Harald Schmidt

# Radical medicine:
## smart drugs to save the brain

**By Loek Kusiak**

A drug that halts the breakdown of neurons after a stroke, diagnostics that detect hypertension before blood pressure rises, and an imaging technique that localises vascular disease even before symptoms occur. This is the work for which Professor Harald Schmidt, MD, PhD, has been awarded a European research grant worth € 2.3 million. Schmidt specialises in researching vascular diseases at Maastricht University (UM), and with this new grant under his belt, further breakthroughs may be just around the corner.

Cardiovascular diseases are the leading cause of death worldwide. And stroke is a particular problem – there is only one drug available to treat a stroke, and it has so many side effects that 90% of patients go without. "We simply need more and better drugs!", says Schmidt, vascular diseases researcher, pharmacologist and UM professor of Personalised Medicine. An important risk factor for a stroke is high blood pressure, which – for those who survive – often results in partial paralysis. "But we can explain at most 5% of the causes of high blood pressure", says Schmidt. "In the other 95% of patients we have no idea what's causing their high blood pressure – and thus no clue how to treat it."

"You can compare high blood pressure with a car that's going too fast without the driver realising his foot is on the accelerator. The drugs currently on the market put the brakes on, but without releasing the accelerator. Which is not the smartest way to reduce a car's speed. What's more, it appears that different patients also have different kinds of accelerators. The challenge is to find a diagnosis and treatment that blocks the individual accelerator for cardiovascular diseases in each different patient."

For his efforts to prevent and treat cardiovascular diseases, Schmidt, a German national, received an ERC Advanced Investigator Grant in 2011. This is the most prestigious European research grant, awarded by the European Research Council to individual scientists engaged in exceptionally innovative research. "I'm incredibly thankful to my peers. You pretty much need a triple-A rating from everyone who reviews your work to make it. I know my research is risky, but it's so exciting to think of the potential benefits."

**Top research**

Particularly gratifying for Schmidt is to have received almost the maximum possible amount of the grant. This allows him to supplement his international team with top recruits and cutting-edge equipment. "All of this underscores that fact that UM really is on the international map. This was also why Martin Paul attracted me to Maastricht from Australia two years ago. I like to work in stimulating environments and focus my research on topics of societal relevance. The importance of the patient and interaction with excellent clinical researchers is paramount in my work."

In 2010, Schmidt demonstrated this importance with a groundbreaking discovery. With his combined Dutch/German research team, Schmidt discovered the NOX4 gene which, during a stroke, produces the reactive oxygen compound hydrogen peroxide (used in bleach and other highly reactive chemicals). This causes neurons to break down in a process known as *oxidative stress*. "This gene was identified ten years ago in the kidneys," says Schmidt, "but back then no-one knew that it would exacerbate the brain damage after a stroke. We were able to demonstrate this by way of gene deletion."

**Promising approach**

Tests on mice with a new drug were shown to halt the production by the gene NOX4 of oxygen radicals during a stroke. The reduction in brain damage was significant, even when the drug was not administered until hours after the stroke. According to Schmidt, this is the "most promising new therapeutic approach" for stroke. For this finding, he was also nominated for the Huibregtsen Award of the Science and Society Evening Foundation in 2011.

"We've also applied for a patent and have been forming agreements with pharmaceutical manufacturers to validate and develop this principle, for example by finding even better compounds or other indications", says Schmidt. It doesn't hurt that all major patents on drugs for cardiovascular diseases have now all run out. "There's been no real innovation in this area for over 20 years. So this medical need drives innovative, fundamental research on new drugs that is just starting to take off."

**Personalised medicine**

Thanks to the ERC grant, Schmidt can set up a broad, five-year follow-up study on the treatment of cardiovascular diseases and the development of new drugs. Oxygen radicals probably contribute to the cell damage in diseases such as Alzheimer's and Parkinson's too, meaning that any new drugs developed may also be used in fighting those diseases. And in addition to this hypothesis-driven research, Schmidt will be able to 'go fishing' for new and unsuspected disease mechanisms. Besides new mechanism-based drugs, this could involve a new diagnostic chip and imaging techniques that allow diseases to be detected at much earlier stages. "The holy grail of medicine now is, for every patient, to find the right drug, at the right time, in the right dose."

***Harald Schmidt***

*Harald Schmidt (1959) did both a medical and a pharmaceutical degree, and is now an international leader in cardiovascular pharmacology and drug discovery. In the lab of the later Nobel laureate, Ferid Murad (USA), he elucidated the biosynthesis of a new vascular factor. His work has led to about 200 publications, numerous patents, two compounds that are now in clinical development, one diagnostic on the market, and two spin-off biotech companies. He has worked as a professor, head of department, centre director and adjunct dean in the USA, Germany and Australia.*

Michael Jacobs

# First Euregional graduates of vascular surgery

**By Loek Kusiak**

The privatisation of healthcare demands that education, research and medical practice all be clustered under a single umbrella. To this end, the Maastricht/Aachen region aims to be a top European centre in the field of cardiovascular diseases. This is the mission of cross-border "quartermaster" Professor Michael Jacobs, head of surgery at the Maastricht academic hospital (azM). "As a hospital, you can no longer afford to go it alone."

On Wednesdays and Fridays, at dawn and weather permitting, the cardiovascular surgeon gets on his racing bike in Maastricht and crosses the 30 kilometres of hilly terrain to the University Hospital Aachen. Then, after a long day in the operating theatre, he gets back on his bike for the return trip to South Limburg. "It's nice to get 60 kilometres' worth of physical exercise, and time to clear your head and think. Golf, my other addiction, gives you no time at all to think about work. Because if you're not concentrating you won't hit the ball well." For the rest of the week, Jacobs (1957) works in the

Maastricht UMC+, directing the surgery department and the Cardiovascular Centre. "In Aachen I'm primarily a doctor; in Maastricht I'm more of a manager and lecturer. When I worked at the Amsterdam Medical Centre I used to lecture as well. I still really enjoy that, as well as passing on operating techniques to surgeons."
Jacobs's life as a Euregional, cross-border physician, scientist and director began around 2005, when the azM and the Aachen hospital decided to establish a joint training institute, the European Vascular Centre. Under Jacobs's direction, the centre aims to become a full-blown hospital with its own intensive care unit, recovery rooms and operating theatres at the Avantis business park, on the border of Heerlen and Aachen. "We have to respond to market forces in healthcare and be conscious of our costs", says Jacobs. "The trend is to move from traditional academic hospitals to networks in the form of centres of excellence. If the azM were to go it alone, in ten years you'd no longer have a leg to stand on."

**Volume**

In the Netherlands alone, more than 40,000 people still die from cardiovascular diseases each year. This amounts to over 30% of total mortality nationwide. Hard figures like these underline the importance of high-quality cardiac care. Jacobs: "By collaborating with Aachen we can create volume, which will make us number 1 in the Netherlands. And by volume I mean: doing many operations. Lots of experience means you end up with fewer complications. That's when we talk about top referral care. Health insurers don't want to pay for anything less."
Because Aachen's vascular surgery unit was not an academic department before 2005, Jacobs was asked if he wanted to set one up. "It seemed like an exciting challenge, which I took on together with three experienced vascular surgeons and five junior surgeons. In 2006, the departments of vascular surgery in Maastricht and Aachen were assessed according to the German criteria for certified vascular centres. The treatment protocols in the two hospitals are now identical, and we've set up a single database of international publications on operations and patient groups."

**Milestone**

Under Jacobs's direction, this year the European Vascular Centre produced four German junior surgeons who were trained in Aachen. "They're now working in German hospitals. But the training requirements between the two countries are still very different. Junior surgeons in the Netherlands who work in a German training clinic don't get that period recognised as training time. The Dutch assessment system doesn't review or accredit German programmes. Conversely, for junior surgeons in Germany the time they spend training in Maastricht or elsewhere in the Netherlands does count. So we also have many junior surgeons from Germany in the Maastricht hospital. For the Vascular Centre to keep on developing, the German and Dutch training requirements and diplomas really should be better geared towards one another. 'Brussels' has a lot more homework to do in that regard. Funnily enough, I also had to retake the surgery certification exams before I could operate in Aachen."
Despite the red tape, Jacobs is witnessing a continuing increase in the dialogue with German colleagues, including at a scientific level. "For example, they're strong when it comes to developing biomechanical equipment, while together with CARIM we're doing good research on cardiac arrhythmias, processes of atherosclerosis and so on. The German work environment is more hierarchical, whereas consultation and participation are more important for us. So it does take some time to find the middle ground between the two cultures."

**Sophisticated techniques**

Jacobs trained with the late Co Greep, a renowned Maastricht surgeon, and in Houston, the Valhalla of cardiovascular surgery. He specialises in surgery for aortic aneurysms (dilation of the artery). "When an aneurysm ruptures, which often occurs in the abdominal aorta, this can lead to life-threatening bleeding and death. We know next to nothing about how aneurysms develop; they're like a black box. On average, there's a 30% chance of losing the patient during the operation, and a high risk of complications even if they do survive. Our surgeons in Maastricht and Aachen have been able to reduce that risk using highly sophisticated surgical techniques, giving us the best results in the world. If I can give a 25-year-old with an aneurysm another 25 years of extra quality of life, it gives me a real kick." Still, Jacobs calls for more attention to be paid to the prevention of cardio-vascular diseases. "Once a cardiovascular patient, always a patient. Doctors are on the damage-control side. Everything we do is secondary prevention. Patients who've suffered a brain haemorrhage are given all sorts of regimens and measures to lower their cholesterol. This can help you dramatically reduce the chance of a second haemorrhage. But of course, prevention and early detection of these diseases, which are often hereditary, ultimately have more effect."

*Professor Michael Jacobs (1957) completed his medical studies in 1982 in Maastricht. He then worked at the Maastricht academic hospital and the Texas Heart Institute in Houston. In 1993 he became head of vascular surgery at the Amsterdam Medical Centre. Since 2000 he has been head of surgery at the Maastricht UMC+, and since 2005 he has also led the vascular surgery department at the Aachen University Hospital. Jacobs pioneered the European Vascular Course, an annual conference with top speakers, lectures and demonstrations of new surgery techniques for heart and blood vessels.*