation. It offers new and improved surgical procedures, better training results and enhanced comfort and safety for patients. After many years of fundamental research and clinical trials, robotic technology will mature to enter the operating theatre and clinic for routine applications. After exploratory missions to Japan and to Boston, Baltimore and Chicago, the initiative is starting to gain a more definite shape. From 2012 onwards, LEO will be housed next to the Centre for Medical Imaging. Our ambition is to turn the east of The Netherlands into a leading player in robotics for healthcare and medicine.

[ chapter 02 ]

# TISSUE REGENERATION

02

[ *intro* ] THE TISSUE REGENERATION RESEARCH PROGRAMME DEVELOPS TECHNOLOGIES THAT RESTORE THE FUNCTION OF DISEASED AND DAMAGED ORGANS AND TISSUES: BIOLOGISTS, CHEMISTS, NANOTECHNOLOGISTS AND ENGINEERS ALL WORK TOGETHER. WITH THIS APPROACH, MIRA HOPES TO REALISE PRACTICALLY APPLICABLE SCIENTIFIC BREAKTHROUGHS AND THUS SPEED UP PATIENT RECOVERY.

## helping the body to repair itself

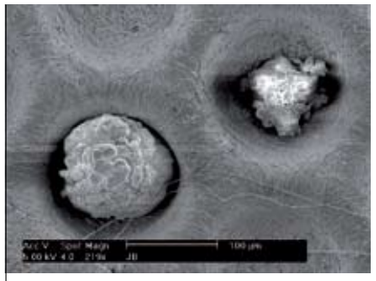
# HOW TO HELP PATIENTS WITH DIABETES TYPE I?

[ *intro* ] GROWING A NEW ORGAN AND IMPLANTING IT INTO A PATIENT IS STILL IN THE REALMS OF THE IMPOSSIBLE. BUT THE TISSUE REGENERATION GROUP IS WORKING HARD ON AN IMPORTANT INTERMEDIATE STEP. THE RESEARCHERS ARE MAKING SCAFFOLDS ON WHICH INSULIN-PRODUCING CELLS ARE GROWN. THESE SCAFFOLDS CAN BE IMPLANTED INTO PEOPLE WITH TYPE I DIABETES.

Diabetes is a serious metabolic disorder. In people with type I diabetes, the pancreas produces too little insulin. The insulin producing beta-cells residing in the so-called islets of Langerhans in this organ are damaged or destroyed by the patient's own immune system by this disease. The body needs insulin to be able to store sugar from the blood after meals. The special groups of cells are not only responsible for the production of insulin but also detect how much sugar is in the blood, and whether more or less insulin is needed to maintain proper sugar levels.

**INEFFICIENT** There are two ways of treating patients with type I diabetes. First, they can inject themselves with insulin several times a day or they can use an automatic insulin pump. However, the side effects of this diabetes can be quite harmful on the long term. Chronic diabetes leads to blindness, kidney failure and impaired blood supply to limbs, potentially leading to amputation. For patients who have severe difficulties in maintaining their sugar levels, an alternative is a transplant of islets of Langerhans from deceased donors. The first form of treatment is fairly stressful, while the second is still very inefficient: around 80% of donor cells are lost during or shortly after transplantation. Consequently, cells from three donors are needed to help one diabetes patient. But there is still a major shortage of donors. So until a way is found to culture new islets of Langerhans, scientists are seeking a more efficient method to introduce donor cells into the patient's body.

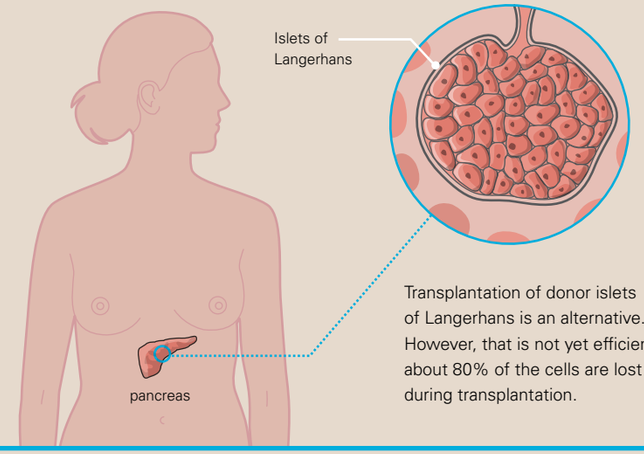
**MICROWELLS ALL IN A ROW** MIRA researchers are working on a very advanced method. They have designed scaffolds made of a special polymer which contain tiny wells. These wells or shallow compartments are arranged in neat rows, in which cells can be grown. The wells are just a few hundred microns wide. They are used to protect the islets of Langerhans, whilst still allowing them to live in an optimum environment. The cells are ultimately transplanted into the patient's body, scaffold and all. This doesn't necessarily have to be near the pancreas; for example, it can be under the skin, in a muscle or in the abdominal wall. In any case, the cells need to end up in a location with a good blood supply. Then they can release their insulin into the blood, and obtain oxygen and nutrients themselves.



Donor cells are grown in tiny protective wells, so they can be safely transplanted.

## [ fig. a ] CULTURING ISLETS OF LANGERHANS

In the case of diabetes the pancreas produces too little insulin, which is needed for the storage of sugar from food. The patient then needs to inject insulin several times per day. However, an alternative is being worked on.

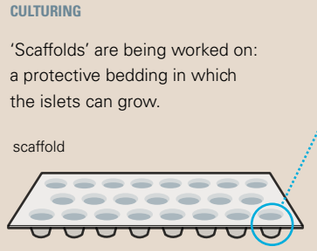



Islets of Langerhans in the pancreas are responsible for regulating the blood sugar level and the production of insulin. In type 1 diabetes patients, the islets are damaged.

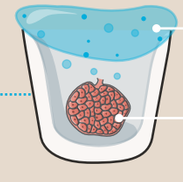
Transplantation of donor islets of Langerhans is an alternative. However, that is not yet efficient: about 80% of the cells are lost during transplantation.

**CULTURING**

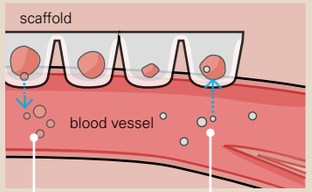
'Scaffolds' are being worked on: a protective bedding in which the islets can grow.




dimensions: several hundred micrometres




The entire scaffold is transplanted into the body, not necessarily in the pancreas but always near a blood vessel.




islets secrete insulin into the blood

islets absorb oxygen and nutrients from the blood

**POROUS MATS** The researchers are currently refining the scaffolds by researching the effectiveness of different materials and designs. Both these factors affect the survival of cells in the wells, and hence their functioning. And because this principle is still so new, the researchers have to discover what works best through trial and error. The first step is to test various ways of making a scaffold out of the polymer material. For example, by compressing mats of thin polymer fibres in pre-formed moulds. This produces a porous film containing the microwells. Because the material is porous, oxygen and glucose can reach the cells easily. The degree of porosity determines not only how well these substances can pass through the material, but also how sturdy it is. The MIRA researchers plan to study the effect of all these variables in greater depth.

**CONDUCTING TRIALS** The next step is to determine the right living environment for the cells. For example, should growth factors be added to the support material to ensure that the blood flow in the islets gets going as quickly as possible? And where is the ideal spot in the body to implant the scaffold? To answer that second question, the researchers are first of all conducting trials in animals. Human trials are still some way off. But the principle works; the researchers are already convinced of that. ■

▶ NEXT PAGE: FOUR QUESTIONS FOR AART VAN APELDOORN AND MIJKE BUITINGA

AART VAN APELDOORN AND MIJKE BUITINGA

# *'You mustn't lose heart when a great idea just refuses to work'*

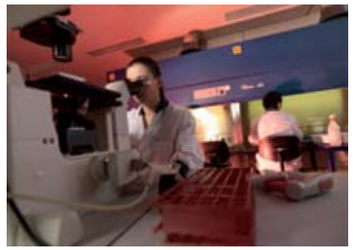
AART VAN APELDOORN IS WORKING ON A RANGE OF PROJECTS TO DESIGN AN ALTERNATIVE STRATEGY FOR THE TRANSPLANTATION OF ISLETS OF LANGERHANS. ONE OF THEM IS MIJKE BUITINGA'S PHD PROJECT.

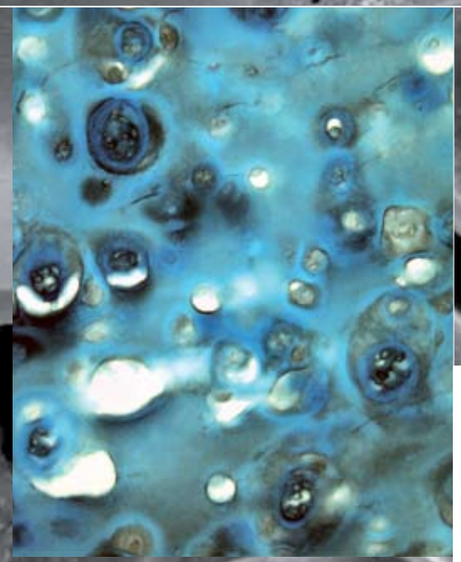
**1** *Why is this research important?*
**BUITINGA:** 'Diabetes is a common illness, and a serious one. There's no satisfactory treatment yet. Patients have to inject insulin throughout their lives, which is stressful and doesn't work well for everyone. And transplants are still not very efficient.'
**VAN APELDOORN:** 'Our research is focused directly on helping patients. The aim is quite clear. We're dealing with a condition where an organ is no longer functioning properly, and we need a solution. The research is extremely application-oriented.'

**2** *Have you found your niche in this department, and in this research?*
**VAN APELDOORN:** 'Absolutely. I can put all of my creativity into it. The subject itself is fairly new, but we can apply a variety of existing knowledge about cell growth and support materials to the making of artificial organs. That's really challenging.'
**BUITINGA:** 'Plus the fact that you're combining several different scientific disciplines. You're working on a technical solution to a clinical problem. One minute you're sitting at the computer thinking about the design of a scaffold, and the next minute you're in the lab testing whether it'll actually work in a living animal. I would never want to do just one thing or the other.'

**3** *What do you enjoy most about this research?*
**VAN APELDOORN:** 'Its interdisciplinary nature. I sometimes joke that we try to steal as much as possible from other groups. An awful lot of research within MIRA is relevant to what we're doing. So we're always asking ourselves: is anyone working on interesting techniques? Can we incorporate them into our research line? It's this talking to other experts, and trying to solve problems together, that makes this work so much fun.'

**4** *Do things sometimes go wrong?*
**BUITINGA LAUGHS:** 'Of course, a lot of things go wrong. Especially on the practical side. Progress is very slow in this sort of research. It's sometimes really depressing when you've thought of a good idea that refuses to work. You've got to be able to cope with that. But as long as you keep focused on your goal, you'll stay motivated.' ■





## HEALING PLASTERS

Worn cartilage in a joint causes patients a lot of pain. Weight-bearing or bending is difficult and sometimes almost impossible. Unfortunately, at the moment there is no curative treatment. The only option is pain control. Marcel Karperien's department is working on a solution to this common complaint: a gel that is injected into the joint. There it hardens to form a protective layer over the damaged cartilage. The gel binds to the cartilage and is biodegradable. The intention is that it will be replaced in time by the body's own cartilage. Initial trials are due to start shortly. Not in humans as yet, but in horses, which also commonly suffer from wear and tear of the joints. This image, made with an electron microscope, shows how the healing plaster cavities capture cartilage cells, which are stimulated to form a matrix. This cartilage matrix is shown by the blue colour in the less enhanced image. ■

Acc.V Spot Magn Det WD Exp 20 µm
10.0 kV 4.0 909x SE 28.7 0 Dextran 31k-10

# TARGETED DELIVERY OF MEDICINES

DELIVERING MEDICINES TO EXACTLY THE RIGHT PLACE IN THE BODY: THAT'S THE CHALLENGE WHICH MIRA RESEARCHERS HAVE SET THEMSELVES. THEY'RE DESIGNING A BROAD RANGE OF SMART TECHNOLOGIES TO REALISE THAT GOAL, RANGING FROM INGENIOUS 'CLOTHES LINES' TO LITTLE BUBBLES THAT STICK TO A SPECIFIC SITE.

When you take an aspirin for a headache, the active ingredient enters the bloodstream via the stomach and the intestines. It goes not only to the head, but to the entire body. And the same is true of all medicines, whether administered in pill form or as an injection. This is far from ideal. It's wasteful and can also be unhealthy: the medicine can cause damage if it ends up at the wrong place.
'It would be ideal', says Professor Johan Engbersen, 'if you could get the medicine delivered exclusively to exactly the right place like some sort of parcel. That sounds simple, but is in fact so difficult that we'll probably never succeed entirely.' But Engbersen and his colleagues, not only at MIRA but also elsewhere in the world, have already made good progress.
Engbersen: 'We use a whole arsenal of chemistry and physics to devise a specific solution for every challenge.'

**PASSIVE OR ACTIVE** One approach to deliver a medicine to the right spot, Engbersen explains, is by using a passive mechanism. For example, solid tumours are well-supplied with blood vessels. And just like the tumour, these blood vessels grow very quickly. As a result, they're not entirely perfect: they leak. 'By making particles loaded with medicine (nanomedicines) so small that they can only leave the bloodstream via such leaks', says Engbersen, 'means they end up just near the tumour cells.' However, Engbersen and his colleagues are working mainly on active mechanisms: systems in which particles are designed to adhere selectively to the right cells. For example, the particle has a specially designed chemical group at its surface that binds specifically to a receptor on a cancer cell. 'We really do work like a postal service', says the professor. 'First we carefully parcel up the vulnerable cargo, then we stick the right address on it, and finally we make sure that the parcel can also be opened again once it has arrived at its destination.' In some cases these parcels contain a medicine, but in others they contain genetic material. For example, a section of DNA can take over the role of a defective section in the target cell. This is a form of gene therapy, a technology which is hardly used yet because it is fraught with snags. 'Gene therapy as it has developed so far uses a virus to introduce the DNA into the target cell', explains Engbersen. However, this has a number of disadvantages, such as adverse immune reactions, which strongly hamper further clinical development. 'We're investigating whether you can design a synthetic carrier instead. With the polymers we are using you can vary the structure, and hence the effectiveness, more easily. And you can make sure that the material is fully biodegradable and therefore has no toxic effects.'

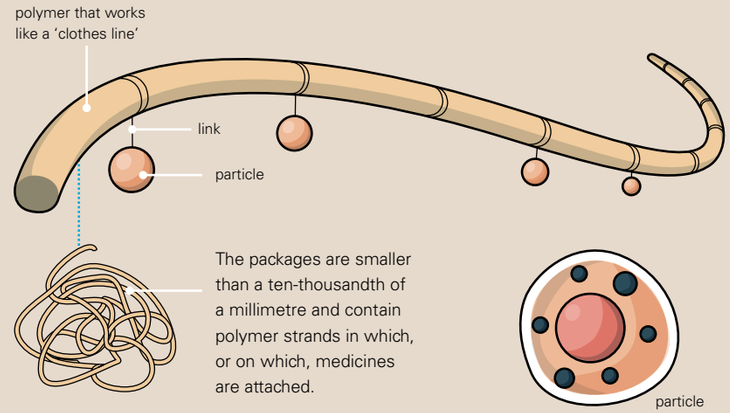
**CLOTHES LINE** Parcels like these can be composed of polymer chains that are fold up to a sort of ball in which the genetic material is packaged, but not necessarily: they can also take the form of a tangled ball. 'We are also designing a sort of clothes line on which you can hang all sorts of stuff ', says Engbersen, 'and which folds itself up to various extents. The kind of chemical groups that you hang on that line determines, for example, whether the parcel is water-soluble or oily. The choice depends on the application.' Moreover, the links chosen for the clothes line determine how and when the line breaks up and releases its cargo, and how easily the pieces of clothes line can be cleared up in the body again. The choice of clothes-pegs can also help to determine the effect of the medicine. 'Imagine a substance that kills cells, which you want to use against a tumour', says Engbersen. 'You want the substance to do its work only in the tumour, and not elsewhere in the body. Therefore we design the chemotherapeutic delivery system in such a way that the substance is not active while it's still attached to the clothes line. By attaching it to the clothes line with a connection that can only be cut by an enzyme that is common in cancer cells, but not healthy cells, it is then possible to activate the medicine only in the tumour cells.'

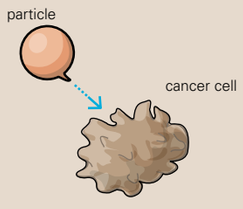
**ENDLESS POSSIBILITIES** Engbersen enthuses about a number of other tricks that the parcels can be equipped with, such as miniscule gold rods that can be heated up from outside the body using a targeted beam of infrared light. This heating causes the package to break down, or to attach itself somewhere. Or you can put magnetic particles in the parcels, and then assemble them at a specific place in the body with the aid of a magnet. The possibilities are endless. Virtually every wish-list can be translated into material properties. But the difficulty lies in actually applying the discoveries into clinical practice. The journey from idea to application is a long one. 'First you have to describe your discovery in miniscule detail, because you're often dealing with very complex particles. And then you have to go through the whole process of cell experiments in the laboratory, animal experiments and clinical trials. It's a lengthy business.' ■

## [ fig. a ] TARGETED MEDICINES

Medicines or genetic material delivered to exactly the right spot in the body, like addressed postal packages.

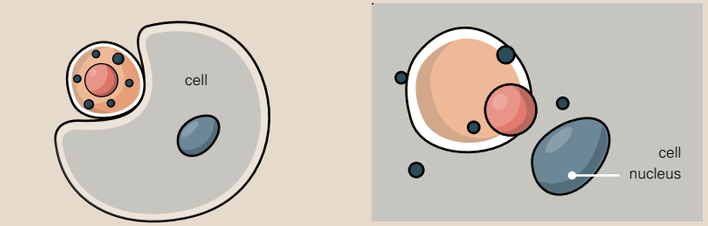
The researchers design a sort of 'clothes line' that you can hang particles on. The design of the clothes line ensures that the links release the particles in a phased manner. That way the particles can do their job only when they reach the right spot.




The design of the particles is such that they preferentially bind to the right cell. For example, they can have a chemical group that preferably attaches to a cancer cell.

HOW DOES IT WORK?




[ 01 ] The delivered particle finds its way to the cell that absorbs it.

[ 02 ] The particle releases its contents. For example, a piece of DNA that activates the cell to to produce a therapeutic protein, or in the case of cancer cells a cytotoxic compound that kills the cell.

[ extracts from the schedules of... ]

CLEMENS VAN BLITTERSWIJK
AND JOOST DE BRUIJN

# ‘it’s the intensity that makes it so much fun’

[ *intro* ] TWO ENTREPRENEURIAL PROFESSORS EXPLAIN WHY THEY EACH HAVE ONE FOOT IN INDUSTRY AND THE OTHER IN ACADEMIA.

CLEMENS VAN BLITTERSWIJK

## 7:00 *Leave the house*

‘I live in Friesland, not awfully convenient when you work in Twente, and have to be in Bilthoven a lot as well. But it’s just such a nice place to live... I stay over in Twente and I work at home one day a week, which cuts down the travelling. But I often put my time in the car to good use. This morning, for example, I had a telephone conversation with a colleague about MIRA’s new Materiomics research line.’

## 9:00 *At MIRA: recordings for television science programme Labyrinth*

‘The programme is doing a series on the theme of “making”. This episode was about making medical devices. I’m happy to contribute. Not just for the reputation of our institute but also because I think we owe that to the public. Our work is largely funded by tax revenues, so you really should take the trouble to explain what you do and why.’

## 11:00 *Consultation on Pre-Seed Grant*

‘Life Sciences Pre-Seed Grant, which I chair, awards grants of up to a quarter of a million euro to new businesses to start up their research line. It’s a Netherlands Genomics Initiative and the Netherlands Organisation for Scientific Research project. I think this sort of work is enormously important. It’s how innovation really gets off the ground.’

*‘It’s always inspiring to think about how you can best guide young people.’*

## 13:00 *Discussion with a promising prospective professor*

‘We’re looking for a new clinical professor, and this is a very serious candidate. In this meeting we’re discussing how he would fill in the details of the post.’

## 14:00 *Discussion with a Canadian colleague*

‘This colleague will be spending a year here as a visiting professor. He is on a sabbatical from his own university. Exchanges like these are vitally important for MIRA’s international character. Very fruitful for both parties.’

## 15:30 *Consultation with the dean of the faculty*

‘We hold these discussions on a regular basis, to look at how we can strengthen the teaching. That’s one of the things I’d miss if I only worked in industry: being involved in teaching. It’s always inspiring to think about how you can best guide young people.’

## 17:00 *Telephone conversation with a colleague in New York*

‘It’s a substantive discussion involving an exchange of ideas. But we’re also looking at whether he might be able to come over and reinforce MIRA’s ranks.’

▶ CONTINUED ON NEXT PAGE

## From chance discovery to million-dollar deal

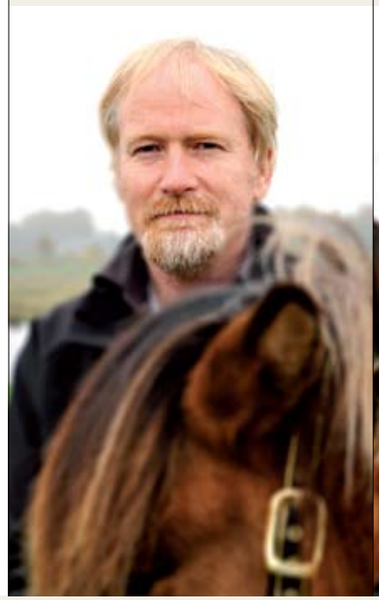
Progentix has its origins in the larger company IsoTis. In the late 1990s, IsoTis was working on growing bone with the aid of stem cells and special support materials. Clemens van Blitterswijk and Joost de Bruijn, who knew each other from their work on biomaterials at Leiden University, were both working at IsoTis. In 2002, however, Van Blitterswijk elected to take up a professorship at the University of Twente, partly financed by IsoTis. ‘I had to choose: carry on in business or go back to academia’, he says. ‘As a CEO I would have to give up research, whereas in Twente I can now do both. I research and teach, but I’m also involved in numerous start-ups and new businesses, such as Progentix, where I’m on the Management Board.’

Progentix was set up in 2004 by De Bruijn, after leaving IsoTis. ‘I was fascinated by the possibility of growing bone without stem cells or growth factors’, he says. ‘Just a support material that stimulates bone growth: it was a chance discovery that seemed too good to be true. But it really worked.’

The large American company, NuVasive, showed an interest almost immediately. NuVasive is a listed company specialised in innovative techniques for surgery on the vertebrae. ‘You need a partnership like that’, says De Bruijn. ‘We could never invest enough ourselves to embark on the long journey to clinical practice.’ In 2009, after six months of negotiations, the two companies entered into a partnership. Under that partnership NuVasive invested 80 million dollars and in so doing acquired a share in Progentix.

[ *who are...* ]

**WHO ARE CLEMENS VAN BLITTERSWIJK (LEFT) AND JOOST DE BRUIJN (RIGHT)?**
Clemens van Blitterswijk (1957) is MIRA’s scientific director and the leader of the Tissue Regeneration track. He is also involved in numerous start-ups. Joost de Bruijn (1966) is the founder and director of Progentix, a Bilthoven-based company associated with the University of Twente. He is also a professor at Queen Mary, University of London. Both lead international lives and work in both industry and academia: Van Blitterswijk at the University of Twente, and De Bruijn at Queen Mary, University of London.



CONTINUED FROM PAGE 029

**18:00** *In the car back to Friesland*
'On the way I have another telephone conversation with one of my PhD students about his research. He's now at the stage of writing his thesis.'

**20:00** *Go for a run*
'On days like these I don't get home until 8 pm. I then like to go for a run in the evenings, although I've not got round to it much recently. I really should start to make time for it again. My ambition was to run the marathon in under three hours, but I haven't managed that so far.'

**21:00** *A quick check on the horses*
'My wife and daughter have a number of Icelandic horses. In fact, we have a sort of small stud farm at home. I get involved with that a bit from time to time. It's great to focus on something completely different from work for a while.' ■

# *Entrepreneur and professor*

*Is it possible to combine being both a professor and an entrepreneur?*

**VAN BLITTERSWIJK:** 'It's mainly a lot of hard work. You work around the clock. In the evening you're often still meeting with US investors, for example, and in the morning you're all set again for a discussion in the lab.'

**DE BRUIJN:** 'But the skills are not so different. In both jobs you have to achieve good results, sell them, be financially responsible and attract and motivate good people.'

**VAN BLITTERSWIJK:** 'That does mean that you can't be a professor who's just at the university. You have a quite different schedule: everything goes on at the same time.'

**DE BRUIJN:** 'It's that intensity that makes it so much fun. The early days of Progentix were incredibly busy, for example. But then it's even better when it works. After that we really had to kick the habit.'

**VAN BLITTERSWIJK:** 'The two jobs often complement each other. And that's only to your benefit when it comes to things like applying for government funding, for example. You're not in your department so much, but your double role does produce more in terms of collaboration and financing.'

*Is such a partnership between a company and a university department common?*

**VAN BLITTERSWIJK (LAUGHS):** 'Our department in Twente has one spin-off a year on average. You mustn't forget: a lab can think up great ideas, but that's still a far cry from a useful product on the market. For that you need investments and long test periods. You can only do that with the help of a company. But large, existing companies are often very rigid and suffer from "not invented here" syndrome: they're only interested in their own discoveries. In that case spin-offs are the ideal solution: the link between a scientific discovery and a patented invention that actually makes it onto the market.'

**DE BRUIJN:** 'Spin-offs are much more dynamic. It's not easy for a large company to develop a new technology. It always has to make a profit, keep shareholders happy, so it doesn't want to take on too much risk. And a large company is less stable. As soon as a new director arrives, its course can change completely. Small ones often concentrate on one technology that they believe in heart and soul. And they have a very tight-knit team.'

**VAN BLITTERSWIJK:** 'A spin-off is very much like a university department in fact. With 40 people, you still have a very strong sense of belonging to a group: this is what we stand for and this is what we want to achieve.'

## JOOST DE BRUIJN

**9:00** *Discuss schedule with secretary*
'And then half an hour answering business emails and signing a pile of documents.'

**9:30** *Interview with a journalist about Progentix*
'Our technology has been in the news a lot lately. A number of articles have already appeared in the national newspapers. Recently, some highly promising results of our technology were published in the renowned American journal PNAS (Proceedings of the National Academy of Sciences). We've received a lot of responses, from colleagues, but also from journalists.'

**10:30** *Meeting with the Progentix Supervisory Board*
'These are very important meetings for us. We discuss the progress made, both technological and commercial. The meeting is also attended by representatives of NuVasive, the American company we have entered into partnership with. They're shareholders in our business, so we are accountable to them. But these meetings always yield useful insights as well.'

**14:00** *Prepare for a lecture on 'industry and future perspectives'*
'Once every two weeks I fly over to London for the day to give a lecture to students. This time I'm

CONTINUED ON NEXT PAGE

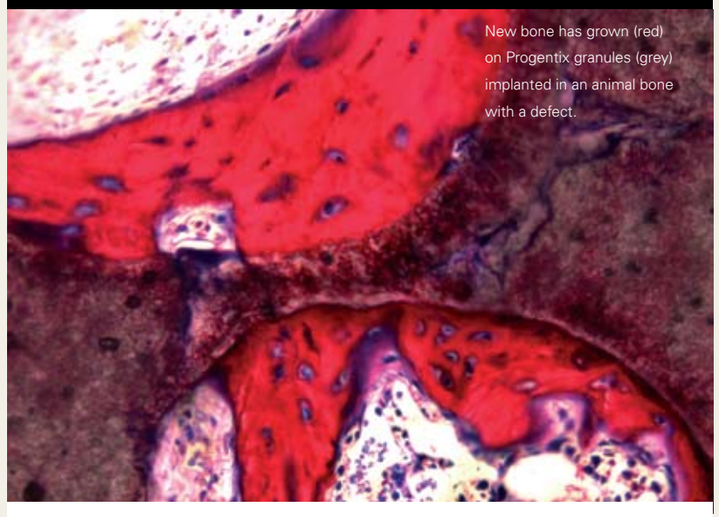
CONTINUED FROM PAGE 031

preparing a lecture about stem cells, tissue engineering and regenerative medicine. It's a lot of fun to do; the lecture is always attended by some highly enthusiastic students who ask lots of questions. On these days I also have meetings with PhD students and colleagues. Yes, I really do feel part of that department, even though I'm only there a couple of times a month. It used to be more often, but it's getting increasingly difficult to combine with Progentix. But at the moment I don't want to give it up altogether; I find teaching much too enjoyable and inspiring for that. Even though these are long days: I leave the house at 5am and get back at 11pm.'

## 16:00 *Dealing with the commercial aspects of Progentix*

'I'm still closely involved in the company's financial and staffing matters, but also in the technology. I think that's important. Talking with people, listening to what's going on. There are 22 of us now, and we're still expanding.'

## Ceramic powder slowly changes into bone



New bone has grown (red) on Progentix granules (grey) implanted in an animal bone with a defect.

A simple fracture usually heals by itself. But sometimes the bone is too badly damaged, or too much is missing. After a serious accident, for example, or after a tumour has been removed from the bone. In such cases, doctors need to give the bone a helping hand. For example, they take a piece of bone from somewhere else in the body, often the pelvis. This has its drawbacks: it creates a hole and the surgery is often accompanied by a lot of pain. An alternative is to use a piece of bone from a donor, or a prosthesis made of metal. But these "dead" materials will never really become part of the bone, and there's always a risk of infection or rejection.

Progentix, a company associated with the University of Twente, is bringing a new alternative onto the market: a powder containing synthetic calcium phosphate. By chance, Progentix director Joost de Bruijn and his colleagues discovered that this material promotes bone growth by attracting stem cells and certain proteins. In time the synthetic material dissolves by itself, leaving just the body's own bone.

Exactly how it works is not clear yet. But the fact is, it does work. Progentix has now further refined the material through trial and error: composition, grain size and porosity have now been optimised to promote maximum bone growth. The researchers have successfully tested their discovery on animals, and initial trials on humans are highly promising. The bone heals neatly and grows only where intended. The results are as good as those of autologous bone transplants, but without the unpleasant side effects.

The material is easy and cheap to produce. It is expected to make its market debut shortly and accelerate the development of bone surgery worldwide. A more user-friendly variant is already in the pipeline, in the form of a paste that is easier for the surgeon to insert.

## 17:00 *Checking and signing potential business partner's term sheet*

'Apart from Progentix, we're also working on other start-ups. For one of them, we're in talks with a major commercial party that's interested in an exclusive licence on our technology. The term sheet containing the terms and conditions of our agreement has been negotiated and we're flying abroad next week to discuss the draft contract.'

## 18:00 *Back home; go for a run*

'I always try to set aside time for running. I'm training for the New York marathon, although I've just put myself out of the running due to a calf injury. It's great to clear my head of everything during a run. Especially when it's busy at work. I find it easy to leave work behind. Some people need a week to wind down on holiday. Not me.'

## 21:30 *Telephone conference with NuVasive colleagues in the US*

'Often I can't avoid having to do some work at home, answering emails, reviewing scientific articles, etc. In view of the time difference with the West coast of the US, there are often conference calls with our NuVasive colleagues as well. Sometimes you really do have to talk live. Luckily it's not too much trouble in my case. I don't have any children and my partner is also closely involved in Progentix as a consultant, so she knows what it's like. In fact, sometimes she takes part in these conversations herself.' ■

*'It's great to clear my head of everything during a run'*

# *A blend of cultures*

*MIRA's employees work a lot across borders, both literally and through their contacts in Twente.*

**VAN BLITTERSWIJK:** 'MIRA aims for a cosmopolitan character. Why is that important? For a commercial reason, first of all. It's essential to have a large international network. Invigorating ideas and chances for collaboration often come from other countries. Institutes with staff from other countries get that for free. Those contacts will benefit you throughout your career.'

**DE BRUIJN:** 'And it also creates a special atmosphere. You develop bonds quicker. Foreign staff don't know anyone else, so they're keen to socialise with their colleagues.'

**VAN BLITTERSWIJK:** 'It's wonderful to see how quickly foreigners feel at home here. Within a year you see Chinese and Indian staff eating Dutch-style sandwiches for lunch. The labs are very friendly. And that benefits the quality of the work.'

**DE BRUIJN:** 'And there's also a practical reason why there are so many foreigners here. Good PhD students are very hard to find.'

**VAN BLITTERSWIJK:** 'There are 17 million people in the Netherlands, and seven billion in the rest of the world. So it's logical that there's more talent abroad than here. And all that debate in society about foreigners and integration... none of that comes into play in the lab.' ■

# WEARABLE KIDNEY

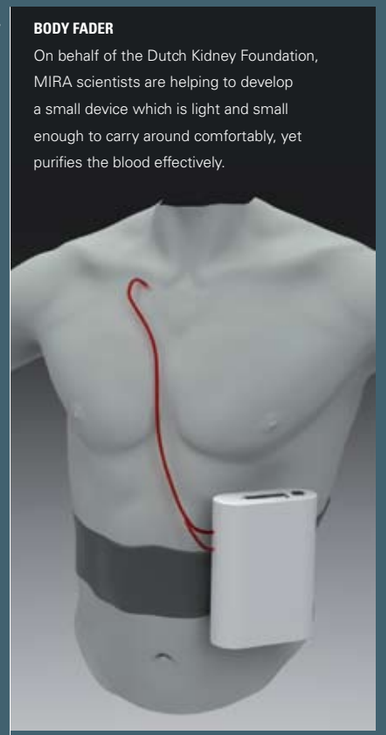
MEMBRANE SCIENTISTS AT MIRA ARE DESIGNING ARTIFICIAL KIDNEYS THAT WILL GREATLY IMPROVE THE LIVES OF KIDNEY PATIENTS. THESE ARTIFICIAL FILTERING UNITS ARE MORE EFFECTIVE IN CLEANSING BLOOD AND SMALLER AND EASIER TO USE THAN THE CURRENT TECHNOLOGY. MIRA'S GOAL IS TO USE THESE NOVEL ARTIFICIAL KIDNEYS IN PORTABLE AND/OR WEARABLE DEVICES.

We don't usually think about it, but our kidneys play a vital role in our bodies. They filter dangerous toxins from our blood and produce various important hormones. If your kidneys don't function properly, this has a major impact on your life. Once a kidney has deteriorated beyond a certain point then there are only two options: receive a donor kidney, or regularly have the blood cleaned outside the body in a treatment called dialysis. Dialysis patients have to visit a clinic or hospital three to four times a week and spend several hours hooked up to a large dialysis machine that cleans the blood.

**QUALITY OF LIFE** In the Netherlands, around 40,000 people suffer from kidney damage. Some 13,000 patients have end-stage kidney disease (kidney failure) 6,000 of those are on dialysis treatment and 7,000 have received a donor transplant. Despite the high costs of dialysis treatment, which amount to over 75,000 euro per patient per year, it only has limited success. The mortality of these patients remains excessively high, whereas their quality of life is generally low.

**AT HOME** Due to a shortage of donor organs, the waiting time for a donor kidney is currently about four years. Scientists are therefore exploring alternatives for improving patients' lives. One option is to improve the current dialysis treatment. Dialysis equipment is being made smaller, portable and more patient-friendly. This allows people to perform the treatment at home, for instance while they are sleeping.
Scientists at MIRA are participating in the consortium funded by the Dutch Kidney Foundation, which aims to develop a wearable kidney: a small dialysis device that can be easily carried by the patient. The challenge is to make this device small enough to be wearable, yet effective in cleansing the blood, safe, and easy to use.

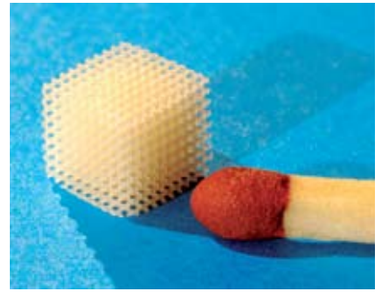
**MIXED MATRIX MEMBRANES**
Dimitris Stamatialis and his colleagues in the Membrane Technology group are working on a crucial element of the wearable kidney: the membrane, a so-called mixed matrix membrane (MMM). This is a filter that selectively removes toxins from blood. This novel filter is prepared by putting small porous particles into a polymer sponge. When this filter is placed in contact with blood, the blood cells cannot enter the sponge due to their size, whereas the smaller toxins pass through and are selectively captured by the porous particles. ■



**BODY FADER**
On behalf of the Dutch Kidney Foundation, MIRA scientists are helping to develop a small device which is light and small enough to carry around comfortably, yet purifies the blood effectively.







To engineer bone, a scaffold prepared from a rigid biodegradable polymer is used. The very small size and the exact features of the structure – prepared by stereolithography – are evident from the comparison with a match.

# Playing with molecules

[ *intro* ] REPAIRING A FRACTURE WITH A SCREW THAT LATER DISAPPEARS BY ITSELF. DELIVERING MEDICINES TO PRECISELY THE RIGHT PLACE IN THE BODY WITH THE AID OF TINY, BIODEGRADABLE CAPSULES. OR MAKING A BLOOD VESSEL FROM A MATERIAL WHICH IS REPLACED IN TIME BY THE BODY'S OWN CELLS. ALL OF THIS IS POSSIBLE WITH BIODEGRADABLE POLYMERS.

▶ CONTINUED ON NEXT PAGE

Polymer chemistry is like playing with Lego. You use molecules as building bricks and put them together to make long chains. By choosing the molecules carefully, you can give the polymeric material the exact properties you require. For example, you can vary its strength, its stiffness, the extent to which it attracts water, its biodegradability and the ease with which it can be moulded into the right shape.

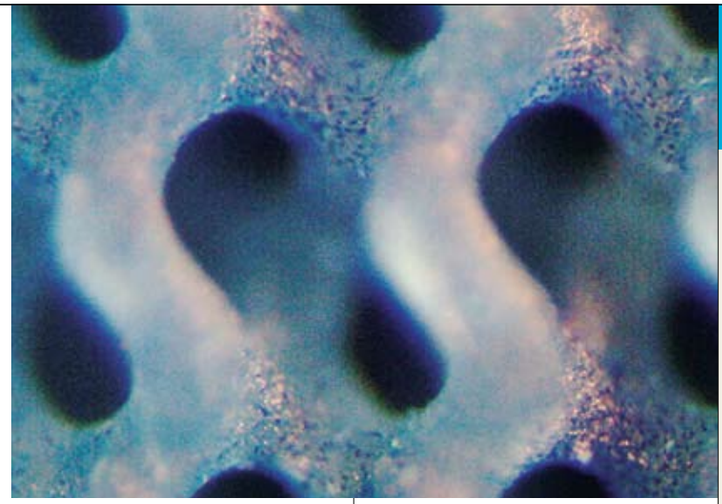
This is what Dirk Grijpma and his colleagues from the Biomaterials Science and Technology group are working on. 'We make a range of plastics which the body can break down itself in the long run', says Grijpma. 'Our materials are compatible with the body's own cells, and are designed in such a way that they get cells to do exactly what we want. For example, growing and forming tissue in a certain shape. For this process we need to design both the material and its shape.'

**IMPLANTS** Grijpma cites the example of implants that promote bone growth. These provide a solution when a bone is missing following a serious trauma or the removal of a tumour. Surgeons sometimes transplant a piece of the patient's own bone from a different part of the body, but this has various drawbacks. It creates a wound somewhere else, and the piece of bone is often not the right shape. And with a non-biodegradable material, such as metal, there's always a risk of infection. 'Those drawbacks don't apply to our alternative: a prosthesis made of a biodegradable polymer mixed with a material that promotes bone growth', says Grijpma. 'You make a scaffold on which autologous cells grow and form tissue. The scaffold is gradually resorbed by the body, ultimately leaving just the patient's own bone.'

**SEEDING CELLS** Bone tissue is not the only thing you can grow on a scaffold: blood vessels are another possibility. 'It would be great if after a heart attack, you could replace the blocked blood vessel with a vessel made from the body's own cells', says Grijpma. 'We're working hard on that at present. We make small porous tubes of a bio degradable polymer and "seed" it with cells. Under the right growth conditions in a bioreactor, these cells start to spread, proliferate and perform the desired function.' Application in humans is not on the immediate horizon, but trials in animals to date have proved very promising. The researchers have already managed to replace a section of the aorta in mice. According to Grijpma: 'The material appeared to be strong enough to be sutured, and there were no leaks. We're now working hard to make experiments on humans possible.'

**NEW RESIN TECHNIQUE** Another development that Grijpma is proud of is a new technique for building three-dimensional polymer structures with considerable accuracy: stereolithography. This technique uses a resin which hardens under the influence of light. In such a resin, a beam of light can build up – layer by layer – a solid structure that precisely matches the structure designed by the researchers on the computer. 'The technique has been around for a while', says Grijpma, 'but so far only using resins that are not biodegradable. Ours are. What's more, we can now build these structures in the presence of living cells using hydrogel materials.' These cells are mixed with the liquid resin. When this hardens, they end up in and on the three-dimensional structure, where they can still perform their function. The technique makes it possible to design an ideal structure for cells. For example, a porous structure which allows the efficient supply of nutrients and removal of waste substances. And you can make sure that a material has the best mechanical properties combined with high porosity.

A tubular scaffold prepared from a flexible polymer (left) next to a pig blood vessel (right). As the implanted scaffold grows its own cells, the polymer base dissolves.

Microscopic image shows how bone cells grow on the scaffold.

The group has now developed a whole series of biodegradable resins with a range of properties: from glassy and hard to rubbery and elastic, and from soft materials with hydrogel-like properties to ceramic-containing materials that promote bone growth. 'The possibilities are endless', says Grijpma, 'especially in combination with the computer-controlled structure design. For example, where a tumour has been removed from a jawbone, you can take a CT scan of the site and then design a prosthesis that fits exactly.'

**NEW CHALLENGES** The next challenge is to grow different types of cell together on a scaffold. This will ultimately make it possible to produce complicated tissues, such as liver tissue or bone containing blood vessels. And then there are also the systems for delivering substances, such as medicines, to exactly the right place in the body. This can be done, for example, by packaging the medicine in tiny capsules made of a biodegradable polymer. Such particles are small enough to be injected into the bloodstream. 'Antibiotics can also be packaged in this way', says Grijpma, 'as equally growth factors which ensure that cells develop into a specific cell type. The latter is useful if you want to culture a certain tissue from stem cells.'
Antibiotics and growth factors can also be incorporated in a biodegradable bone screw. 'You can kill two birds with one stone', says Grijpma. 'You can fix a fracture with a strong material that in time disappears, while at the same time you release antibiotics and growth factors aimed at specific targets.'
Does the group have any other plans? 'Yes of course, there are many more possibilities', says the researcher. 'There's an enormous demand in the medical world for new materials: better, stronger, more flexible, better geared to the function. The challenge is to devise materials that are demonstrably better. And then to convince the regulatory authorities and doctors of that.' ■

## Bringing an anti-adhesion agent on to the market

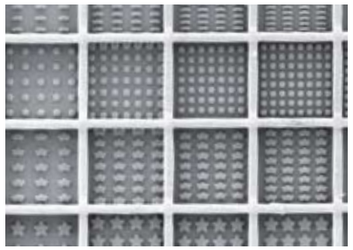
'By chance, we made an interesting discovery', says Dirk Grijpma. 'When sterilising a certain polymer with gamma radiation we found that the radiation makes the material not only more flexible but also elastic. It becomes a sort of biodegradable rubber. This appealed to us immediately: nothing like it existed as yet.' The department applied for a patent and sought funding to do something with the idea.

'But bringing a product onto the market ourselves is not our priority of course', says Grijpma. 'So we set up a company called Medisse, which makes materials that prevent adhesions after surgery.' Almost all operations, around 80 to 90%, result in an adhesion somewhere in the area affected: scar formation binds together tissues that should remain separate. This sometimes necessitates further surgery. 'So there is an enormous market for a product that prevents adhesions', says Grijpma. 'Medisse makes a thin film of biodegradable material that is placed between the organs during surgery. After two weeks the risk of adhesions has passed and the material is reabsorbed.'

The first investors have now come forward and the product is currently being tested by an external party. Once it has been approved as 'safe', Grijpma believes that clinical experiments will soon follow. 'I have every confidence in it.'

# BERNKE PAPENBURG AND MATERIOMICS

BERNKE PAPENBURG IS THE PROJECT LEADER OF THE MATERIOMICS START-UP. MATERIOMICS RESEARCHERS WORK ON HOW THE PROPERTIES OF MATERIALS – SUCH AS STRUCTURE AND SURFACE – INFLUENCE BIOLOGICAL PROCESSES. FOR EXAMPLE, THEY SCREEN MATERIALS FOR USE AS SUPPORTS FOR CELL GROWTH. OR THEY WORK ON SURFACES WHICH CAN REDUCE THE VULNERABILITY OF MEDICAL IMPLANTS TO INFECTION. MATERIOMICS IS CURRENTLY STILL PART OF THE UNIVERSITY, BUT DURING 2011 IT WILL BECOME AN INDEPENDENT PRIVATE COMPANY.



A high-magnification picture of a chip where each of the nearly 4,400 small compartments contains structures with different shapes, dimensions and/or spacing.

1999

## 1999-2004:

### Degree in chemical technology at the University of Twente

What do you do if medicine is too ‘medical’ for you, but physics and chemistry by themselves are too technical? Then you go for a combination. In any case, that was the strategy adopted by Bernke Papenburg. Courses in biomedical technology or technical medicine didn’t exist at the time, so she went for chemical technology.

*‘Above all, I didn’t want to go into research. I was afraid that it would be too theoretical. It was only when I was about to graduate that I became fascinated by research. You devise a specific theory, think about how you can test it, and then go and do it. It’s much more applied than I thought.’*

## 2004-2009:

### Graduation research project and then PhD research at the Membrane Technology Group, in collaboration with the Tissue Regeneration Department

Papenburg studied scaffolds as supports on which cells can be grown. The whole scaffold can subsequently be introduced into the body, where the cells then start to perform their natural function. To replace a vein, for example. She developed this principle further during her own PhD research.

*‘It was tremendously exciting research. We had found a broadly applicable method that can change the surface of a scaffold, exerting a strong influence on the cells growing on it. I was keen to develop it further as a PhD student. And fortunately, I could. This was a fascinating time as well. Especially thanks to the collaboration with other disciplines and the freedom I had to fill in the details of my own research.’*

2005

## 2009-2010:

### Postdoc position at Tufts University in Medford, greater Boston area, MA, US

Papenburg had the opportunity to do postdoctoral research in Boston, where she worked on biomedical implants made of natural silk. But after a year she returned to The Netherlands, mainly because her boyfriend lives here.

*‘The University of Twente had contacted me. Did I want to help set up the Materiomics start-up? It was a unique opportunity for me. But I’m glad I had that year in Boston first. It was very inspiring to do research outside Europe for a change. You see how people from other cultures tackle things. For example, Americans work far more on short-term goals. They just go for it, with no ifs and buts.’*

2009

2010

## 2010-present:

### Project leader Materiomics, MIRA

Together with her colleagues, Papenburg designs chips with nearly 4,400 compartments, each of which is just a few hundred microns wide. The compartments vary in shape and structure. Stem cells are seeded into them. Using the chip, the researchers can investigate how the nature of each compartment influences the growth of the stem cells and their development into specialised cells, such as fat cells or bone cells.

*‘Using our chips you can study a huge number of different variables quickly and efficiently. With that information, our ultimate goal is not just to control cell growth but also, for example, to reduce the risk of clotting and infection with various medical implants.’* ■

[ chapter 03 ]

# IMAGING & DIAGNOSTICS

# richer images for better treatment

03

[ intro ] THE IMAGING AND DIAGNOSTICS PROGRAMME TRIES TO PICTURE AND UNDERSTAND THE PROCESSES IN CELLS AND ORGANISMS. ITS NEW METHODS FOR ULTRASENSITIVE DIAGNOSTICS ARE EXTREMELY CLEAR AND PRECISE. ALSO, IMAGING THE BODY WITHOUT OPERATING OR INJECTING A CONTRAST FLUID SIGNIFICANTLY REDUCES THE BURDEN FOR THE PATIENT. OUR ULTIMATE AIM IS TO CREATE TECHNIQUES THAT ENABLE PHYSICIANS TO OFFER THEIR PATIENTS A TREATMENT THAT IS MORE FOCUSED, CAUSES LESS DISCOMFORT AND PROVIDES A FASTER CURE.

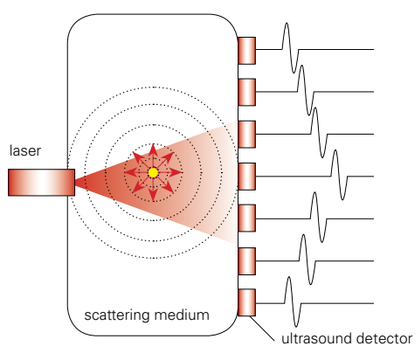
# DIAGNOSIS OF BREAST CANCER WITH SOUND AND LIGHT RESEARCH

[ *intro* ] BREAST CANCER SCREENING NEEDS TO BE IMPROVED. SO SAY MIRA RESEARCHERS WHO ARE WORKING HARD TO DEVELOP AN ENTIRELY NEW METHOD OF SCREENING. NOT BASED ON X-RAYS, BUT USING A COMBINATION OF LIGHT AND SOUND. THIS METHOD IS MORE ACCURATE AND ALSO MORE PLEASANT AND SAFER FOR THE PATIENT.

Breast cancer is the most common form of cancer in women; one in nine women develops it at some time in her life. Every year some 13,000 women in The Netherlands are diagnosed with the disease and around 3,000 die from it. To detect breast cancer at an early stage, women between the ages of 50 and 75 are invited to attend breast screening every two years. This is traditionally done using X-rays. The breast is clamped firmly between two plates: an unpleasant and even painful experience. The method is far from foolproof: doctors sometimes fail to spot tumours and sometimes they refer women who don't have cancer, causing them needless worry. And X-rays aren't without risk. Some groups of women, for example women who have already had breast cancer or have a hereditary variant in the family, are screened every year, sometimes from as early an age 30. In such cases, total lifetime radiation exposure can really mount up.

**LIGHT AND SOUND** MIRA researchers are working on an alternative method of breast cancer screening: a brand-new technology. It uses not X-rays but laser light. Laser light is absorbed well by haemoglobin, the protein in the blood that transports oxygen. Where the blood flow is greater, more light is absorbed. And it just so happens that a characteristic of malignant tissue is an increased blood supply. Indeed, various new blood vessels grow in and around the tumour to supply the fast-growing tissue with oxygen and nutrients. This increased vascular growth can be detected using laser light. When the blood absorbs the light, it becomes a tiny bit warmer. As a result, it expands a little locally. This causes a miniscule pressure wave in the tissue: like a sound wave. It can be measured using special equipment, giving you a three-dimensional image of the tumour.

[ fig. a ]




**COLLABORATION** The MIRA researchers are currently working on a second, improved version of their invention. The technology is not yet on the market; experts believe that will take a few more years.

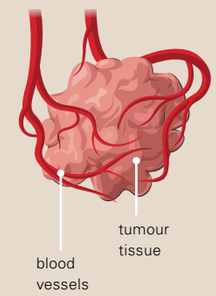
**EXTREME PRECISION** In theory, this method can be used to detect tumours only a few millimetres in size. This makes it considerably more accurate than traditional X-ray screening, in which small tumours are often overshadowed by other tissue. And the smaller the tumour when it is detected, the better. In future, the light and sound method may also be suitable for detecting other forms of cancer. ■

▶ NEXT PAGE: FIVE QUESTIONS FOR MICHELLE HEIJBLOM

## [ fig. b ] USING LIGHT AND SOUND TO DETECT BREAST CANCER

Laser light can be used for the detection of cancer tissue as an alternative to painful mammography.

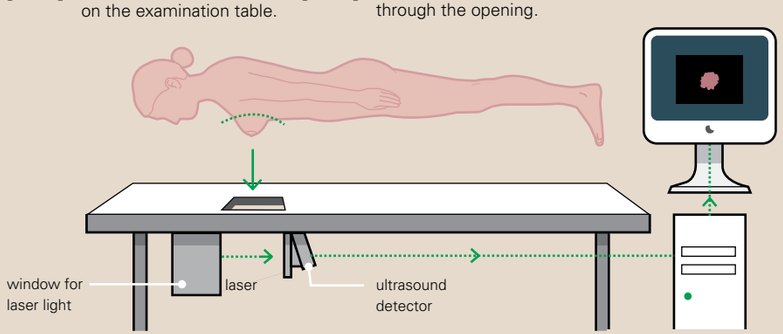
Blood vessels grow around malignant tissue to provide it with oxygen and nutrients. The new technique makes use of these blood vessels to detect cancer tissue.




**THE SCAN**

[ 01 ] Patient lies on stomach on the examination table.

[ 02 ] Breast protrudes through the opening.



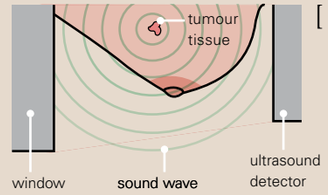

[ 03 ] Laser sends light through the breast.

[ 04 ] The detector is connected to a computer.

[ 05 ] The computer converts the information into a 3D image.

**HOW DOES IT WORK?**

[ 01 ] Haemoglobin in the blood absorbs laser light, which causes the tissue to heat up and expand slightly.




[ 02 ] The expansion produces a miniscule sound wave that is picked up by the ultrasound detector.

MICHELLE HEIJBLOM

# *'Our lab is the world leader'*

MICHELLE HEIJBLOM WAS AN OUTSTANDING STUDENT AND COULD TAKE HER PICK OF CAREER OPTIONS. SHE OPTED FOR PHD RESEARCH IN TWENTE.

**1** *How did you end up in technical medicine?* 'I've always found medicine interesting, but I also had a passion for maths and physics as well. Technical medicine seemed an ideal combination to me. I never really saw myself as a doctor in a hospital, but would rather be involved in the development of new equipment. So I came to do the technical medicine course here in Twente. Due to a combination of luck and specific interest, I was then able to start a PhD project in the department.'

**2** *So it wasn't because you don't like dealing with patients?* 'Of course not!' (laughs) 'In this research we also work a lot with patients. It's that variety that I enjoy so much. You're dealing with people, but also with the technology.'

**3** *Has this decision brought you what you wanted?* 'I found it hard to picture in advance exactly what the discipline entails. I was part of the first batch of students on the technical medical course, and didn't really have a career profile in mind. But if you just do what you're interested in, it'll always turn out right in the end. And yes, if given the chance I would make the same decision again.'

**4** *Are there also some things you dread when you come to work in the morning?* 'Just the general things that every PhD student faces: Will I get my project done in time? What if my results are disappointing? When will we finally get such and such a piece of equipment going again?'

**5** *You were one of the very best students in your year; why didn't you go to work at a top foreign university, such as Harvard or MIT?* 'I'd come from the other side of the country, and it had taken me long enough to get used to living in Twente.' (laughs) 'What's still most important to me is to do what I enjoy. This job is just what I was looking for, and I feel at home here. Our lab is the world leader. Why would I go anywhere else? Perhaps it's better for your career to have foreign experience as well, but I'm not really concerned about that.' ■





# Measuring the success of technology

DEVELOPING A SMART TECHNOLOGY IS ONE THING. BUT GETTING IT ONTO THE MARKET IS A COMPLETELY DIFFERENT BALL GAME. MANY INVENTIONS, HOWEVER BRILLIANT, NEVER GET FURTHER THAN THE TEST PHASE. MIRA'S HEALTH TECHNOLOGY AND SERVICES RESEARCH DEPARTMENT LED BY PROFESSOR MAARTEN IJZERMAN, IS TRYING TO DO SOMETHING ABOUT THIS. IT WAS FOR INSTANCE CONSULTED BY PHILIPS CONCERNING ITS TECHNOLOGY FOR MALARIA DIAGNOSIS.

▶ CONTINUED ON NEXT PAGE


Philips' invention of a new technology for the diagnosis of malaria made the Dutch national news. Philips asked MIRA to evaluate the technology and its usability.

▶ CONTINUED FROM PAGE 045

Take a newly developed technique for breast cancer examination: photoacoustics. A sort of echo based on light; the technique dispenses with the need for harmful X-rays. The Health Technology and Services Research (HTSR) department is attempting to answer two questions regarding this new technique. First, is it really as good as the current technique? Is it more expensive and, if so, is it so much better that we're prepared to pay extra for it? And second, how do you make sure that it can be used in practice?

Getting a new technique used in practice is far from simple. It's not just a matter of replacing the existing apparatus; the doctors and analysts also need to be trained in using the new equipment. And who's going to pay for this transition? So besides the technical aspects this research also has medical and socio-scientific elements. What are the consequences of introducing a new technology? Does it improve healthcare? Or just make it more expensive? And is that worth paying for?

**CONSULTANCY** The HTSR group certainly doesn't work on the basis of scientific curiosity alone. 'It's important that our work is useful to society', says IJzerman. 'We use our knowledge to give advice, for example advising the government on whether a population study into intestinal cancer is a good idea. And we advise businesses on the right way to introduce a technology. Sometimes we do that as a department, but we've also set up a separate consultancy business especially for this purpose.'

IJzerman cites another example. Malaria is a huge problem in many developing countries. People often live far away from a hospital. So when they fall ill it's not easy for them to find out if they have malaria. Therefore they often fail to get the right medicines, or they don't get them on time. Philips is currently developing technology which allows malaria diagnoses to be made without complicated hospital apparatus. People can do it themselves, or have it done in a local health centre. An invention like this makes healthcare more accessible. If people no longer need to go to hospital for a diagnosis, they can obtain medicines sooner. This could prevent many deaths. Philips has approached HTSR for advice. According to IJzerman, 'We're currently trying to answer a number of questions. Which of the various possible technologies is the most promising? How big is the risk of people making mistakes when using it? What are the costs? What are the consequences of earlier diagnosis: how many deaths can you prevent? How much does it save you in costs? And of course: is it a smart approach to the problem, or would you do better to invest in more health centres?'

**SUPPORT IN THE DESIGN PHASE** This type of research isn't new. It's also being done in other places in The Netherlands and elsewhere in the world. 'What is new', says IJzerman, 'is that at HTSR, we're also looking at techniques that are not yet fully developed. We can support businesses in making decisions as early as in the design phase.'

**AND ARE BUSINESSES INTERESTED?** 'Of course. It's becoming ever clearer that success is not just about scientific excellence. The real challenges are often in an entirely different area. You can't let every technology loose on society just like that.' ■





# IN PURSUIT OF CIRCULATING TUMOUR CELLS

[ *intro* ] LEON TERSTAPPEN HAS DEVELOPED A TECHNOLOGY FOR DETECTING TUMOUR CELLS IN THE BLOODSTREAM. THIS SURPRISINGLY SIMPLE INVENTION IDENTIFIES THE TYPE OF TUMOUR CELLS INVOLVED AND REVEALS IF A TREATMENT IS WORKING. AN AID LIKE THIS IS MUCH NEEDED IN THE MEDICAL WORLD.

Doctors today can detect and treat cancer much more effectively than they could, say, ten years ago. But it's still hard to check if a given treatment is working. Wait-and-see is the motto. It takes months, and many sessions of chemotherapy, before doctors dare to conclude that the treatment isn't working. Such a conclusion is drawn when scans show that tumours are still present. But then it's sometimes too late to change strategy. In any case, much unnecessary suffering has already taken place. Sometimes it's just easier on the patient to discontinue the chemotherapy if it isn't helping.

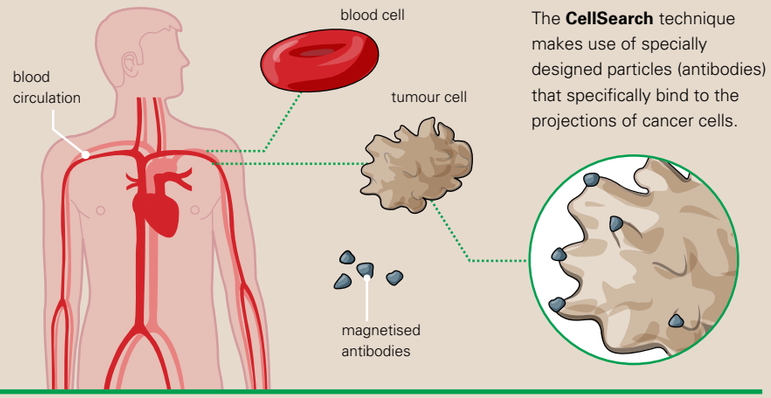
**CIRCULATING CELLS** Leon Terstappen, a medical biophysicist at the University of Twente, and his colleagues have found a way to establish far earlier if a treatment is working. He has developed a technology that doctors can use to detect individual tumour cells in the blood. These 'circulating' tumour cells are a sign that the cancer is spreading or 'metastasising'. If cells are still found after one round of chemotherapy, that's not a good sign. Then you may as well discontinue the treatment.

**LOCK AND KEY** The technology, named CellSearch, uses the fact that tumour cells are an entirely different cell type than blood cells. Every cell type has specific projections on the

▶ CONTINUED ON NEXT PAGE

## [ fig. a ] TRACKING DOWN MIGRATING TUMOUR CELLS

Migrating tumour cells in the blood are a sign that cancer is spreading. The number of such cells indicates the aggressiveness and type of cancer. Doctors can use this information to select a treatment.




The **CellSearch** technique makes use of specially designed particles (antibodies) that specifically bind to the projections of cancer cells.

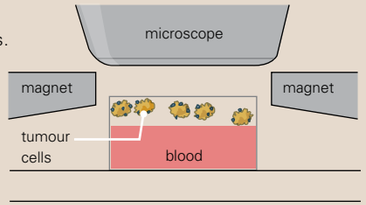
Tumour cells are entirely different from blood cells. They have characteristic projections on the cell wall.

**HOW DOES IT WORK?**

[ 01 ] Antibodies are fitted in conjugated magnetic particles.

[ 02 ] They are then added to a blood sample.

[ 03 ] Tumour cells present in the blood will adhere to the antibodies.




[ 04 ] The particles can be removed from the blood with a magnet.

[ 05 ] Once special stains have been added, the tumour cells can be detected and counted under the microscope. This information is used to select a treatment.

▶ CONTINUED FROM PAGE 047

outside of the cell which are typical of that cell type. CellSearch uses specially developed particles that specifically adhere to the projections of tumour cells. These particles are antibodies: proteins which adhere only to certain other particles via the lock-and-key principle. The CellSearch antibodies are fitted with small magnetic particles so they can be 'fished out' from the blood again using a magnet. If tumour cells were present in the blood, some of them will have stuck to the antibodies. After a special staining, they can then be detected and counted under the microscope.

The number of tumour cells in the blood is a measure of the cancer's aggressiveness. The tumour cells also reveal what type of cancer it is. Based on this information, doctors can infer which treatment has the best chance of success.

**RETICENT** CellSearch is already on the market but, especially in Europe, is used mainly in a research context. The medical world is still hesitant: first, it wants to see more research results showing how the technology can best be applied, and that it is indeed worthwhile. In addition, doctors are very reticent when it comes to discontinuing treatment. They don't want to run the risk of missing a chance of a cure, even a very small one.

### AVOIDING SUFFERING AND COSTS

For the time being, the American Food and Drug Administration has only approved CellSearch for the monitoring of patients with metastasised breast, prostate and colorectal cancer. But in the near future other forms of cancer will also be added, and the technology will probably find its way into European practice as well. The health insurers will probably be the ones to tip the balance: CellSearch can avoid not only a lot of suffering, but also a lot of costs. ■



LEON TERSTAPPEN

# *Converting clever ideas into clinical applications*

CELLSEARCH, A TECHNOLOGY THAT DOCTORS CAN USE TO DETECT TUMOUR CELLS IN THE BLOOD, WON AN AMERICAN PRIZE LAST YEAR: THE PRIX GALLIEN, A PRESTIGIOUS PRIZE FOR THE BEST SCIENTIFIC INVENTION TO HAVE MADE IT AS A SUCCESSFUL TECHNOLOGY. CELLSEARCH WAS DEVELOPED UNDER THE DIRECTION OF LEON TERSTAPPEN.

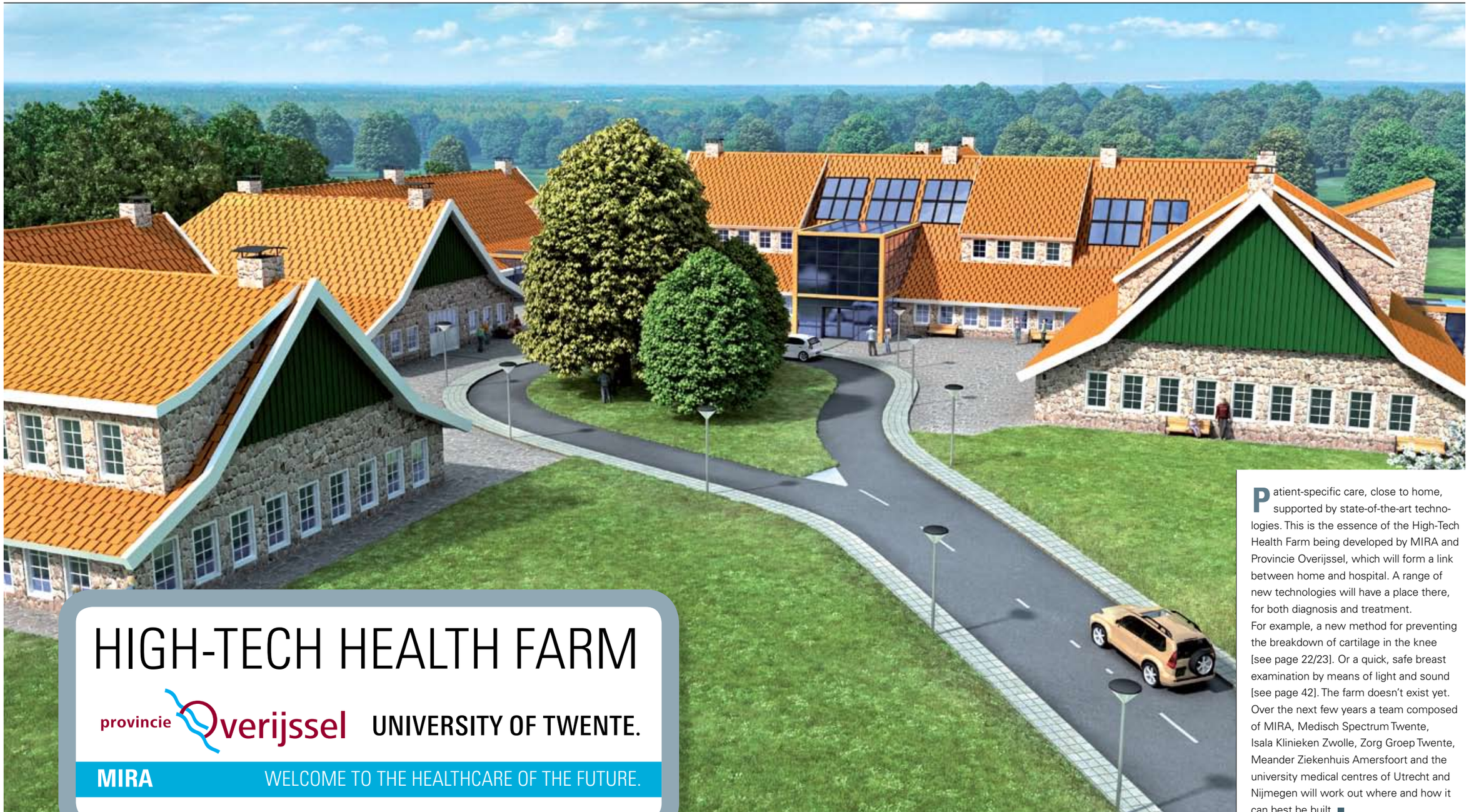
**1** *Are you pleased with the prize?* 'Outside applied medicine, few people will have heard of it.' (laughs) 'But within our discipline it's a very valuable award. So yes, I'm very pleased with it. No, there's no financial reward attached. It's purely the honour. Perhaps I should mention it on my CV.'

**2** *Does this prize open new doors for you, and for CellSearch?* 'I think so. This is something very specific that I can show to investors. In 2008, Johnson&Johnson took over the company that I'd set up to launch CellSearch. But I'm still involved as a consultant. And until the technology is fully developed, new investment will be needed.'

**3** *But why did you go back to academia after setting up your own company?* 'Science is important, and I'm passionate about it. And where can you do science better than at a university? Moreover, I've now gone through the whole journey from idea to execution once. So I've been there, done that. Now I'm much more interested in tackling new projects and guiding young people.'

**4** *As a professor, do you still draw on your experience in industry?* 'I try to teach my students about everything that's involved in bringing a new technology onto the market. What challenges do you meet? How do you apply for a patent? How much money do you need? Many students haven't the faintest idea that it can easily take hundreds of millions of euro, especially in the clinical test phase.'

**5** *So purely fundamental research is not for you?* 'No, or I wouldn't be here. At MIRA we convert smart ideas into clinical applications. In that respect, I've found my niche.' ■




Patient-specific care, close to home, supported by state-of-the-art technologies. This is the essence of the High-Tech Health Farm being developed by MIRA and Provincie Overijssel, which will form a link between home and hospital. A range of new technologies will have a place there, for both diagnosis and treatment.
For example, a new method for preventing the breakdown of cartilage in the knee [see page 22/23]. Or a quick, safe breast examination by means of light and sound [see page 42]. The farm doesn't exist yet. Over the next few years a team composed of MIRA, Medisch Spectrum Twente, Isala Klinieken Zwolle, Zorg Groep Twente, Meander Ziekenhuis Amersfoort and the university medical centres of Utrecht and Nijmegen will work out where and how it can best be built. ■

# THE IMPORTANCE OF TINY BUBBLES

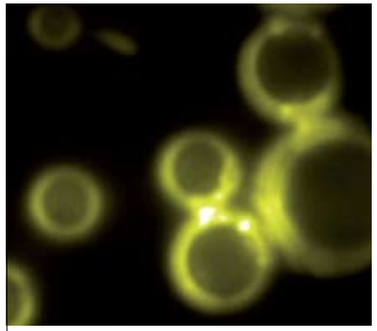
BUBBLES ARE MORE USEFUL THAN YOU THINK. THEY HAVE NUMEROUS APPLICATIONS IN THE MEDICAL WORLD. FOR EXAMPLE, YOU CAN USE THEM TO CLEAN ROOT CANALS IN DENTISTRY OR TO INCREASE THE CONTRAST OF IMAGING TECHNOLOGIES. YOU CAN ALSO USE THEM TO DELIVER DRUGS TO EXACTLY THE RIGHT PLACE IN THE BODY. THIS IS WHAT RESEARCHERS IN MIRA'S PHYSICS OF FLUIDS DEPARTMENT ARE WORKING ON.

Imagine a typical foetal ultrasound scan in the hospital. You can see all sorts of tissue, bone and cartilage, but it's hard to see the blood flowing in the organs. This is because blood doesn't reflect ultrasound that well. In medical diagnosis, however, the blood flow is often the subject of interest. In the case of a heart attack, for example, you want to know where the blood flow is disrupted. And when looking for a tumour, you want to know where there's increased blood supply, as that is a sign of malignancy.

Tiny bubbles can help to make that blood flow visible. That's because the ultrasound waves cause the bubbles to vibrate. The bubble vibrations produce a characteristic echo which can be measured with the handheld probe. A single microbubble reflects ultrasound a billion times better than a red blood cell. But if you simply inject these bubbles into the bloodstream, they'd dissolve immediately because they're so small. So researchers coat the microbubbles with a monolayer of phospholipids. That's the same substance as our cell membranes are made of. The precise application determines the choice of material for the coating. For imaging applications you want a thin and flexible skin; for drug delivery applications it needs to be thick and firm.

**DELIVERING MEDICINES** Yes, another application for tiny bubbles is as carriers for drugs. Using ultrasound at the right frequency, you can burst them open at precisely the right location, near a tumour site where you want to deliver the drug. Or you can design them to adhere specifically to cancer cells. The bubbles have a receptor on their coating that precisely matches an abnormal protein molecule on the outside of a cancer cell. They can then deliver their cargo with utmost precision. That's far more beneficial than the typical chemotherapy administered today, which works throughout the whole body, killing both tumour and healthy cells alike.

**SUPERCAMERA** MIRA's Physics of Fluids team has one of the most advanced pieces of research apparatus ever built: a camera which can take 25 million images per second to closely examine how tiny bubbles vibrate or burst. This camera was developed at the University of Twente and is the only one of its kind. Everything that researchers see with the camera is new to science. Many of these tiny bubble technologies are already applied in clinical practice. New technologies are tested extensively to investigate whether the principle works and if it is safe. However, clinical tests are not the prime focus of the Physics of Fluids researchers. Their main aim is to understand the underlying physical mechanisms. What exactly happens to these tiny bubbles? How do they behave under different conditions? How can you boost the contrast, or direct the local injection of drugs? Only when more is known about these physical processes will researchers be able to refine even more of these exciting new medical applications. ■



Tiny bubbles sent into the blood stream can help to make blood flow visible because of their ability to reflect ultrasound much better than blood itself.

[ extract from the schedule of... ]

VINOD SUBRAMANIAM

# ‘I love it when I see a spark in their eyes’

[ *intro* ] VINOD SUBRAMANIAM IS FASCINATED BY THE ‘PUZZLING PARKINSON PROTEIN’ (*ALPHA-SYNUCLEIN*) AND ENJOYS WORKING WITH YOUNG PEOPLE.

## 08:00 *Dropping off my daughter at daycare*

'I have a two-and-a-half year-old daughter called Mira. In fact, our MIRA institute was named after her – although I had little or nothing to do with that. The anecdote is that at the time, Clemens van Blitterswijk, the scientific director, was mulling over the name of the institute. He saw a picture of my newly born daughter, and liked the look of wonder in her eyes. Mira is short for "*mirabilis*", which means "wonderful" in Latin.' He felt that described the spirit of the institute. As they say, the rest is history.'

## 9:00 *Meeting with the research group*

'On Monday mornings, we usually get together with the entire research group to discuss science and listen to informal presentations. When people explain their line of reasoning to their colleagues, they're challenged to think about why they do certain things in a certain way. That's really enriching. You become far more critical towards your own approach. And others may come up with solutions to your problems from unexpected angles.'

## 11:00 *Walking around and drinking coffee with colleagues*

'What happens in the corridors is incredibly important. This is a small university where you always meet people who are working on interesting projects. There's a highly collaborative atmosphere. You start talking about your research and the other person says: "Hey, perhaps you want to try this or that experiment." You start out with a particular idea and end up with something completely different. That's how the best scientific ideas are born.'

*'Mira is short for "mirabilis", which means "wonderful" in Latin.'*

## 11:30 *Brief meeting with our new communications officer*

'I spend a lot of time meeting with people, and these meetings are not always about science. I find it rewarding to contribute my knowledge and expertise to the university. But I have to keep the balance in mind. Sometimes I need to step back and return to the core business of doing actual science.'

## 13:00 *Meeting with a PhD student*

'I like teaching. I'm a professor, and teaching is what I do a lot of the time. I'm in this business because I like working with young people. I love it when I see a spark in their eyes: "Hey, I've got it now!" Unfortunately I barely have any time now to do experiments myself, but I often visit my students in the lab. When I see what they are doing, I say: "Wow, can you really do that? Try doing this or that for a change. Or perhaps run this experiment, or turn that knob." It is fantastic to see that they can use your advice to improve their research.'

## 14:00 *Attending an undergraduate diploma ceremony*

'In itself these ceremonies are perhaps not the most exciting events. However, I find it important to show up in my penguin suit together with my fellow professors and make a true show out of it. You want to contribute to these kids' memories of the experience. It's such a dramatic event, also for their parents. The toga is not the handiest garment, but I quite like it, because it lends a sort of formality and style to the academic world. I can see the value of it.'

## 16:00 *Meeting with a Masters student*

'These meetings are much more basic than meetings with PhD students. In this meeting we discuss, for instance, how to formulate a decent hypothesis, how to set up

▶ CONTINUED ON NEXT PAGE

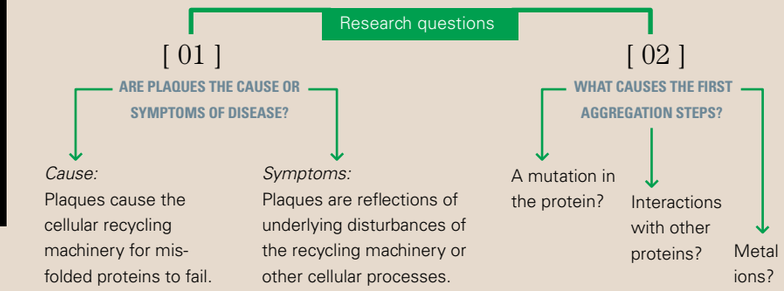
### [ *who is...* ]

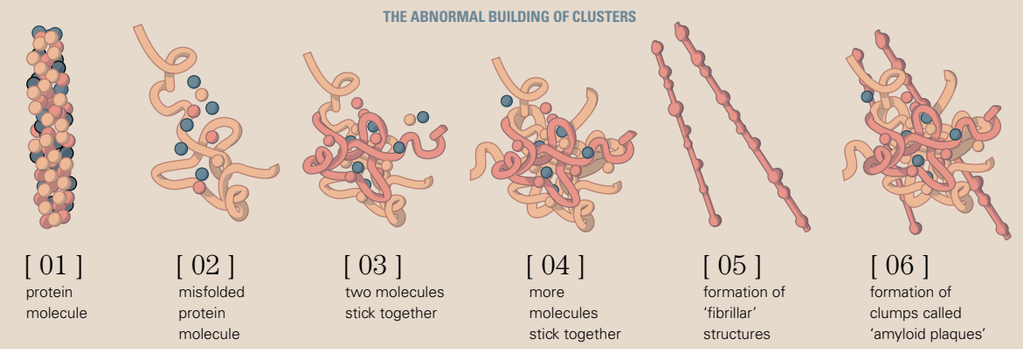
WHO IS VINOD SUBRAMANIAM?

Vinod Subramaniam (1967) is a biophysicist who was born in India, but who has spent his entire adult life in other parts of the world. After obtaining a Masters and PhD degree in the US, he worked in Germany and England for some time before coming to Twente in 2004. At MIRA, he leads the Imaging & Diagnostics group. His own research focuses on the biophysics of protein aggregation in Parkinson's disease. Subramaniam lives in Enschede together with his wife Sowmya and their daughter Mira.

## [ fig. a ] ABNORMAL CLUSTERS OF PROTEIN IN THE BRAIN

Neurological diseases like Parkinson's and Alzheimer's are characterised by 'abnormal' protein clusters in the brain. The main question in this research project is: "What causes these clusters?"




▶ CONTINUED FROM PAGE 057

a smart experiment, and how to present the results.'

### 17:00 *Meeting with a postdoc who is working on a grant proposal*

'This meeting is again entirely different. The postdoc and I communicate on a much more equal level. I try helping him with the experience that I have when it comes to applying for funding. We discuss different ways of formulating the proposal, and weigh the various options.'

### 18:00 *Telephone conference with a colleague in the US*

'Sometimes I get a call from colleagues who are working on a certain research question, and who are interested in experiments

*I have a Twents dictionary on my night table*

that we do. They wonder if they can apply our experiments to their work. I always try to help them as much as I can. We're all working on the same fundamental problems. We all just want to find out what is really going on with these proteins.'

### 18:30 *Cooking dinner*

'I love cooking. Dutch, Indian, Chinese, anything. My wife and I like to invite people over for dinner parties. Nowadays we don't do that as much as we used to, unfortunately. But I still enjoy making our daily dinners.'

### 20:00 *Tying up some loose ends*

'In the evenings I usually have a couple of hours of work left to do. Different things: answering emails, grading papers, reviewing articles. I work 50 or 60 hours a week, if not more. Is that absolutely necessary? No, perhaps not. But I like it.'



### 22:30 *Reading a book*

'I read voraciously. All kinds of things: novels, autobiographies, other non-fiction like Freefall by Joseph Stiglitz, about the collapse of the financial markets. But I also like Harry Potter. And I have a Twents dictionary on my night table. This whole notion of dialects is fascinating.' ■

## Clusters of proteins in the brain

Neurological diseases like Parkinson's and Alzheimer's result from 'abnormal' proteins that build up in the brain. 'Abnormal', in this case means that the proteins are folded incorrectly. And since their function is intimately connected with their structure, this misfolding can have major consequences.

**AGGREGATING PROTEINS** 'Normally, the body has a mechanism at its disposal that recognises such misfolded proteins, and then gets rid of them', says Vinod Subramaniam. 'In Parkinson and Alzheimer patients, however, this mechanism does not work properly. We still don't quite know why that is.'
In patients with neurological diseases, these misfolded proteins start to aggregate. They form stiff, thread-like structures of about ten nanometres in diameter. These will then further clump together to form larger structures called plaques. 'The fundamental question that puzzles me as a biophysicist', says Subramaniam, 'is: what are the forces that cause these proteins to aggregate? Is it happening because this correcting mechanism is failing? Or is it the other way around: is the mechanism failing because these proteins aggregate? Are these aggregates a symptom or a cause of the disease? In fact we still don't know.'

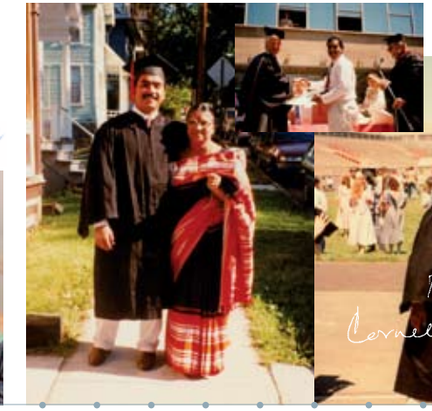
**FIRST STEPS** Another question that Subramaniam is trying to answer is what triggers the very first aggregation steps: two protein molecules that stick together, and then stick to other molecules. 'The focus in this kind of research has always been on the end stage', explains Subramaniam, 'in other words, on the large protein aggregates. But what if the real toxicity lies in the initial stages? What if the molecule pairs or small aggregates are toxic, and the formation of larger aggregates is actually a defence mechanism, pushing the proteins towards the more harmless stages? If that is true, all efforts to break down the larger aggregates through medication are counterproductive. This kind of basic information is therefore absolutely vital.'

**CHAMELEON** 'More than 4,000 papers have been written about apha-synuclein', Subramaniam concludes, 'but nobody actually knows what it does. We all have it in our brains in the "normal" form, but we don't know its function. Yet it must have evolved for a reason. The Parkinson research is pretty fascinating. And great fun. Although I am under no illusion that we will solve the problem any time soon. The thing is that there's still a vast amount of information to be gathered and knowledge to be learned for the next 20 years. Yes, of course that's frustrating. We still have no idea about this protein. It's like a chameleon: it constantly changes shape and structure. But that's what makes it so fascinating. Every day I wake up and I say: "ha, that's a puzzle that I still need to solve".'

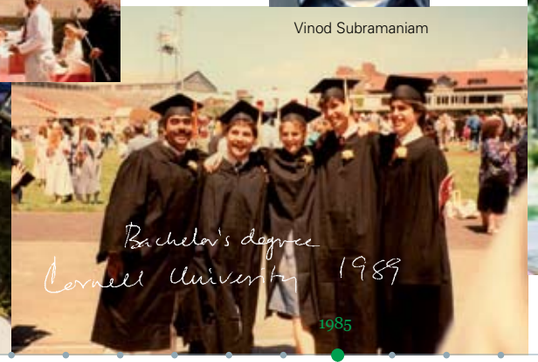
# THE COSMOPOLITAN CAREER OF VINOD SUBRAMANIAM

Vinod Subramaniam

high school mates
VS on left 1984







Bachelor's degree
Cornell University 1989

Grad school
ca 1994/95

Max Planck Institute 1999

1967 1985 1989 1996 2002 2004

## 1967-1985:

### Childhood in India

Vinod Subramaniam was born in Madras. He grew up and went to school in New Delhi.

*'My childhood was happy, absolutely. New Delhi is a huge city, teeming with life and humanity. Chaotic at times, but the sights, sounds, and smells are like nothing else I've ever experienced.'*

## 1985-1989:

### Cornell University, Ithaca, New York, US: College of Engineering

Subramaniam obtained a scholarship to go to Cornell University.

*'I went there to study computer science. It was the eighties, and everybody wanted to be a computer scientist. But as soon as I did my first programming class, I said: "No way! This ain't for me." Instead I studied electrical engineering with a focus on lasers and optics. I was fascinated by all those upcoming laser technologies.'*

Summer 1986
Archaeology

## 1989-1996:

### University of Michigan, Ann Arbor: PhD research

Yet the more he submerged himself in the advanced spectroscopy of semiconductors, the less Subramaniam seemed to like it.

*'I soon realised that semiconductor physics didn't really interest me. But my supervisor was a really great guy: a fantastic physicist and a remarkable human being. I wanted to keep working for him. Luckily, he also had another lab, where he used laser technology to study protein folding. So I asked him if I could work there, and he said yes. I loved the stuff.'*

## 1996-2002:

### Max Planck Institute for Biophysical Chemistry, Göttingen, Germany

After gaining his PhD, Subramaniam had plenty of options in the US. However, he chose to move to Germany instead.

*'They do top-level research over there, fantastic. I thought I'd stay there for a year or two and then return to the US. But I stayed for six years. It was one of the best periods of my life.'*

## 2002-2004:

### Pharmaceutical company Astra-Zeneca, Loughborough, United Kingdom

By that time, Subramaniam had met his wife and got married. His wife also comes from India but had lived in the US. She liked the idea of living in Europe but preferred an English-speaking country.

*'It was good for me to see the other side of the coin. Ninety percent of the students I teach end up in industry. Seeing things from an industrial perspective has helped me as a scientist. And my students can only benefit from knowing what industry wants.'*

## 2004-present:

### Professor at the University of Twente

While working in England, Subramaniam was approached by University of Twente: they were recruiting a professor of biophysical engineering.

*'But I liked my job in England, and I'd only just got started. So I said no. But a few months later they came back and said: we really want to speak with you. Several months passed and they persisted, and in the end I said yes. Twente has a world class package of knowledge and infrastructure. Top-notch people.'* ■

[ chapter 04 ]

## NEURAL & MOTOR SYSTEMS

# getting on the move again

04

[ *intro* ] THE NEURAL & MOTOR SYSTEMS RESEARCH TRACK EXAMINES THE INTERPLAY BETWEEN BRAIN, NERVES, MUSCLES AND THE SKELETON. THE WORK HAS A FIRM SCIENTIFIC BASIS, BUT IS DRIVEN BY SPECIFIC QUESTIONS FROM HEALTHCARE. OUR PIONEERING RESEARCH FOCUSES ON RESTORING FUNCTION TO THE NEURAL AND MOTOR SYSTEMS. CURRENT TOPICS INCLUDE HELPING PATIENTS TO REHABILITATE WITH THE AID OF ROBOTS, SELECTIVE ELECTROSTIMULATION, AND INNOVATIVE BODY PROSTHESES.

# REMOTE CARE VIA YOUR UNDERWEAR

[ *intro* ] THE POPULATION IS AGEING AND SO THE NUMBER OF CASES OF CHRONIC DISEASE IS INCREASING. TO STOP THE HEALTHCARE SYSTEM BECOMING OVERBURDENED IN THE LONG TERM, RESEARCHERS AT MIRA ARE DEVISING TECHNIQUES FOR SUPPORTING PATIENTS AT HOME.

Using modern sensor and computer technology to monitor patients recovering from an illness or accident seems straightforward enough. You give them a device they can use to report their own blood pressure and heart rate and that keeps an eye on what they're getting up to each day. The device sends all of the data to a computer. If the computer notes any abnormalities or discovers that the patient is failing to comply with the treatment prescribed, it sends a warning to both patient and doctor. The doctor can then intervene quickly or the patient can get a fully-automated rap on the knuckles.

Home monitoring of patients is done by means of a Body Area Network.

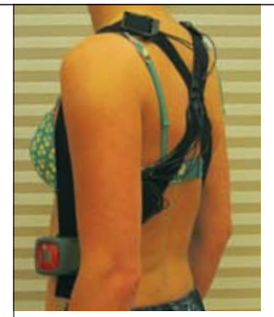
### TURNING THE PROCESS ON ITS HEAD

Yet it's not quite that simple in practice. As many as three-quarters of 'telemedicine' applications fail and never reach a large group of patients. This might be because most of these programmes are developed too much from the perspective of technology. Researchers at MIRA are therefore attempting to turn the development process on its head: first go and see what the user needs. And then devise technology to fit. Patients and their care providers can therefore indicate how a programme should function. And they can test the prototype first. Only then do you end up with an application that patients will actually use.

**INVISIBLE TECHNOLOGY** The experts in information, communications and biomedical technology who are collaborating in the MIRA research focus mainly on rehabilitation patients. The majority of these are older patients who have difficulty in moving, and patients with cancer, respiratory conditions or chronic pain. But patients who are obese or suffering from psychiatric problems are also eligible. The home monitoring of such patients is often done by means of a Body Area Network (BAN). This consists of a sensor system and a Personal Digital Assistant (PDA), a device around the size of a mobile phone. From the world of sport, people are familiar with special sensor bands placed around the chest, which measure heart rate and respiration or even record ECGs. The researchers in Twente have also developed tops and underwear which incorporate activity sensors. As a result, the technology is almost invisible but nevertheless ensures that a supervising healthcare provider can tell at a distance whether a rehabilitating patient is keeping to his prescribed programme of activities. And with very little effort from the patient.

### AVOIDING REVOLVING DOOR PATIENTS

Isn't it hard to teach older people how to work with such complicated computer-controlled programmes? 'Nonsense', says researcher Miriam Vollenbroek-Hutten. 'You just have to make it easy: big letters, not too many buttons. I always say: if it's no more complicated than using a cash point or the remote control, then anyone can handle it.' The devices record everything. Are patients spreading their prescribed exercises properly throughout the day? Or are they crumpling in a heap after over-exerting themselves in the morning – a common phenomenon? By keeping a close eye on this sort of thing, individualised support and efficient follow-up care is possible. This stops you getting 'revolving door' patients.
On balance, it saves on costs. Which is important, because healthcare is at risk of becoming unaffordable. This is partly due to the increasing number of older people and chronically ill. The ageing population, moreover, means that there are fewer and fewer staff to do all the work in healthcare facilities. If the current trends continue, around 25 percent of the working population will have to work in healthcare by 2025. Which is of course impossible. Thinking up clever applications which reduce the pressure on hospitals and staff is therefore a research field with huge (market) potential for MIRA.



The Body Area Network consists of a sensor system and a personal electronic device.

### LESS PAIN DUE TO MUSCLE RELAXATION

MIRA was recently involved in a highly successful trial with chronic pain patients. The patients were given a device that measured, among other things, how much strain they put on their muscles. The Twente researchers monitored the patients continuously and consulted them extensively about how satisfied they were with the device. With the measurement results obtained, the healthcare providers then went back to the patients. They could show them precisely whether they had relaxed their muscles enough. The result? Within a few weeks, the pain patients were not only much more aware of what they were doing with their muscles, but they also had significantly less pain. The success of the trial can't just be put down to effective technical gadgets. An important aim of the Twente telemonitoring project is of course to develop high-quality measuring equipment. Contact points and sensors shouldn't break down if a patient starts to sweat, and technical aids should be easy to operate. But good coaching for rehabilitating patients is at least as important. The researchers discovered that people need help with integrating their exercises into their daily lives. And although it's an enormous advance for doctors to be able to monitor people 24 hours a day instead of just during a consultation, it drives patients crazy if they're given feedback too often. So the results should be discussed regularly, but not excessively.

### THE HUMAN TOUCH IS STILL IMPORTANT

What is the ultimate aim? A care robot that analyses the incoming data in a fully automated manner and then, independently, sends instructions, advice, reprimands or indeed compliments to the patient, who is sitting at home by himself? Intelligent decision support is very important but fully controlled by technology is not what Miriam Vollenbroek-Hutten believes in. 'The human role will always be important. Research shows that patients need trusted relationships with others in order to persevere.' For that very reason the MIRA researchers plan to launch virtual group training courses in the near future, teaching patients to use the technology to contact and support each other. This seems to be the ideal way to outsource care and also make it more fun for the patient. ■

▶ NEXT PAGE: FIVE QUESTIONS FOR MIRIAM VOLLENBROEK-HUTTEN

MIRIAM VOLLENBROEK-HUTTEN

# *'I don't want to work in a vacuum'*

PART-TIME PROFESSOR MIRIAM VOLLENBROEK-HUTTEN WORKS FOR MIRA IN DEVELOPING TELEMEDICINE APPLICATIONS. AS A SPECIALIST IN THE BIOMEDICAL HEALTH SCIENCES, SHE ALSO WORKS ON REHABILITATION TECHNOLOGY FOR ROESSINGH RESEARCH AND DEVELOPMENT IN ENSCHEDE.

**1** *Isn't it difficult being at the University of Twente amongst all those techies?* 'Interacting with 'techies' is of course vital for developing innovations. My role is to bridge the gap between care and technology. I've learned to speak the techie language well and I'm learning more every day. Every so often, though, I have to admit that I'm not a techie myself. But luckily the culture here is so open that you can just say if things are getting a bit too complicated.'

**2** *Do you enjoy the work?* 'Yes, my work is my hobby as well. It's very invigorating on the one hand, and is a new challenge every time. On the other hand, I'm working to develop very practical applications. I'm doing something for society. That's very important to me. I don't want to work in a vacuum, I want to stay in contact with the people who are actually involved in healthcare.'

**3** *And if it doesn't work as you want then where do you channel your frustration?* 'Then I look for a different way of doing it. There's always more than one road that leads to Rome. I'm an optimist by nature. For me, the glass is half full rather than half empty.'

**4** *Do you like it in Twente?* 'I'm a born and bred 'Tukker', so I feel right at home here. I wouldn't want to be without the peace and space you find here.'

**5** *What do you hope to achieve at MIRA?* 'I want us to achieve an international top position in telemedicine. The combination of information technology and biomedical technology that we have in house is fairly unique in the world. We can use that to create a profile for ourselves. We certainly don't need to confine our ambitions to The Netherlands.' ■





# Robotic system for prostate cancer diagnosis

[ *intro* ] EVERY DAY COUNTLESS MEN HAVE TISSUE SAMPLES REMOVED FROM THEIR PROSTATE FOR BIOPSY TESTS. AN INTERVENTION THAT IS PAINFUL FOR THE PATIENT AND CHALLENGING FOR THE DOCTOR. A ROBOTIC SYSTEM THAT CAN WORK UNDER THE GUIDANCE OF AN MRI SCANNER CAN PROVIDE A SOLUTION.

Currently it's quite a hassle for a doctor to remove a small piece of tissue ('biopsy') from the prostate, if a tumour is suspected. An MRI scan is used to determine where exactly the tissue sample must be taken from. The doctor then has to insert a needle through tissue and muscles in search of suspected cells. Difficult, because when a sample is being taken the prostate can suddenly move, causing the needle to miss its target. Therefore, in practice the doctor pricks three or four times to make sure the job's done. Painful for the patient, but also far from ideal for the doctor who has to keep on walking in and out of the MRI room. And if the sampling goes wrong, the analyst will receive healthy-looking prostate cells even though cancer cells might have been right next to them. Therefore, a doctor can never be absolutely certain if a reassuring diagnosis is right.

**GOOGLE MAPS** Performing the intervention inside the MRI scanner would be far easier. Then the doctor could see in real time if he has reached the target. That's not possible, however, as the doctor cannot work in the MRI scanner's strong magnetic field. And using a robot system to obtain a piece of tissue from the prostate is also easier said than done: the strong magnets in the MRI room would still form an obstacle. That might all change in the future though. Because in the five-year project Minimally Invasive Robotics In An MRI Environment (MIRIAM), MIRA is working on a solution to the problem. A multidisciplinary team, which includes Radboud University Nijmegen Medical Centre and commercial partners, is building an advanced robotic system from non-magnetic materials. The system receives continuous feedback from the MRI scanner about where the needle is. If the needle deviates from the predetermined route, the robot can bring it back on course.
The MIRIAM project team is also developing models to predict the movements in the organ tissue. The researchers describe it as 'a sort of Google Maps for the body'. This give

▶ CONTINUED ON NEXT PAGE

SARTHAK MISRA

# *From space robotics to prostate interventions*

SARTHAK MISRA STARTED HIS CAREER IN SPACE RESEARCH. THE CANADIAN MADE THE SWITCH FROM THE JOHNS HOPKINS UNIVERSITY IN BALTIMORE TO THE CONTROL ENGINEERING GROUP OF MIRA, WHERE HE LEADS THE MIRIAM PROJECT.

**1** *What exactly did you do in space research?* 'In the International Space Station Program, Canada is leading the construction and operation of the Space Station robotics. For example, Canada built the robot arm for the space shuttle. As a dynamics and control analyst I looked at what sort of movements a robot must make to transfer a payload safely from the space shuttle to the space station. The payloads are sometimes the size of a bus. I also developed emergency scenarios in the event something goes wrong. This work involved working closely with mission planners at NASA in Houston.'

**2** *Isn't the switch from space to the prostate a 'giant leap'?* 'No. Of course modelling tissues is different from working in aerospace engineering. And the ultimate objective – improved patient care – is also different. But the fundamental engineering principles for robotics are the same. In both cases you develop techniques to move robots in safety critical environments. My background in aerospace engineering is a big advantage in the work I'm doing now.'

**3** *What attracted you to Enschede, after gaining your PhD at the world-famous Johns Hopkins University in Baltimore?* 'MIRA was simply the best choice for me. I valued how I could set up my own line of research here and the funding I could receive for this. On top of that, I already had various contacts with researchers at Twente and also other Dutch universities, such as Delft, Nijmegen and Utrecht. And on a more personal note, my wife is Dutch. She didn't object to returning to The Netherlands. We live in Zwolle, which is a very different environment for me – compared to living in Montreal or Baltimore, but that's simply a matter of adjustment.'

**4** *Is research your mission or merely a stepping stone to a spin-off company?* 'I enjoy the freedom that an academic environment offers and I've got no plans to leave it. Of course it would be great if my research led to a spin-off. But my work with students, fellow researchers and colleagues isn't something I'd give up lightly. I'm now an assistant professor and that position gives me plenty of opportunities to develop myself.' ■

▶ CONTINUED FROM PAGE 67

the doctor step-by-step information about the route the needle must take to reach its target. The computer model also helps to accurately predetermine where the needle can best be inserted.

**TESTS ON CADAVERS** With MIRIAM, the researchers want to develop a surgical technique that minimises the inconvenience of a prostate intervention. No less than one-in-six men in the Western world experience prostate cancer at some point in their lives. In Europe alone this translates to more than 300,000 new cases a year. For the time being, the researchers are concentrating on prostate cancer. However, in the future this technique could be used to investigate liver ablations or breast biopsies as well.

The greatest challenge is getting the different systems to faultlessly communicate with each other. Yet the project team is confident that in five years time they'll have a prototype ready to undergo tests on cadavers. ■

# OPERATION ROBOT NEEDS JUST A SINGLE INCISION

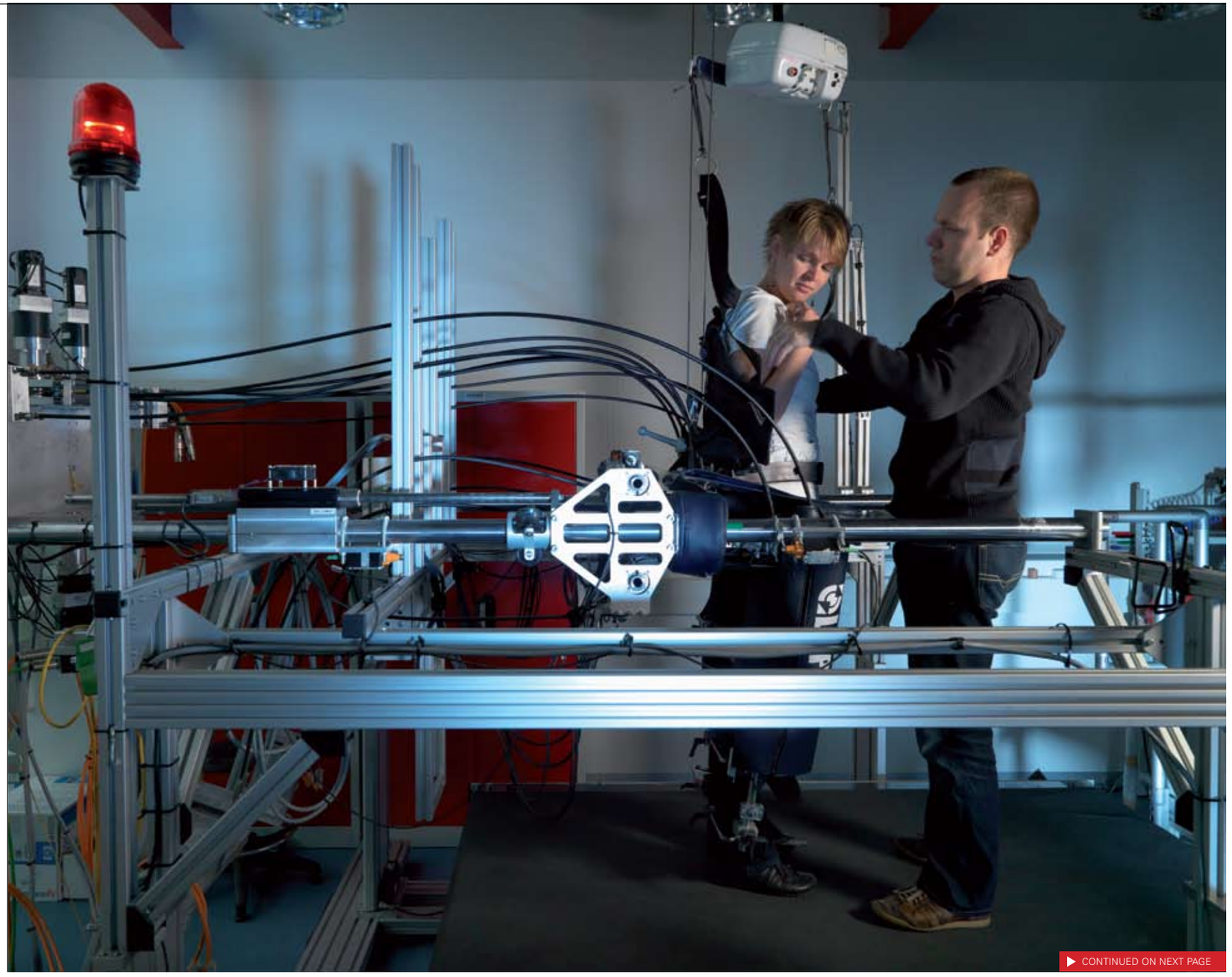
Below surgeon Ivo Broeders working in a present day operating room. To the right a future surgeon at work with the help of a robot.

'Keyhole operations' are a welcome outcome for patients because they are not left with a large scar but three or four small incisions. Single incision operations are even less demanding as only a single small entry point to the body is made. Robots play a valuable role in supporting the surgeon during such challenging operations. For example, they can work very precisely, never suffer from shaking hands and never experience backache when operating from an inconvenient angle. MIRA is working on the 'TeleFlex' robot in close collaboration with surgeon and clinical professor Ivo Broeders.
Using this robot the doctor can operate a flexible tube from his cockpit chair with the aid of a computer and joysticks. This tube is equipped with a camera and various work channels. These allow the surgeon to observe the body and perform small interventions. ■

REHABILITATION ROBOT

# gets paralysed patient walking again

[ *intro* ] IN THE FUTURE, PEOPLE RECOVERING FROM PARTIAL PARALYSIS AFTER A STROKE WILL GET HELP WITH WALKING FROM A ROBOT. THE COMPUTER-CONTROLLED LOPES MACHINE DEVELOPED BY MIRA LITERALLY GIVES THEM A BIT OF A LEG-UP. IT'S UNIQUE IN THE WORLD.



Laced into the LOPES (Lower extremity Powered ExoSkeleton), the patient looks like a sort of Robocop from the well-known film by Paul Verhoeven. A frame wraps around the pelvis, the legs are laced into two huge bundles of mechanics. Taking heavy mechanical steps, the

CONTINUED ON NEXT PAGE

CONTINUED FROM PAGE 72

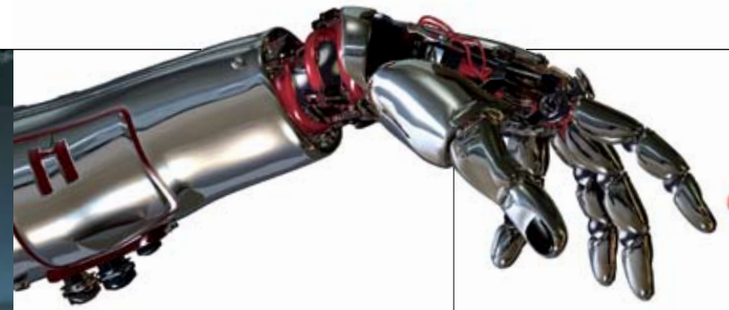
patient walks on a treadmill, while suspended in a safety harness and controlled by brake cables connected to the robot motors. ‘The patient feels stabilised, but the machine doesn’t take over completely. The rehabilitation robot is intended as a support, not a replacement’, explains researcher Edwin van Asseldonk in the laboratory which is home to the LOPES machine. ‘If your tennis coach holds your racket constantly when you’re hitting the ball, you won’t learn to play tennis. The same applies to a person who has to learn to walk again.’ From his place at the computer, movement scientist Van Asseldonk can make the patient do what he wants. Take big steps, bend or swing the legs out better? A piece of cake, a couple of mouse clicks and the patient’s movements have been adjusted. But Van Asseldonk only does that if it is really necessary.

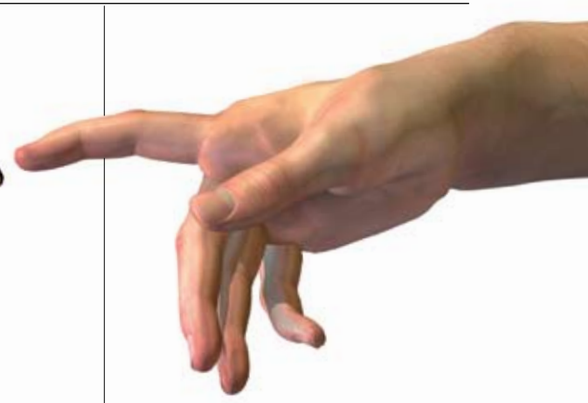
**RED AND BLUE LINE** The computer screen displays two lines: one blue, one red. The blue line is the patient’s current gait, while the red represents the way an able-bodied person walks. The aim of practising with the rehabilitation robot is to bring the two lines closer and closer together. The machine has sensors at the pelvis, hip and knee joints which monitor the patient’s movements closely. The sensors send their information to the computer. Based on this data, the researchers can compute each movement separately. For each individual patient, they can also determine how movements should normally be performed and how they are restricted. For example, if a patient has trouble walking because his knee doesn’t bend enough as he swings his leg forward, this is unerringly recorded by the sensors. After analysing the data, the computer issues a tailor-made recommendation as to how the movement can best be adjusted. The protective ‘exoskeleton’ prevents injuries from to the over-stretching of joints and muscles.

The rehabilitation robot stabilises the patient while stimulating her to make the right moves.

**ROBOT REPLACES PHYSIOTHERAPIST** The intention is that the constant corrections will lead to changes in the brain. Because, in fact, it’s mainly the brain that the LOPES robot is training. In people who’ve had a stroke or a brain haemorrhage, the problem lies not in the muscles but in the control of the muscles. As a result of getting patients to walk on a treadmill and adjusting their movements at the same time via sensory information, the brain adapts. The outcome is that patients gain more control over the way they walk.

The LOPES robot is doing the same thing that physiotherapists do at present. A patient who’s unable to walk as the result of a stroke, partial spinal cord lesion or serious orthopaedic surgery usually receives training from two physiotherapists. One provides support and gives instructions while the other helps the patient to take steps on the treadmill. But this is hard physical work for the physiotherapists and takes up a lot of their time. As a result, it’s becoming increasingly difficult to continue these types of therapy under the continued pressure on healthcare. In The Netherlands alone, there are forty thousand cases of stroke or cerebral haemorrhage every year. In a large proportion of these cases, patients are left with partial paralysis of the legs. The idea behind LOPES is to get the robot to do the heavy physiotherapy work, thus relieving the care providers of a substantial burden.





**SENSATION OF FREEDOM** Rehabilitation robots are already on the market, one producer being the Swiss company Lokomat. ‘But those machines’ range of movement is much smaller than that of LOPES’, says Van Asseldonk. ‘In our machine people don’t need to move along set lines, thanks to special mechanical additions and advanced control of the robot. The sensation of freedom that the patient gets in the LOPES makes our technology unique.’ To achieve this, mechanical engineers build complicated frame structures which are designed using a virtual centre of rotation at the point where the patient’s pelvis is located. These ensure that patients barely notice that they are being supported from behind, but nevertheless don’t fall over.

**NEW PROTOTYPE** Before LOPES makes its debut in rehabilitation clinics, however, there’s still a lot of research and development to be done on the gait robot. In collaboration with Het Roessingh rehabilitation centre in Enschede, the Sint Maartenskliniek in Nijmegen and technology firms MOOG and Demcon, MIRA researchers are currently pulling out all the stops to improve the control systems. The machine also needs to be more compact, more user-friendly and lighter. One option in this respect is to alter how the forces are transferred from the motors to the legs. The aim is to have a second, completely new LOPES prototype within 18 months. The research at MIRA also focuses on the precise learning mechanisms of people receiving gait training in the machine. We know that patients who are unable to walk, or walk normally, as the result of a stroke immediately try to counterbalance this by adopting different gait patterns. The question for the researchers is whether they should encourage this effort or curb it. Does every patient find his own alternative gait strategy, or is it better to encourage gait patterns found to be ideal for the average walker?

**MINDWALKER** MIRA has been given a grant to investigate whether rehabilitation in the LOPES robot is quicker when combined with a technique that increases the excitability of areas of the brain. Van Asseldonk: ‘We attach electrodes to the patient’s head, near the command centre in the brain. Our aim is to stimulate that centre while the patient is training in LOPES.’ Short magnetic pulses are sent out from a coil of copper wire on top of the patient’s head, generating tiny currents in the brain. These pulses stimulate the areas of the brain responsible for walking movements.

**SCIENCE FICTION** Couldn’t the patient’s brain ultimately control the robot legs? Van Asseldonk: ‘That would be great, and that’s why we’re investigating that possibility now. If this so-called Mindwalker works, then in the future patients will be able to send commands to the robot legs using a specially developed helmet. And, in a manner of speaking, take their exoskeleton to the supermarket.’ It sounds like science fiction. Van Asseldonk: ‘Yes it does, and that’s what makes our discipline so exciting. Combining fundamental research with robot technology to help patients with serious motor problems. What more could you want?’ ■

[ extract from the schedule of... ]

MICHEL VAN PUTTEN

# ‘deep insights require long contemplation’

[ *intro* ] MICHEL VAN PUTTEN IS A RESEARCHER, PROFESSOR, DOCTOR AND PHYSICIST. HE REGARDS MIRA’S HIGH AMBITIONS AS AN INTELLECTUAL CHALLENGE.

*‘In the holidays I may spend three hours a day at the grand piano, in my music room.’*

## 7.00 *Getting up*

‘Always hard. I have a coffee with my girlfriend and try to get going. I like to go on until very late in the evening. I wish I could get by on four hours’ sleep, like Napoleon, because there’s such a lot of fun stuff to do. But I need my seven hours.’

## 8.00 *Meeting with Edwin van Asseldonk*

‘Edwin is keen to start using a technique that sends a small direct current through the brain from a band placed around the patient’s head. Administering those few milliamperes in certain areas of the brain might help in rehabilitating patients after a stroke. Effects have already been measured, on muscle control for example, but the results in patients are still modest. For measurements in patients, the medical ethics committee must give its consent of course. That’s what we’re talking about.’

## 9.30 *Patient consultations*

‘Consultations are still important to me. My core business is clinical neurophysiology – measuring and interpreting signals and (increasingly) ‘adjusting’ functions using signals. But we’re developing that technology for people made of flesh and blood. Which is why it’s good to keep seeing patients as well. On the other hand, it’s not easy to do eminent science with a pager in your pocket. Because you can be torn away from your contemplations at any time. Deep insights require a lot of time and energy, long brooding. Einstein said: “I’m not cleverer than other people, I just think about things for longer.” There’s a grain of truth in that.

Today I have to tell a patient that he’s probably suffering from one of the most serious neurological conditions there are: ALS. It’s an incurable disease in which the patient becomes progressively paralysed. Usually, you die of it within a few years. Of course, I don’t enjoy having to tell someone this, but it’s part of the job. Still, an odd contrast if the next patient is suffering from a sore leg due to a hernia.’

## 11.00 *Meeting with Tom Schwarz, venture capitalist (Twente Technology Fund)*

‘Tom is someone who looks at whether new developments can potentially lead to a spin-off. And whether it’s attractive to put venture capital into them. I want to set up a Centre for Clinical Neurosciences, in addition to the Centre for Medical Imaging. I’m interested mainly in the brain, especially epilepsy, how you can diagnose the disease and how it comes about. Epilepsy is common and there’s still much to discover about the networks within the brain that result in the disease. In the Centre for Clinical Neurosciences, we hope to be able to work with new techniques and make progress as a result. By combining the expertise and technical facilities jointly built up by MIRA and University of Twente, we can make real breakthroughs. I’m convinced of that. Shoot for the stars and you’ll reach the moon.’

## 13.00 *With Chin (PhD student) to the hospital’s stroke unit*

‘Chin is investigating if activity occurs in the brain when a person merely looks at a movement. Studies in monkeys point to this. The main thing we want to know is whether it can help someone who’s been left paralysed by a stroke. We’re therefore looking at EEGs from stroke patients. Apart from the stroke unit, I also visit the intensive care unit a lot, to see patients with brain injury due to an accident or severe epilepsy, or because they’ve been resuscitated. As neurologists, we play an important role in deciding whether or not to continue treatment as we try to predict the extent to which the brain will recover.’

### Automatic brain monitoring

At MIRA, Michel van Putten is developing a system that automatically analyses the graphic reproduction of measured brain waves (EEGs). This makes it much easier to diagnose brain conditions. This means that in critical situations in the operating theatre or intensive care, a neurologist no longer needs to be continuously present to monitor brain activity. A machine can (to some extent) take over that task.

## 14.30 *Guest lecture on epilepsy*

‘I really enjoy doing this, especially the challenge of having contact with the audience. The nicest compliment I ever had was from the father of a student: “My daughter says: it’s like cabaret, what Van Putten does.” It’s true, of course, that your lecture needs an element of theatre if you want to keep an audience captivated.’

## 17.30 *Meeting with Marleen Cloostermans (PhD student)*

‘The topic is a study of patients following resuscitation in our intensive care unit. We’re also going to discuss the algorithms she’s developed, which give us a real-time understanding of the functioning of the brain, and the scientific article she’s written about these. Writing things up is not only important because it enables you to show colleagues elsewhere what you’re working on. It also helps to bring structure to what you’ve done. The best thing, of course, is when it leads to other people picking it up elsewhere.’

## 19.00 *Playing the piano*

‘I’ve been playing since I was 11 and having lessons since I was 16. I play a couple of times a week. I’m no great talent, but I like practising and I practise hard. At the moment I’m doing Grieg’s *Lyrische Stücke* and Gerschwin’s *Preludes*. In the holidays I can spend three hours a day at the grand piano, in my music room. But when it’s as busy as now, it sometimes gets forgotten. It’s a real shame, because you soon notice it in your playing; playing the piano requires motor skills that you have to practise almost continuously.’

### Brain signals should be measured more often

One way of studying the condition of a person’s brain is to attach electrodes to his head and measure brain signals. Using a computer, you can display the frequency of brain waves, whether they match on left and right, and whether they show regular patterns. Van Putten believes that such measurements are still under-used in intensive care units in The Netherlands. Consequently, we’re missing out on information about the condition of the brain. Using computer algorithms, Van Putten attempts to convert the patterns in which brain signals are reproduced as symbols that are easier to ‘read’. This allows you to develop a system that can be handled, in principle, by any healthcare provider instead of just a handful of brain specialists.

## 20.00 *Giving a presentation to neurologists from the region*

‘Once a month there’s a scientific presentation for current and future neurologists in the region. Usually we have a speaker from somewhere else, but the speaker dropped out this time. So I’m giving a presentation myself about EEG monitoring in the intensive care unit.’

## 23.00 *Home to my computers*

‘A quick pop upstairs to look at my algorithms. I’m a reasonably good programmer. I normally have two desktops rattling away day and night. I get them to “look” at brain signals. They’re currently comparing EEG patterns in patients under anaesthetic with measurements from the same patients in a waking state. It’s exciting. You’re trying to identify the characteristic differences in the interactions of neural networks in the brain between a person who’s awake and a person who isn’t.’ ■

### [ *who is...* ]

**WHO IS MICHEL VAN PUTTEN?**

Michel van Putten (1963) has been professor of Clinical Neurophysiology at the University of Twente since December 2009. He is also head of the Clinical Neurophysiology Department at Medisch Spectrum Twente. Van Putten studied technical physics in Delft and did his PhD in measurements using advanced flow meters. He had previously completed a degree in medicine as well, specialising in neurology and clinical neurophysiology. Measuring and analysing measurements are in Van Putten’s blood: his father has a laboratory at home where he develops new techniques for gas measurements, among other things.

**TLEMSAFE**
The basis of TLEMsafe (Twente Lower Extremity Model) is a dataset compiled by dissecting the leg – the 'lower extremity' – of one person.

# A navigation system for surgeons

[ *intro* ] DURING COMPLEX LEG OPERATIONS, SURGEONS OFTEN DECIDE WHERE TO RECONNECT MUSCLES BASED PURELY ON INTUITION AND EXPERIENCE. WITH VARYING DEGREES OF SUCCESS. MIRA RESEARCHERS ARE DEVELOPING A DETAILED COMPUTER MODEL OF THE MUSCULOSKELETAL SYSTEM OF AN INDIVIDUAL PATIENT. THIS MODEL CAN GUIDE THE SURGEON UNERRINGLY AND INCREASES THE CHANCES OF A SUCCESSFUL OPERATION.

A computer animation shows the contours of a leg with a pattern of brightly-coloured lines. The animation shows precisely how the forces are distributed between the muscles. With split-second accuracy, you can determine how the forces must have changed during a movement. And with considerable accuracy you can calculate how much power a muscle must deliver for the patient to move as efficiently as possible. This is important because it shows which muscles the surgeon can cut in and which he must spare at all costs to ensure the patient will walk again after the operation. Crucial knowledge, especially during radical surgery in which the surgeon has to remove a large part of a muscle or bone due , for example, to a tumour. Muscles sometimes have to be re-routed. The model can also be useful in treating a common congenital deformation of the hip joint. The head of the femur sometimes has to be relocated to enable a person to walk normally. The computer model can tell the surgeon exactly where it should be located in the pelvis.

**DRUDGERY** The basis of TLEMsafe (Twente Lower Extremity Model) is a dataset compiled by dissecting the leg – the 'lower extremity' – of one person. All the muscles, tendons, insertions and bones were picked apart, measured in the smallest detail, and digitised. However, the resulting wealth of information cannot be applied to every patient on a one-for-one basis. Therefore a method has been devised for adapting the model to the individual

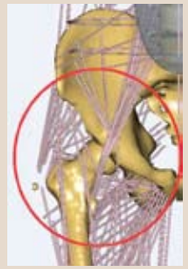
▶ CONTINUED ON NEXT PAGE

## [ fig. a ] SURGEON'S NAVIGATION SYSTEM

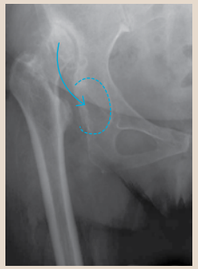
A dataset for surgeons that provides a detailed picture of the musculoskeletal system of the leg. The TLEM system helps the surgeon to prepare for the operation.

The surgeon enters the information obtained from the X-ray or MRI scan into the computer. Then the system issues a patient-specific advice about how the operation can best be performed.

**HOW DOES IT WORK?**

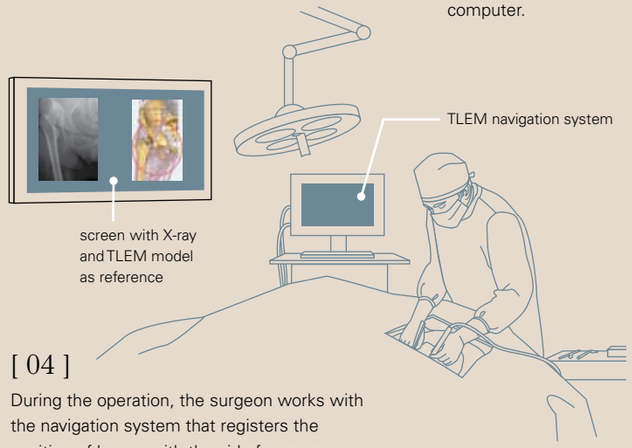


[ 01 ]
The TLEM basic model on which the muscle line of action and attachment points can be seen.



[ 02 ]
X-ray image of the damage in the patient. This information is entered into the TLEM system.

[ 03 ]
The TLEM patient-specific model. The surgeon practises by performing a test operation on the computer.



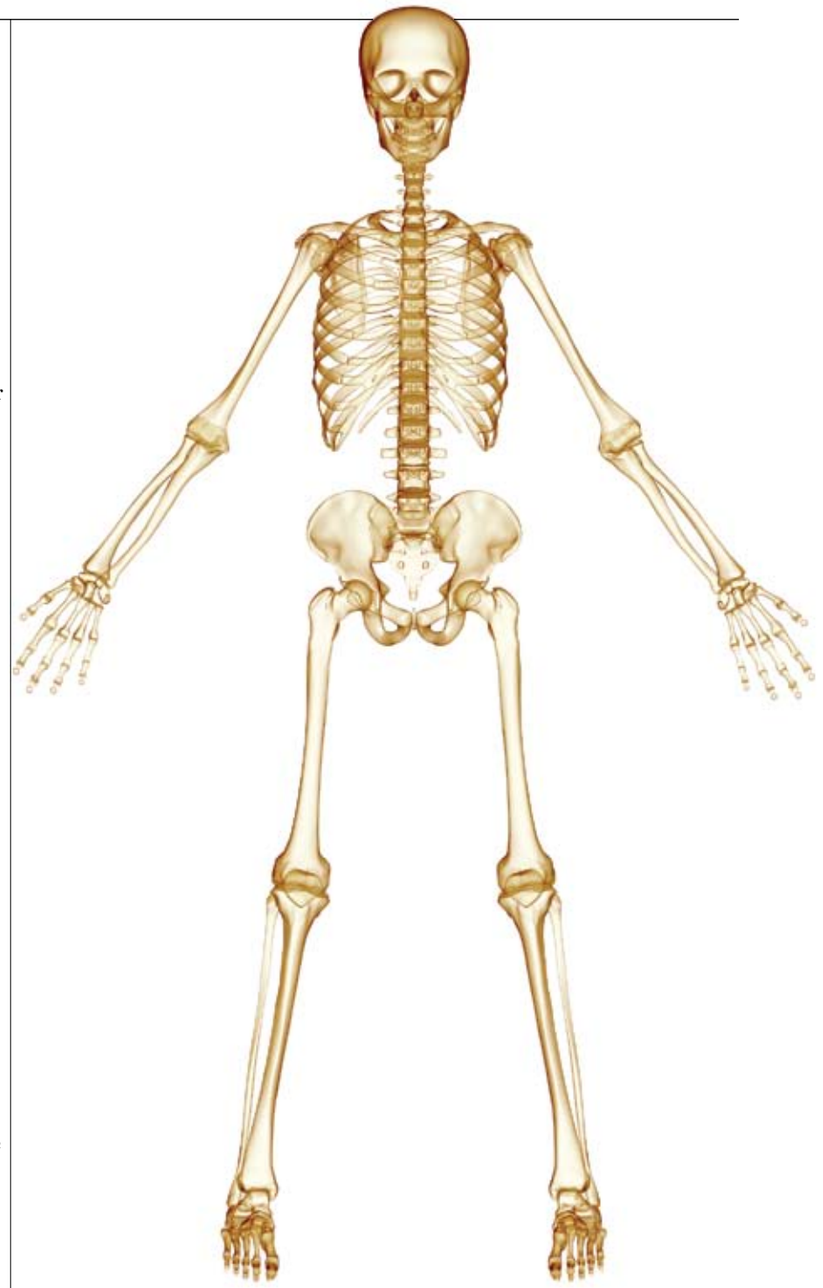

[ 04 ]
During the operation, the surgeon works with the navigation system that registers the position of bones with the aid of cameras. Then the surgeon can see on the screen if the operation is being performed accurately.

Source image TLEM model: AnyBody Technology

CONTINUED FROM PAGE 081

patient. This is done by mapping differences in muscle geometry and size using an MRI scan. Researchers translate these data into a three-dimensional computer model. Surgeons can use the model to prepare for their operations more effectively. And even practise virtually beforehand. This way it will be easier to predict whether a person will indeed be able to walk again after radical surgery.

**LESS RISK OF A WHEELCHAIR** Researchers compare the computer navigation system that they are developing for surgeons to a TomTom: it tells the surgeon exactly where certain muscles should be moved to, just like a car being guided to its destination along a predetermined route. For example, if a surgeon wants to turn a muscle or section of bone through ten degrees during an operation, he can do so with extraordinary accuracy using the navigation system, assisted by cameras and markers which are attached to the bone. Over the next four years, MIRA will work to refine the system further by means of laboratory tests. After that the model should be ready for the trial phase. The researchers from Twente are working closely with colleagues from Radboud University Nijmegen Medical Centre, Warsaw University of Technology and a number of specialist companies. It is expected that several hundred people a year in The Netherlands who need to undergo a serious leg operation will benefit from TLEMsafe in that their chances of ending up in a wheelchair will be reduced. ■







MARJOLEIN VAN DER KROGT

# *'No-one is in this to get rich'*

HUMAN MOVEMENT SCIENTIST MARJOLEIN VAN DER KROGT HAS BEEN WORKING ON MIRA'S TLEMSAFE PROJECT SINCE MARCH 2010. THE POST-DOC FROM AMSTERDAM IS A SPECIALIST IN GAIT ANALYSIS AND MODELLING AND THE EFFECTS OF CEREBRAL PALSY.

**1** *What attracted you to the human movement sciences?* 'I've always played a lot of sports and was very interested in how people can achieve top performance. That's one of the questions that human movement science seeks to answer.'

**2** *Have you reached a top level in sport yourself, perhaps as a result of that?* 'No such luck, I'm an enthusiastic amateur racing cyclist and speed skater.'

**3** *Can you get rich from your work?* 'If that's what you want, you'd be better off doing something else. For me, that's not what it's about. But the idea is, of course, that you develop things there's a demand for. And if that means I get a nice patent to my name one day then I might become rich after all.' (laughs heartily)

**4** *But why would a city girl come to the provinces?* 'Well I don't live here. Enschede is definitely a nice place, and quick to get to, but for the time being I'm staying in Amsterdam. I also work at the VU University there three days a week. And my husband works in the Amsterdam area. The atmosphere in Enschede is quite different from Amsterdam. I'd miss life in the big city if I lived in Twente. But I'm really glad to be part of a very enthusiastic and active workgroup here.'

**5** *What goals do you have in your work?* 'Who knows, perhaps becoming a professor. But mainly, continuing to enjoy my work.' ■

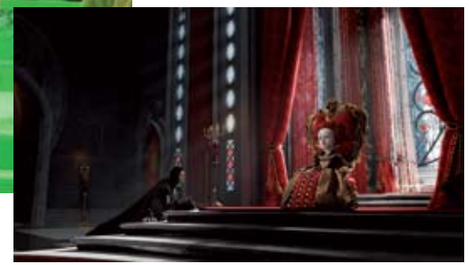
# PER SLYCKE, PETER VELTINK AND XSENS

HOLLYWOOD FILMS LIKE 'ALICE IN WONDERLAND' AND 'IRON MAN 2' USED THE SPECIAL SENSOR SUITS FROM XSENS TO MAKE PERFECT ANIMATIONS. THE MOVEMENT MEASUREMENT SYSTEMS OF THE TWENTE COMPANY ARE ALSO USED WORLDWIDE BY THE GAMING AND ROBOT INDUSTRY AND BY MOVEMENT SCIENTISTS. XSENS WAS FOUNDED IN 2000 BY TWO FORMER STUDENTS FROM THE UNIVERSITY OF TWENTE: PER SLYCKE AND CASPER PEETERS. RIGHT FROM THE START THEIR SOURCE OF INSPIRATION WAS PROFESSOR PETER VELTINK, WHO NOW WORKS AT MIRA.

Per Slycke

Peter Veltink

Scene from the 3D animation film Alice in Wonderland with actors Crispin Glover and Helena Bonham Carter. (Photos Disney Home Entertainment)



1998 2000 2002 2005 2010

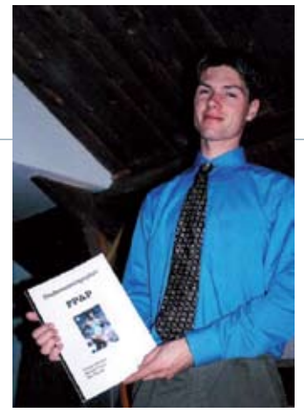
## 1998-1999

### First experiments with sensor shoes

Veltink and Slycke worked on a method to improve estimation of orientation and change of position during a movement. The advanced measuring equipment they developed for this can record body movements in 3D.

**SLYCKE:** ' We had the idea of developing a speedometer for runners. We needed help to develop the sensors we wanted to use for this. We were lucky. One of the leading groups in this area, that of Peter Veltink, was at the University of Twente.'

**VELTINK:** 'They came to me as young recently graduated physicists who were determined to set up a company. Their 'RunnersWatch' was interesting, as it was more than just a step counter.'



## 2000

### Founding Xsens Technologies

Market interest became more serious. The company was set up with support from the University of Twente's TOP funds.

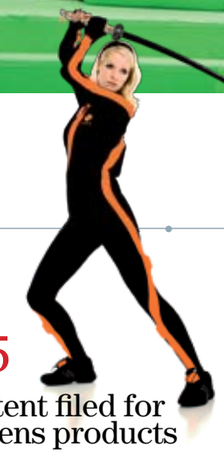
**SLYCKE:** 'The real start'
**VELTINK:** 'The concept worked, with a gyroscope and acceleration sensors that formed the basis of the speedometer. They tested it here on the athletics track with this sensor on the shoe.'

## 2002

### Xsens falters

Just before the sale of the invention, the intended client, a heart-rate meter manufacturer, pulled out. That was hardly surprising as it was the middle of the 'dot-com crisis' when the Internet bubble burst. After all the investments made, Xsens was left with empty hands.

**SLYCKE:** 'At such a moment you need to be flexible as a company and find other opportunities. In that same year we sold the first 3D movement technology to completely different markets, such as stabilisation and navigation for unmanned underwater robots. The basis for a new product line had been laid.'
**VELTINK:** 'A disappointment, but not a failure.'



## 2005

### Key patent filed for new Xsens products

**SLYCKE:** 'A milestone, although you still have to wait five years before a patent is actually granted. Meanwhile we also concluded three important license agreements with the University of Twente that formed the basis for the ForceShoe. That's a shoe which measures the ground reaction forces and foot movements in order to create 3D images of the walking patterns and study balance of gait. It will be marketed in 2011.'
**VELTINK:** 'A working sensor system for measuring relative distances on the body did not yet exist. It's therefore very important.The concept of a ForceShoe and, related, powersensing/powerglove has, in my view, high potential.'

## 2010

### Tenth anniversary of Xsens

Some 70 people now work for the company, which has opened a second office in Los Angeles and has agents all over the world. Veltink has been honoured with the 'Partnership Award': a bronze gyroscope.

**SLYCKE:** 'Peter Veltink has always been a source of inspiration, due to his clear vision. He provides a broad framework that we develop further in our products for measurements on people.'
**VELTINK:** 'I'm proud of course. Six of my PhDs are working at Xsens. We benefit enormously from the relationship. Their elaboration of ideas continually yields new research questions.' ■

Los Angeles, United States, Italy, France, Ireland, Enschede, Sweden, Germany, Bulgaria, Hungary, East Turkey, Japan, China, Korea and India.

[ chapter 05 ]

# EDUCATION AT MIRA AND UNIVERSITY OF TWENTE

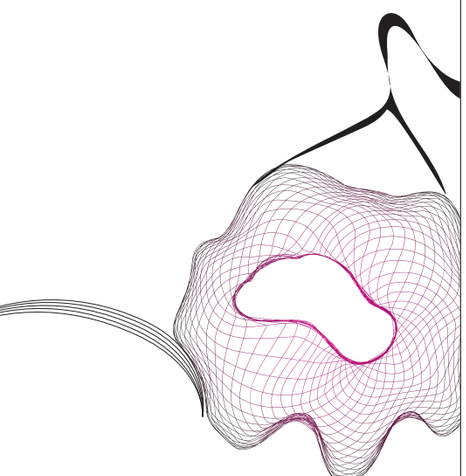
05

# training tomorrow's health professionals

# EDUCATION AT MIRA

AS A RESEARCH INSTITUTE OF THE UNIVERSITY OF TWENTE, MIRA IS A GENUINE ACADEMIC COMMUNITY IN WHICH RESEARCHERS AND STUDENTS INSPIRE EACH OTHER. RESEARCH AND TEACHING ARE CLOSELY INTERCONNECTED: RESEARCHERS ARE ALSO TEACHERS AND SUPERVISE PHD STUDENTS WORKING ON THEIR THESIS OR STUDENTS DOING THEIR FINAL PROJECT.

The University of Twente is an entrepreneurial university. Our students look beyond the boundaries of their own disciplines and across national borders as well. Teaching has both a multidisciplinary and international focus.
MIRA is involved in two degree programmes at the Faculty of Science and Technology: technical medicine and biomedical technology.



## Technical medicine

**PROGRAMME:** Bachelor's and Master's
**LANGUAGE OF THE DEGREE PROGRAMME:** Dutch
**DURATION:** three years for a Bachelor's, three years for a Master's
**PRIOR EDUCATION:** university preparatory education (VWO) with subject cluster nature & technology with biology, or nature and health with maths B and physics
**STUDENTS ARE TRAINED TO BECOME:** health professionals who improve and modernise patient diagnosis and treatment with the aid of technology
**SPECIALISATIONS:** medical signalling, reconstructive medicine, robotics and imaging
**GRADUATES WORK IN:** academic institutes, hospitals, companies

Technical medicine is a young and growing science. Technology has brought about impressive improvements in medical diagnostics and treatment options. It's not only increasing in importance but also in complexity. A new generation of trained professionals is therefore needed: experts who can apply this specific medical technology properly.

## Biomedical technology

**PROGRAMME:** Bachelor's and Master's
**LANGUAGE OF THE DEGREE PROGRAMME:** English
**DURATION:** three years for a Bachelor's, two years for a Master's
**PRIOR EDUCATION:** university preparatory education (VWO) with subject cluster nature and technology, or nature and health with maths B and physics
**STUDENTS ARE TRAINED TO BECOME:** biomedical engineers, capable of designing and developing new technology for the health sector
**SPECIALISATIONS:** human function technology and molecular, cellular and tissue engineering
**GRADUATES WORK IN:** academic institutes, hospitals, companies and engineering firms

The biomedical technology degree programme trains students to become engineers capable of designing and developing new technology to benefit human health. They push back the frontiers of technical possibilities in prevention, treatment and care and they come up with solutions to improve people's quality of life. Areas of application include body-friendly implants, tissue engineering, three-dimensional imaging of organs and rehabilitation aids.

[ extract from the schedule of... ]

HELEEN MIEDEMA

# ‘we have the nerve to take risks’

[ *intro* ] HELEEN MIEDEMA, PROGRAMME DIRECTOR FOR BIOMEDICAL TECHNOLOGY AND TECHNICAL MEDICINE, WANTS TO MODERNISE EDUCATION AND HAS A KEEN EYE FOR DEVELOPMENTS RELEVANT TO THIS. THAT’S WHY HER SCHEDULE INCLUDES SO MANY MEETINGS.

## 7.30 *Breakfast*

'I'm not really a morning person. I'm not grouchy, but I like a quiet start to the day. And with a daughter in Leiden and a son in England, I can have that. My husband leaves for work early, so I have plenty of time to myself.'

## 9.00 *Meeting of MIRA management team*

'Research and education are inextricably interlinked. Good scientists can explain the essence of their discipline to students and encourage

> *'Good scientists encourage students to develop their own ideas.'*

them to develop their own ideas. And the converse is also true. A lecturer is inspired by his or her undergraduates and PhD students. The directors of MIRA believe it is vital to develop a clear line in research and to merge it with education. So, as the director for education I'm also a member of the MIRA management team. Today's agenda includes how we can translate the entrepreneurial nature of scientific research to the teaching programme. The entrepreneurial professors have an important role to play in this respect.'

## 10.00 *On to meeting of the biomedical technology curriculum committee*

'The University of Twente is an entrepreneurial university. That means we have the nerve to take risks. We don't train people through pre-programmed instruction. We aim to develop professionals who take initiatives; so we shouldn't teach them to imitate their lecturers. Instead of a dusty book, we present them with a real-life problem and information; they find the solution themselves. With this we challenge students to get the best out of themselves. We encourage them to come up with their own solutions and keep each other sharp. It's important to recognise this attitude when designing new educational initiatives. The discipline of biomedical technology is constantly developing. So we regularly take a critical look at the teaching to see if the objectives are still being met. These are very stimulating meetings, where a lot of creative ideas are shared.'

## 11.00 *Meeting with a team of educational researchers*

'Working in science is not just a job, it's also an attitude. With technical medicine, we've devised and set up an entirely new degree programme. Now we want to check if we've made valid decisions. So we've made the teaching a subject of research. We're not just exploring the question of what technical medicine students should think and learn; our interests are broader than that. How do people acquire skills? How do you teach people to think creatively? How do you teach them to position themselves? We do this with a team of cognitive psychologists and educationalists.'

## 12.00 *Lunch with anniversary committee*

'An entrepreneurial university is characterised by the relationship it has with the society it serves. Researchers derive their questions from society, and provide it

> *'I experience the University as a collegial environment and a warm nest'*

with answers. So for our 50th anniversary, we want to throw a party that includes our neighbours and shows people what we do. I'm keen to contribute to that.'

## 14.00 *Meeting of the Board of Directors of Medisch Spectrum Twente*

'The Board of Directors of Medisch Spectrum Twente sent me an invitation. They want to modernise the training for anaesthesia assistants. They believe we can play a role in this with the Experimental Centre for Technical Medicine. We already contribute to the Bachelor's and Master's teaching. And in the future we'll play a growing role in postgraduate teaching and in the professional development of various health professionals.'

## 15.00 *Meeting with the secretaries of the biomedical technology and technical medicine degree programmes, Rita ter Weele and Danielle Heskamp*

'Being the programme director of two degree programmes is a challenge. It's only possible with good support. I sometimes joke that they're my guardians. That's putting it a bit strongly. But essentially they contribute to and monitor my schedule. As they know what I'm doing and, more importantly, understand what the various meetings are about, they can be proactive and make sure that what we agree upon happens. This afternoon we're discussing the schedule for the immediate future.'

## 17.00 *Meeting of vocational service committee, Enschede Rotary*

'I'm a member of the Rotary Club. I like the fact that it takes you outside your own little world. I'm on the vocational service committee. Vocational service lies at the heart of the club. What drives people in their work and what dilemmas can they be confronted with? We invite people to come and talk to us about this. It could be a lawyer who can get a rapist off on a technicality, although it conflicts with his own sense of justice. When you're struggling with something in your own organisation, discussing the problem with outsiders can be a breath of fresh air. They can look at it from a different angle. My penchant for broadening horizons fits in well with my job. On a professional level I'm also constantly monitoring what's going on in society. I've noticed that University College in Utrecht is very successful. That makes me wonder if it's possible to create a University College for Engineering here.'

## 20.00 *Housewarming party at Kim's*

'My colleague Kim moved to an unusual house recently. A converted barn, in fact. We're going to celebrate that. I experience the University of Twente as a collegial environment and a warm nest. A psychologist once told me that to be known, recognised and acknowledged as a person is important for your well being. This applies to everyone, both students and staff. I'm trying to create an organisation which puts that principle into practice and respects people's individuality. I tell students and colleagues: "go on, surprise me". You can be yourself, and if you work hard you're also allowed to make mistakes. All you need is the guts to try something. Plodders don't interest me very much.' ■

### [ *who is...* ]

**WHO IS HELEEN MIEDEMA?**

Heleen Miedema (1956) holds a Master's in Educational Psychology from Leiden University. She has held various positions in vocational education and since 1998 she has been developing teaching programmes at the University of Twente. According to her, you can only do this if you have a good understanding of the discipline you're teaching in and the profession you're training for. This means talking to people, listening carefully and inspiring people at the same time. Heleen lives in Enschede with her husband and has two grown-up children.

JARICH SPLIETHOFF

# *Suddenly you find you can save lives*

JARICH SPLIETHOFF IS SET TO GRADUATE IN TECHNICAL MEDICINE. AFTER FIVE YEARS OF STUDY, LOTS OF JOBS ON THE SIDE AND FOUR PLACEMENTS, HE'S ALMOST READY TO MAKE THE BIG LEAP.

**1** *How do you look back on your degree programme, now it's almost finished?* 'Technical medicine is seen as a hard degree programme within the University of Twente: six years, with a timetable of up to eight hours a day. But I've always really enjoyed it, so I didn't mind working hard. The typical technical medicine student is energetic and enterprising; it's no coincidence that I often meet fellow students on committees of student associations.'

**2** *During your placement, was it a shock to suddenly find yourself in a hospital, with real patients, some of whom seriously ill?* 'Yes, but mainly in a positive sense. During my degree, I'd mainly been concerned with solving theoretical problems and doing sums. Suddenly, you realise you can use that to save people's lives! That was a real eye-opener.'

**3** *Soon you'll have graduated. What then?* 'I can see myself starting up my own business some day, once I've had a good idea. But first I want to get to know the medical world a bit better.'

**4** *How has that medical world welcomed you so far?* 'There's a small group of doctors who still have to get used to our role. They sometimes make disparaging comments like: "So you've come to twiddle the knobs then?" But most doctors are surprised about what we can contribute and say that there's an enormous demand for our know-how.' ■





ANA BARRADAS

# *My research is all about two worlds meeting*

ANA BARRADAS CAME TO ENSCHEDE FROM PORTUGAL IN 2006 TO STUDY BIOMEDICAL ENGINEERING. AFTER GRADUATING SHE WAS ASKED TO CONTINUE AS A PHD STUDENT. SHE DIDN'T HAVE TO THINK TWICE!

**1** *What brought you to MIRA?* 'I wanted to take some classes at master's level and combine this with experiencing a different lifestyle. I considered Norway and Sweden but the change in climate would have been too dramatic. Then a friend told me of these two interesting research groups in Twente: Polymer chemistry and Biomaterials and Tissue Regeneration.'

**2** *And how do you like our Dutch lifestyle?* 'Everything here seems to flow far easier than in Portugal. Things are less rigid and bureaucratic. And people are more helpful, both in science and in private life. I fit well into this pragmatic, direct culture. Like most foreigners, it's only the food and the weather I complain about.'

**3** *Was the educational programme also different?* 'Very much so. I was used to seven or eight hours a day of lectures: just sitting back and listening. When I came here, it was two hours of that. The rest of the time, we were challenged to explore what we liked, talk to lecturers and develop our own thoughts.'

**4** *Does that make you a better researcher?* 'Yes it does, provided the lecturers keep you on the right track. Nowadays, you can see a shift to more active forms of education everywhere. Holland is a trailblazer in this respect.'

**5** *What do you want to do after this?* 'I'm torn between academic research and business. Science attracts me because it's challenging and vibrant. Yet I'm also pulled to business because from an almost limitless range of scientific ideas it selects just a few that can change people's lives.' ■

[ chapter 06 ]

# there's more to MIRA than meets the eye!

06

# AT MIRA...

# from 250 to 400

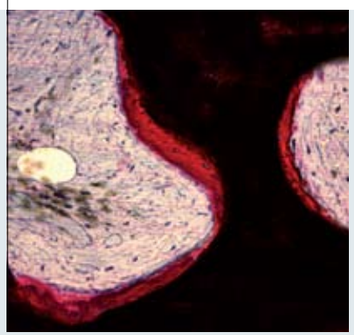
## ...WE REACH FOR THE SKY

Over the next few years we'll expand from 250 to 400 employees.
By 2015 we'll have double the financial resources we had when we started in 2009. MIRA aims for four spin-off companies per year.



## ...WE MAKE THE MOST OF OUR CHANCES

Our project manager Jojanneke Schuiling-Jukes was the first in the world to develop bone tissue from mouse embryonic stem cells. It was a chance discovery and the breakthrough gave her instant fame.



## ...WE LOOK ON THE BRIGHT SIDE OF LIFE

Science should also be sheer fun. That's why MIRA scientists worked together with artist Joris Laarman in creating his incredible 'living lamp'. The so-called Half Life is made out of living hamster cells, which give off a soft glow. They are cells from a Chinese hamster enriched with firefly genes. No hamsters were killed for this 'science meets interior design' project. The cells come from a tissue culture that has been kept alive since 1957. The lamp has been exhibited at several renowned museums and galleries, including some in New York.

## ...WE PRACTICE WHAT WE PREACH

MIRA encourages the commercialisation of technology and sets a good example in this area. Our scientific director professor Clemens van Blitterswijk and professor of Medical Cell Biophysics Leon Terstappen together have more than 100 patents to their names!

## ...WE MAKE PRAGMATIC USE OF SPIRITUALITY

Our head of Imaging & Diagnostics professor Vinod Subramaniam spent two weeks in a monastery. The Indian-born scientist returned speaking fluent Dutch!

## ...WE BELIEVE IN THE MULTI-TALENTED

Our Tissue Regeneration postdoc Lorenzo Moroni has won more than just the European Biomaterials and Tissue Engineering International Doctoral Award 2007 for his PhD thesis. He is also the proud winner of the international '*Voci e Silenzi 2003*' literature prize for his book entitled '*Generazione Erasmus*' about his experiences as an Erasmus student.

## ...THE WORLD IS OUR OYSTER

At the last count, scientists from 22 different countries worked at MIRA. They come from nations such as China, Russia, India, Canada, the United Kingdom, Portugal, Italy, France, Colombia, Turkey and Korea. We collaborate with a large number of foreign universities, sister institutes, research centres and companies. They include: Medtronic (Fridley, Minnesota), MIT (Massachusetts), Imperial College (London), University of Oxford, University of Chicago, University of Washington and Harvard University. Each year the Technical Medicine student group Paradoks makes a study trip to a far-off country. For example, they recently visited Tokyo.

## ...WE START YOUNG

Our robotics professor Stefano Stramigioli built his first alarm when he was just five years old.
Of course he needed a few more years to build his first complete robot. By then he was 17. He got the robot to pour a glass of water for the graduation committee of the technical school he attended before university.

# 70+

## ...AGE IS IRRELEVANT

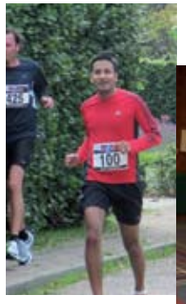
Our Medical Director Peter Vooijs is well into his 70s and therefore our oldest member of staff. In his scarce leisure time he enjoys fixing up old boats.

▶ CONTINUED ON NEXT PAGE

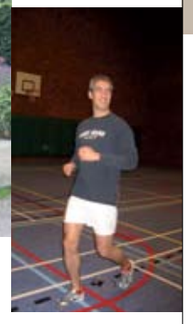
# AT MIRA...

## ... WE LIKE TO KEEP FIT

Some of our dedicated runners are assistant professor Control Engineering Sarthak Misra, postdoc Hugo Fernandes and (barefoot running!) PhD student and ironman Jetse Scholma. Scientific director Clemens van Blitterswijk is celebrated for his marathon running (goal: less than three hours).



Hugo Fernandes



Sarthak Misra

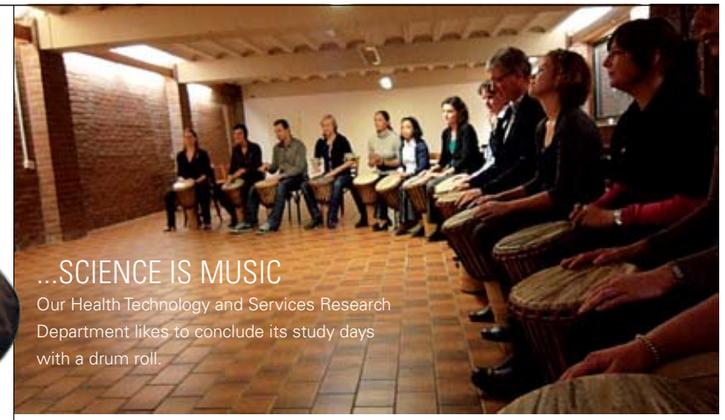
Physiology teacher and researcher Benno Lansdorp plays top level volleyball (including beach volleyball).

Associate professor Membrane Technology Dimitrios Stamatialis (besides cooking excellent Greek food and being elected teacher of the year at the University of Twente in 2008) was a basketball top scorer in Athens.


PhD students Nathalie Groen and Joyce Doorn from Tissue Regeneration are fanatical women footballers.

Martin Piest from Biomedical Chemistry combines his PhD research with the martial arts. He's a Jiu Jitsu instructor with a second level Dan. Furthermore, he's directed a 75-minute martial arts movie.

## ... WE HAVE A LIFE OUTSIDE THE LAB TOO



...SCIENCE IS MUSIC

Our Health Technology and Services Research Department likes to conclude its study days with a drum roll.

Assistant professor Jeroen Rouwkema collects spiders and reptiles. His collection includes two rattlesnakes and one hog-nosed snake.

PhD student Hans van der Aa loves old houses and completely restored his 1902 home in just three years.

Assistant professor Bert-Jan van Beijnum of the Biomedical Signals and Systems Group runs a dog kennel together with his wife.


Assistant professor André Poot of the Biomaterials Science and Technology Group restored a classic BMW car so well that a renowned car magazine featured him.

## *Would you like to join us?*

MIRA is young and growing fast! We're always on the lookout for talent. Can you help us to realise the following ambitions:

- excel academically
- provide top technology for patients
- create economic value to speed up the availability of innovations

And would you like to work in an international, vibrant, performance-oriented atmosphere, with lots of hard work but also plenty of fun? Then please get in touch.


# MIRA

BIOMEDICAL TECHNOLOGY
AND TECHNICAL MEDICINE

**WEBSITE** www.utwente.nl/mira | **TELEPHONE** +31 (0)53 489 3367
**FAX** +31 (0)53 489 2319 | **EMAIL** mira@utwente.nl
**VISITING ADDRESS** University of Twente, Building Zuidhorst
Room ZH 116, Enschede, The Netherlands
**POSTAL ADDRESS** University of Twente, Building Zuidhorst
P.O. Box 217, 7500 AE Enschede, The Netherlands

UNIVERSITY OF TWENTE.

## *Credits*

**PUBLISHED BY** G+J Corporate Media on behalf of University of Twente, MIRA Institute for Biomedical Technology and Technical Medicine

**PUBLISHER** Petra Schuttel

**EXECUTIVE EDITORS** Marcel Hammink and Martijn Kuit

**DESIGN** Sjoukje Kloostra, Amsterdam

**TEXT** Edo Beerda, Nienke Beintema and Mariette Huisjes

**EDITOR IN CHIEF** Mariette Huisjes, Amsterdam

**INFOGRAPHICS** Steffie Padmos, Schwandt Infographics, Houten

**PHOTOGRAPHY** Marsel Loermans, De Beeldredactie, Evelyne Jacq, Jaap Spieker, Nanodialysis BV, Progentix, Walt Disney Studios Home Entertainment, Joris Laarman studio, NOS.
And also the professional and personal archives of MIRA staff

**PRINT** Italy



G+J Corporate Media
www.corporate-media.nl