

# A breath of fresh air in cardiovascular research

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**Prof. dr. Judith Sluimer**

Faculty of Health, Medicine and Life  
Sciences

A fresh breath of air in cardiovascular research

Dear pro-rector, family, friends, and colleagues it is a great pleasure to welcome you today to my inauguration. It is exactly 15 years and one day ago since I was last standing here doing my PhD-Defense. At least today there is no crossfire of questions.

My research over this time has led to my appointment as professor of cardiovascular pathophysiology. These last two words mean that I study the heart and blood vessels, in health and disease.

I have given my inaugural lecture the title “a breath of fresh air” for two reasons. First, the title refers to the air that blood vessels transport. Second because of its metaphoric meaning. Someone or something that is new and different and makes everything seem more exciting. I believe this is important for research. I will discuss both meanings in this lecture.

Phew, that sounds like a lot. It certainly calls for getting out for a breath of fresh air right now, doesn't it?. I certainly would not mind escaping this auditorium at this moment.

What do you imagine when you think of getting a fresh breath of air?. For me, it is a walk in the rolling hills around Maastricht, the openness of the grassy meadows reaching the horizon around Gouda, the place where I grew up or standing on top of a snowy mountain range. Like here in the Rocky Mountains in the USA, which I visited this spring. Funny though, because although my mind thought the air was fresh and invigorating, my body did not agree. Why is that?

The amount of oxygen, O<sub>2</sub>, in the air is much lower in the mountains, than here at sea level. If you go to high altitudes too quickly, your body does not have time to adapt and cope with these low levels. You can even

develop high altitude sickness, which is not fun, I can personally assure you. Why do not you take a short moment to hold your breath and experience the importance of oxygen

It soon gets a bit uncomfortable, doesn't it?. It's good I did not keep my breath, while waiting for this ceremony to take place, since my appointment as professor happened 2.5 years ago.

The lack of oxygen is ultimately life threatening, and we all have seen examples in our life. Small, like a child nearly suffocating in a piece of orange, or spinach leaf. Or more serious, like a stepson swimming too long under water, which stopped his heart beating. Thankfully, these events all ended well, as oxygen supply restarted and Jasper, George and I are still her.

Oxygen is essential for all organs in our body and the cells they are made of. Cells need oxygen to produce the energy they need to perform their functions. Muscle cells in the heart need it to contract and pump blood around the body, immune cells need it to remove unwanted things, like bacteria or lipids. For anything and everything actually. How does oxygen reach all these cells?

Through the cardiovascular circulation. A closed system of the heart, and blood vessels. Blood passing through the lungs will receive oxygen, and is transported with every beat of the heart towards the rest of the body in arteries. After delivering oxygen, blood is transported back to the heart and lungs via veins to start another cycle.

So, in addition to oxygen, a healthy, functional cardiovascular system is needed to keep us healthy. There are several threats to this system, making it function less. These threats include ageing, smoking, no exercise,

and an unhealthy diet, leading to high cholesterol and sugar levels in the blood. I will explain for some of these threats how they change the function of blood vessels.

In young people, blood vessels are elastic. The blood exerts a certain amount of pressure on the vessels, the blood pressure. With age, connective tissue, bindweefsel in Dutch, builds up in our arteries, making them stiffer. The reduced flexibility increases blood pressure. Imagine pushing the same volume through a stiffer tube. It simply requires more pressure. High blood pressure in turn increases the risk of developing atherosclerosis. Atherosclerosis is the disease of the blood vessels causing a heart attack or stroke. To prevent this disease, we need to know more about the development atherosclerosis. I will tell what we already know.

Here you see a drawing of the heart and a cross-section of the blood vessels that supply oxygen to the heart muscle. The artery consists of three layers, the intima with endothelial cells lining the vessel, making sure the blood does not clot. The media with smooth muscle cells. If these contract or relax the vessel will become smaller or bigger, regulating the blood pressure. And the adventitia, with nerves, fibroblasts, which are cells that produce connective tissue, and miniature vessels for oxygen supply of the media. An unhealthy diet increases cholesterol in the blood, which will enter the vessel wall. There it will trigger immune cells, like macrophages here in blue to remove the cholesterol deposits. The contractile smooth muscle cells from the middle layer migrate into to the plaque and deposit connective tissue. A thick cap of connective tissue, here in purple, shields the plaque from the blood, to prevent the blood from clotting. We call this

build-up of cells and cholesterol a plaque. With time the plaque grows, narrowing the area where blood can flow through. But more importantly, the connective tissue is degraded by macrophages, and both muscle cells and macrophages die, leaving a graveyard of cell debris, here in in yellow. We call this graveyard the necrotic core. These advanced plaques can rupture at the site of a thin cap, causing the blood to clot. If this blood clot or thrombus is very large, it blocks blood flow. The heart muscle will no longer receive oxygen. This is a heart attack. If this would happen in your carotid artery, a stroke will occur. These advanced plaques without a thrombus come in two flavors, a stable plaque with a lot of connective tissue, and a thick cap, and unstable plaques with many macrophages and a large necrotic core. The plaque on the right has a higher risk to rupture. The main aim of scientists in my field is to discover how we can stabilize plaques. This was also the goal of my PhD-project. But, the approach we used to do that changed completely, when my project turned out to be technically impossible. Luckily, my promotor Mat Daemen was an experienced supervisor and had a back-up project. For this project, he sent me to the lab of Dr. Jean-Marie Gasc in the College-de-France in Paris for 3 months. Not a bad deal, right?. It turned out the back-up idea was not supported by the data I gathered, so that project went down the drain as well.

Challenging times I can tell you. Here I was with all my hard work and ambition and 1.5 years into a 4-year project, and I had nothing. But every cloud has a silver lining.

Jean-Marie was a thinker, a very curious scientist, who never worked with human arteries before. He wanted me try one of his probes on the arteries I brought. This probe detected the oxygen-sensor HIF. This was the first time HIF was detected in human plaques. So, JM's curiosity sparked my interest in this oxygen sensor, and with coaching of Mat I developed my own project to focus on the function of this novel process in atherosclerosis. To explain what we investigated, I will first need to explain the function of HIF in the biology of cells. The three scientists who discovered how HIF worked received the Nobel prize in 2019.

Here, you see a schematic of a cell with its nucleus. Our genetic material DNA is contained in the nucleus. This DNA holds genes that encode for all building blocks in our body. This not only determines the color of your eyes, but also the function of a cell. HIF can modify the amount of certain genes, and change how a cell functions when there is little oxygen

In normal oxygen conditions, HIF is modified by enzymes, called prolyl hydroxyl domain or PHD protein. The addition of a hydroxy group will lead to degradation of HIF. These enzymes need oxygen to work properly. In hypoxia, these enzymes no longer work, and HIF will bind to the DNA and trigger changes in genes to reduce oxygen demand and increasing supply.

Thanks to JM we knew HIF was present, but not why. Was there hypoxia in plaques? So we first set out to detect this lack of oxygen in human atherosclerosis. As plaques in the carotid artery of the neck are removed in patients with symptoms, we often use these tissues. We started a collaboration with the vascular surgeons, like Geert Willem Schurink, Jan

Willem Daemen, and more recently Barend Mees. I am still very happy with this great collaboration.

Before surgery, we gave patients a tracer to mark hypoxia in cells, and processed the tissue in the lab to detect hypoxia. Under the microscope, hypoxic cells will appear with a brown color. After all these steps, I was very impatient and eager to see the results. You can imagine how excited I was, that I indeed saw a brown signal. Plaques were indeed hypoxic. This is a cross section of an actual human plaque. This was the original lumen, where blood flows through, and these brown areas are cells experiencing hypoxia. Plaque hypoxia was related to plaque instability, and to consequences of HIF signaling, such as the presence of miniature vessels. I studied these micro vessels further during a work visit to the states to Dr. Renu Virmani, iron lady of CV pathology. I was very pleased that all this work gave me enough data to finish my PhD in 2008.

Thinking about my next job, I wanted to get trained more in the biology and function of macrophages. Because we noted that it was mainly the macrophages that were hypoxic. I went to New York City to work on macrophages in the lab of Prof Ira Tabas at Columbia University. I was funded by a Rubicon grant of the Dutch research council NWO, and a Kootstra talent fellowship from Maastricht University. It was a good thing I was paid in euros and the dollar was low, so we could enjoy all aspects of life in the city. An excellent time and training. Although professionally, it was a tough and very competitive environment, I still use many insights I gained during that time.



Coming back to the Netherlands, Mat hired me as a postdoc in the Parisk consortium to collaborate with Eline Kooi, Joachim Wildberger, and Felix Mottaghy. We used advanced imaging tools, such as PET, CT, and MR to detect hypoxia on scans of patients without the need for surgical removal. The blood vessel in this MRI image is outlined by the dotted lines, and the turquoise signal over here indicates hypoxia. By now I knew for sure that hypoxia was there, but still had no clue what effect it had on the development of atherosclerosis. Was it a consequence or a cause of atherosclerosis, that we could use to treat the disease?

That was the main aim of my group for about 10 years. With funding of a VENI early career grant from NWO, I deciphered the role of oxygen, hypoxia and the PHD enzymes in the development of atherosclerosis by changing the amount of oxygen supply, increasing oxygen signaling, and blocking oxygen-dependent processes. Jenny de Bruijn, and Renée Tillie explored the consequences of hypoxia, like the malformation of microvasculature, changes in energy production without oxygen (glycolysis), and processes to recycle building blocks, like chaperone-mediated autophagy. This work was funded by the Leducq foundation and a senior postdoc grant of the Dutch Heart Foundation. It was a great collaboration with Ana Maria Cuervo in the US.

Today, I will highlight the work on oxygen and PHD signaling in more detail. The first quick and dirty approach I took was to increase oxygen supply in an animal model of atherosclerosis using a gas with an extremely high oxygen content. We compared mice breathing this gas with 95% O<sub>2</sub> to mice breathing normal air with 21% oxygen. This prevented plaque hypoxia

and plaque instability. Here you can see a tissue section of mouse atherosclerosis. The white areas indicate the graveyard area, the necrotic core. With this purple overlay of the tissue, you can see there is a smaller white area, and necrosis in mice breathing high oxygen. When we quantified this in all plaques, there was indeed less necrosis. This study showed that hypoxia was causal in the development of atherosclerosis.

We next tried a more sophisticated method by focusing on the enzymes modifying HIF. The PHD enzymes. Elke Marsch, Thomas Theelen and Jasper Demandt blocked the PHD sensors in all cells of the body, using what we call a KO mouse. We received these mice through a collaboration with Peter Carmeliet in Leuven. These mice have exaggerated hypoxia signaling, as if they are experiencing hypoxia, even if oxygen is present. They showed unexpectedly that blood cholesterol levels were much reduced in the absence of the PHDs. This blocked development of atherosclerosis in our experimental models. Others showed that drugs blocking the PHD oxygen sensors also reduced cholesterol levels in humans as an unexpected, but positive side effect. Perhaps a new drug to treat atherosclerosis?

As I said before, it was mostly macrophages that were hypoxic. Kim van Kuijk, Jasper Demandt and Thomas Theelen studied the role of PHDs, specifically in macrophages. We studied atherosclerosis in mice that missed PHDs only in the macrophages. We compared them to mice with PHD in their macrophages. When Marion Gijbels our animal pathologist looked at the plaques under the microscope, she was struck by the enormous amount of connective tissue. To find out why, we studied the macrophages and smooth muscle cells in the plaques. We know these are normally

responsible for the accumulation of connective tissue. But, these cells did not show differences between mice with and without PHD. To dig a little deeper, we set-up an assay to measure connective tissue production by cells in culture. Kim cultured the macrophages with PHD in green and without PHD in red. During culture, macrophages secrete mediators in their culture medium. These mediators are used to communicate to other cells. Kim transferred the medium with these signals to smooth muscle cells and fibroblasts. She then measured if this communication changed connective tissue accumulation. Fibroblasts given the red medium, of macrophages without PHD, made more connective tissue. But smooth muscle cells make the same amount of connective tissue in red or green medium. This suggests that fibroblasts, but not smooth muscle cells are responsible for the increased connective tissue in the plaques.

To find out what mediator could be responsible, we looked at the genetic material of the cells. Changes in genes change the amount or type of signals. Javier Perales and Julio Saez from Heidelberg performed a clever analysis. They compared changes in the genes expressed by the sending macrophages, together with changes in genes by the receiving fibroblasts. This analysis predicted that enhanced secretion of osteopontin by macrophages caused the increase of connective tissue in fibroblasts. We showed that their prediction was true in mouse and human plaques. We used two large studies of human plaques to compare the genetic material of stable and unstable plaques. We used the Maas-HPS cohort from my colleagues Erik Biessen, and Han Jin, and the BIKE cohort in collaboration

with Ljubica Matic from Karolinska. These important resources have and will make sure our work is relevant for the patient, not just for mice.

Our chance finding of the communication between macrophages and fibroblasts intrigued me. At the time, nobody had detected fibroblasts in plaques. They were just known to reside in the outer layer of the vasculature. The adventitia. When we tried to detect fibroblasts in plaque, we could not distinguish them from the smooth muscle cells. The markers that others had used until then, were also expressed by smooth muscle cells. We needed better markers to identify fibroblasts. We found better markers using a new technology, called single cell sequencing.

With this technique you are not looking at a soup of all cells of the vascular wall and a mix of their genetic material, but you look at the individual ingredients, or genetic material of the cells one by one. You could say we created a fingerprint of each cell. This work by Kim, Ian McCracken, and Renée Tillie, was started thanks to my affiliation with Edinburgh University. My team performed the experiments in collaboration with Andy Baker and Neill Henderson in Edinburgh, Rafael Kramann's lab in Aken, and Leon Schurgers's lab in Maastricht. Funded by a next career grant from NWO, the VIDI, we are now deciphering the function of fibroblasts, and the new markers in healthy and diseased arteries.

This again led to a new and exciting avenue of studying ageing of the blood vessels, vascular ageing, and high blood pressure. One of the fibroblast markers had no known function in the vasculature. Lower levels of the marker in humans are associated with ageing and high blood pressure. To prove that loss of the marker is a causal to the development of

hypertension, Sebastiaan Asselberghs, Dizar Kheder, and Baixue Yu used mice that lack the marker. They found that old mice actually feel older without this marker. Their blood vessels are less flexible, and they have a higher blood pressure.

By now you may start to shift in your seats. Aging? That is not for me. I do not feel old. To be fair, I do not feel old either, but I am starting to need some therapy for ageing. I am always looking for my phone, wallet, or keys. I can always find them, so they are not lost. I just cannot find them straight away. This has been fixed by an age-therapy from my team: they gifted me a GPS tracker with an iPhone app. To be honest, I do not need one tracker, but several.

Of course, this is a minor issue, and effects of diseases associated with old age are more severe. We all want to *grow* old, but we do not want to *feel* old. I used to shrug off this quote by my grandmother, but I have since realized its truth. The world health organization shows that we indeed get older and older, but we do not stay healthy. Our health span is shorter than our life span. You may think there is no solution: I cannot change the date I was born. This is true, but we can change our *biological* age. The biological processes that change with ageing can be modified.

My vision of the future is to change the vascular effects of ageing. I will aim to rejuvenate the blood vessels, making or keeping the vasculature healthy for a longer period. With this approach I hope to increase the time we live a healthy life, making us feel young into old age.

After this first part on blood vessels, I have come to the second topic of my inaugural lecture. I would like to address the metaphorical meaning

of that breath of fresh air and its importance for scientific research in general. A breath of fresh air means finding a source of innovation and excitement. Great science brings something new and exciting to existing knowledge, be it a small or a giant innovation. I believe this can only be done if there is a continuous source of innovation and excitement of the scientists. How then can we obtain that fresh air?

The concept that unites this in my opinion is diversity. A wide variety of different people, experiences, views, tools, or approaches stimulates innovation. This diversity concept is close to my heart for many reasons, Not in the least as I am still recognized as different to the local population. Even after 28 years, Even though I make a mean Maastricht stew, or zoervleis. The way I speak with a hard G differentiates me from the locals, who speak Maastricht dialect. But you know, I am a “Maastrichtse”, I am just a little different.

On a more serious note, being different, diversity, should be part of various aspects of science to keep academia healthy. Diversity in people when composing teams, consortia, and management, but also in the types of research stimulated by policy makers. Research can be roughly categorized as clinical or preclinical research. Clinical research focusses on diagnosis or treatment of people with a disease. Preclinical, or basic science studies how exactly a healthy person develops a disease. More and more, funding agencies try to push researchers to focus on clinical science. To avoid animal research. To focus only on predefined topics without free choice what you investigate. There are advantages to this, like focusing more money and efforts in one area to push it forward. But they seem to

ignore there are also disadvantages. Certain things can only be tested in animal models, as testing in people might be harmful. And simple cell cultures do not represent the full complexity of a living being. Of course, the benefit of these experiments *is* and *should* be weighed carefully against the discomfort of the animals. Any innovation in animal-free testing should be used *before* in vivo animal studies. I had to pleasure to work with Erik Biessen on such alternatives, like the Macroscreen developed and tested by Lieve Temmerman, Margaux Fontaine, and Adele Ruder. Now, this is being adopted for vascular fibroblast by Baixue Yu and Lieve. A good example of basic science.

Basic research without predefined topics is usually the source of ground-breaking, or disruptive, new inventions. Less freedom and money for basic research is a threat for innovation. Indeed, disruptive science has generally diminished over recent years as shown by a study in the journal Nature this year. The average disruption of papers declines in all areas of research, likewise for patents. The absolute number of disruptive papers does remain stable, but we just publish so many more papers than before. The authors further show that the decline is also due to the focus of scientists on a much smaller area. Super specialization and publishing many, lower quality papers increases the chance to get funding. But, it reduces innovation. I suggest Universities and funding agencies to allow researchers time to think and read, to focus on quality, and to allocate more funding to basic research with a free choice of topic.

In addition to diversity in funding, diversity within teams is important. Team diversity will foster a healthy academic environment. Fresh input of

new team members with a different cultural or educational background, different age, sex, or gender brings new ideas, and ways of working. The German university system actively stimulates changing university before becoming a full professor. In my opinion, employing scientists and management from outside the university helps to revive existing systems. This has certainly worked for the previous and current rector, and the faculty's university professors. Of course, it is not always easy or possible to change institutes. My personal circumstances prevent me now from relocating. But I can use my honorary position in Edinburgh for new input to stay fresh. As you will know my husband Andy has his main job in Edinburgh, and we work in both places. Andy and I are pretty complimentary. In life and science. This resulted in several joint grants, joint papers, and my co-supervising of two Edinburgh PhD students, John Hung, and Francesca Vacante. It also introduced me to single cell sequencing, this new technology I described earlier. This certainly contributed to getting the VIDI career grant.

These facts make it seem so obvious to stimulate diversity. Still I see it being ignored, leading to loss of diversity. Until recently national consortia, such as CVON or OncoCode, included only the same incrowd, ignoring what younger scientists or those located outside the Randstad can offer. To receive a certain heart foundation grant, I was required to connect with existing consortia. But some consortia refused to open up. "We already stimulate our *own* talent" is what I heard. For sure no breath of fresh air, no diversity, and potentially damaging for innovation. At the same time this is also damaging for the motivation and career of young scientists. Particularly



in the already tough funding climate. This is due to the low budget for scientific research in general. The low budget leads to many people applying for the same grant. So, for every ten grants I write, I might receive one. Might. Since this costs me at least two-three weeks each, I waste up to 20 weeks. Excluding holidays, this is 50% of my yearly effort. So much wasted time. Do you know any other business allowing such inefficient use of resources?

You can imagine this wasted time puts pressure on people, as we still must fulfil so many duties and criteria. We need to acquire funding, write papers, supervise students, teach, review other people's papers, grants and PhD-theses, be an active part of the scientific community in our own institute, but also internationally by being member or chair of councils, editorial boards, or societies; we need to present our work at national and international meetings, preferably upon personal invitation, organize meetings, post on social media, reach out to the general public, read other people's work, think and plan experiments, all this while going through at least a 100 emails a day. I need some air!

Like I mentioned earlier, we really need more time to think, and read. Thankfully, I am very efficient, and the support and freedom that Axel zur Hausen and Erik Biessen give me is crucial for my life-work balance. They let me plan my working hours flexibly. I can spend quality time with my kids in the week they are with us, and work more in the week they are not. And thankfully, I really like this job. I just love interpreting graphs, coming up with my own ideas, and when I am so lucky to get them funded, I can

actually bring them into practice. All, while working with a bunch of motivated young people and skilled colleagues. What is not to love?

However, I do feel the pressure too. And I see both peers and younger scientists turning away from academia. It seriously depresses me, and I call for a change to increase resources for science and an open scientific community embracing diversity.

This call for diversity is already being pushed by the nationwide initiative to redefine the recognition and reward of academics. This initiative led by the chair of the University board, Prof. Rianne Letschert, recognizes that people have different talents, cannot excel in all tasks, and wants to ensure that good teachers and teamplayer feel rewarded. I am chair of the committee that advises the Dean on promotions. In the last 3 years, we adapted the promotion guidelines to pave the way towards this new policy. We focus more on quality of accomplishments. We keep an open mind for non-standard career tracks. This year, the new career policy is implemented, led by vice-dean Stef Kremers, our pro-rector today. The latest, long discussions in our committee show it has not become easier to formulate an advice. The balance between an individual's CV and faculty standard is ever more complex. The committee takes great care and time to evaluate the career and accomplishments of nominees. We are dealing with our colleagues and want to avoid unnecessary damaging effects of a negative advice. However, quite often we evaluate CVs where it is clear that a lack of mentoring has not prepared colleagues for a next job function. Their disappointment when not promoted, could have been avoided. I urge both head of departments and colleagues looking to be promoted, to

carefully discuss talents, accomplishments, and career development. This will be an important task for the new development boards to mentor each scientific employee. If the new policy is able to stimulate people feeling rewarded, and to increase diversity, is something we will see in the coming years.

In my opinion, mentoring, like in the development boards, is a good solution to prevent young scientists to leave academia and keep diversity. Thankfully, I had some good role models and mentors. As a new PhD-student, I thought having a successful academic career as a women meant I should *not* have children. How could I combine the long hours, and travel abroad with family life? Women showing me it *is* possible to do so, were Esther Lutgens and Sylvia Heeneman. Now, I try to be a good example for young scientists, sharing that I am a mother as well as a scientist in career talks for the MSc Biomedical sciences. For the last 13 years, I have been a mentor during the BSc program, and for the PhD-students and postdocs I guide or meet. I also take time to excite kids in primary school for science, actively changing their image that scientists are men, like Einstein, Gyro Gearloose and professor Calculus, known in Dutch as Willie Wortel and professor Zonnebloem. The kids were excited by blood vessels and the microscope. But, they were more impressed that I made balloons from gloves, and that I can still dress up at work, like a wizard from Harry Potter.

Good mentoring has become even more necessary to keep junior faculty in biomedical sciences after the pandemic. And we did not even manage to prevent the drain of women in academia in all these years. Although we start with more women during BSc and MSc studies, this

switches from assistant professorship onwards. This leaky pipe, or glass ceiling is caused by lack of support during child-raising years, a socially unsafe or even hostile work environments, and the old-boys network. Men promoting men. I do think we have come a long way in the latter. The struggles that female leaders like the former hospital director Marja van Dieijen-Visser describes, are mostly alien to me. Maastricht is basically ruled by women at the moment, as the Mayor, President of the University, the rector magnificus, director of the hospital and our dean are female. Hmm, does this need more diversity?

Nevertheless, I struggled sometimes as a young parent. I was member of a committee that held 8:00 AM meetings. This meant I could not attend half of them, as I was a divorced mom taking my kids to school. My request to change the time was rejected. Did they even value my opinion? In any case, I did not let this demotivate me and when I became chair of the committee, I changed the meeting time immediately.

In the UK, there is a policy that prevents any meetings taking place before 10:00 AM and after 16:00 PM to allow female and male staff with young children to perform their caring duties. This policy is enforced with financial consequence. If universities do not adhere, certain research funding cannot be applied for. Perhaps some something to consider for our government and University board.

Unfortunately, several cases of intimidation or even worse have recently come to light in this university. However appalling and sad, it is actually good that the system is now safe enough for people to step forward, and management is not sweeping it under the carpet. You see, I

did experience some form of intimidation during my international jobs. Back then, I never felt safe to address this and just made it smaller. Not the best solution. Thankfully, here and now, the University and the cardiovascular institute CARIM are actively trying to keep our scientists in academia, to improve safety, diversity, and inclusivity.

I have told you diversity is lost by several reasons, including lack of social safety, time, and funding. The lack of time and funding also jeopardizes diversity in personal skills and qualities. There is just not enough time anymore to explore what excites you, to deviate, understanding where your talents lie, to think. In my case, the story of my career I told in the beginning seemed like a straight line towards a goal, and in line with the strong focus people say I have. But actually, I started out with many explorations during my internships. The first quite smelly, studying the effects of garlic on bacteria with Daisy Jonkers. The second, on molecular biology of cancer cells in Maastricht with Ton de Goeij and a third one in Australia with John Hancock. The Australian adventure was possible thanks to support of my parents, Maastricht University, and the Wilhelmina cancer foundation. These internships let me develop skills as a scientist and a person. Getting the small grants for Australia probably helped in acquiring funds afterwards. My first job after the master, was not a conscious choice. It just come came on my path. As clinical research manager I worked with orthopedic patients with a hip or knee replacement. Although I had a great time, clinical science didn't excite me as much. I discovered *because* of my deviations and experiences, that I really wanted a basic science challenge. Although wanting to turn back to cancer research, Mat Daemen soon

convinced me to work on cardiovascular disease. Which ultimately ended up being a pretty good choice, considering I'm standing here today. *Despite* the hurdles I described earlier. Or maybe even because of them? As they strengthened my problem-solving skills, confidence in my abilities and broadened my knowledge and mind, making me into the scientist I am today. Open for the breaths of fresh air by people and topics I encounter, allowing me to develop new and innovative concepts at every stage of my career until now, and hopefully in the future.

To be able to get to this day and stage in my career, I am grateful to many people. For their support with this appointment, I would like to thank my supervisory committee, Nanne de Vries, Annemie Schols, Stef Kremers in changing composition, and the steady crew Axel zur Hausen and Tilman Hackeng. CARIM, in general for all the support with a tenure track early on, and giving me chances to develop skills in the Strategic, and Division board, and for advice on grants from the research council. I thank the PhD-students, technicians, and postdocs I supervised, and those that I worked with side-by-side: it was great working with you and learning from you. You have seen your picture or heard your name. My supervisors along the way, Mat Damen, Ira Tabas, Erik Biessen, whom I already mentioned during this lecture. The technicians and secretary who have helped me out with a many different things, Mat Rousch, Clairly Dinjens, Anique Janssen, Erwin Wijnands, Jacques Debets, Gregorio Fazzi, Peter Leenders, and Audrey van Golde. Thanks to all my co-authors, local and international colleagues, the Animal facility, and the animal well fare body for support with our experiments over the last 23 years. I enjoy organizing scientific meetings for

the Dutch and European vascular community, thanks to my science buddies from the DEBS now NEVBO, Jaap van Buul, Boy Houben, Ed Eringa, Stephan Huveneers, and Guido Krenning. My peers and the trainers from the top talent program all filled my bag with experience, tools, and some friendship to handle this job: Raimon, Daniel, Kasper, Joost, Jacqueline, Mechteld, Gera, Jos, and Jim.

I am also happy to be part of talent program of the Dutch Cardiovascular alliance, and the UHD-committee of this faculty, both with a truly diverse group of peers. The committee only runs so smoothly thanks to our board secretary Sylvia Bastiaanssen.

My friends in and outside science let me unwind, enjoy life together, and have been there for me at various times and diverse ways. Thanks Paula, Marion, Sylvia, Veerle, Sietske, Danycia, Mirjam and my SATC crew from university, Audrey, Céline, Penny, and Marret.

I am happiest when all my family members are together in the same country, like today. Pap en mam, merci! You always supported me while growing up, studying, giving me confidence and care during good and challenging times in life, and as the most amazing grandparents. The road to Maastricht became much shorter after Sophie and Jasper were born. It is a joy to see how you enjoyed early retirement with each other in good health, travel a lot, and see how use your passion for teaching, when you helped home-school my kids.

Olivia, Sam, Serena, George, and Sarah, thanks for your openness to be part of our modern-day, stitched-together family, coming on family

holidays, visiting us in Maastricht as often as you can, and being the heroes, the little ones look up too.

Thanks to my little ones: Sophie and Jasper. Niet meer zo klein, maar altijd mijn kindjes. Ik ben trots op jullie allebei. Op alles waar jullie zo goed in zijn, maar nog meer voor het doorzettingsvermogen bij die dingen waar je wat meer je best voor moet doen. Als jullie er zijn is er geen cel in mijn brein die nog denkt aan experimentjes.

Andy, you make everything better, life, science, and me. No more words needed to explain that. With this I have come to the end of my inaugural address. Ik heb gezegd.