A chemist’s adventures in immunology

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A chemist's adventures in immunology

Inaugural lecture by

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Molecular Immunology

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Dear Colleagues, Family and Friends,

Did you know that during an oratie, the academic free to talk about any topic of their choosing. In that spirit, I am going to start with a story, a random story.

The date is January 24th, 1975. We are standing at the Cologne Opera House with Vera Brandes, a 17-year old woman who is eagerly awaiting the arrival of none other than Keith Jarrett, one of the most famous pianists of his day. In what can only be described as 'a massive fluke' she managed to book him for a gig for her jazz night – one where usually only amateurs play! To boot, she even managed to book the 1300-seater Cologne Opera House to host the gig. And sell it out! All that at the age of 17.

However, very shortly after Keith's arrival it all went rapidly South for her. Keith is a very particular piano player. He will only do concerts on one type of piano: a Bosendorfer 290 Imperial Concert Grand. When they walked onto the stage together to inspect the piano he was going to play on, they found that the stagehands *had* put a Bosendorfer on stage. But instead of a Bosendorfer 290 Imperial Grand, it was their own baby Bosendorfer from the ballet practice studio!

And that was not even the worst. It was a really, really, bad Bosendorfer. Its low notes were super-quiet and its high notes painfully shrill. In no way an acceptable piano for Keith. To top it all off, it was horribly out of tune.[1]

Unsurprisingly, Keith did what any sensible artist would do: he walked out.

This is where the story gets interesting. Vera ran after Keith and pleaded with him to please play. I imagine here that she outlined the extent of her ruin if he were not to. And Keith with the kindness of his heart, relented. He agreed that, if they could at least get the piano in tune, that he would play. But, he warned them, it was not going to be good. You see, Keith Jarret improves all his concerts and such a bad piano, could only mean a bad concert.[1]

How wrong he was: the concert was miraculous. Keith turned the limitations of the piano into a thing of beauty. He adapted his style of playing to fit the broken instrument and played one of the most beautiful pieces he had ever played.[2] You can listen for yourself. The recording of the concert, called 'The Köln Concert' went on to sell over four million copies, becoming the best-selling piano and jazz album of all time.[3]

The immune system has been *my* broken piano. Since I started developing chemistry to study it, it has been a huge source of frustration and I have often wanted to slam the lid down on my research and storm out. Yet, every time I was lured back by its beauty. And in doing so, it too became a muse to me, forcing me to change the way I thought about doing chemistry, pushing me to new levels of creativity. What I now call Molecular Immunology.

So, what is this beauty? It is simple:

> The immune system is the only thing that stands between you and certain death.

We are exposed to huge numbers of bacteria, viruses, protozoans and worms and even our own mutating cells on a daily basis. Yet, we survive. And it is our immune system that makes sure we do. It finds, tracks, and kills all these dangers with such ruthless efficiency that most of the time you do not even notice. At the same time, it also makes sure we do not attack harmless and useful things, like the trillion-plus bacteria in our gut that digest food for us.

The most striking example of how good your immune system is, comes from a disease: the human immunodeficiency virus, or HIV infects one of the pivotal cells of your immune system,

the helper T-cell. In doing so, it slow kills all of them when you are infected, leading to their number dropping.

When this number gets too low, latent HIV causes the Acquired Immune Defence Syndrome, or AIDS. If left untreated, this kills the patient. Not HIV itself, but the absence of these helper T-cells leads to the patient is in all kind of trouble: fungal infections, tuberculosis, bacterial skin infection, sepsis, other viral infections, and many different cancer types end up eventually killing the patient.[4] And this all happens because of the absence of only *one* immune cell type! And we have 10s to 1000s of different ones (depending on how you count). When you are born without many of those, you also get sick and over two hundred such diseases exist, each affecting their own immune cell type.[5]

When we do get sick, your immune system shows its second amazing feature: it can tune its response to best fight the pathogen that is making you sick. If you get infected with a worm, anti-worm cells get activated. If you get a cold, anti-virus cells get activated. This means, that you usually survive. And once you have survived, a final amazing feature of the immune system kicks in: *it will remember the pathogen and the response against it!* So, the next time you catch that same virus, your immune system clears it so quickly that most of the time you do not even *get sick*.

In the 10th century, doctors in Africa, India and China even learned how to use this feature. By giving their patients a tiny amount of smallpox, they could prevent a full-blown disease from occurring during an outbreak. So-called variolation. And in 1796, Edward Jenner learned that you could even fool the immune system: by showing your immune system a safe, or dead version of a virus, rather than the real thing that you did during variolation, you can also train this memory without even the risk of getting sick from the variolation.[6,7] These trained immune cells could now kill the pathogen, before it could do you harm. This, in the smallest of nutshells, is how vaccination works.

The reason that HIV is so dangerous, aside from us having not being able to make a vaccine against it yet, is that those helpers T-cells I mentioned that are infected by the virus are a large part of what gives your immune system this memory. This is why killing them off is so incredibly devastating for your health and suddenly makes all these harmless bugs pathogenic again.

It is not all fun and games though, the immune system itself can also be dangerous: activating an immune response in the wrong way, or against the wrong thing, can have debilitating consequences that affect many of us. And because of this memory, these symptoms will likely stay with you for the rest of your life.

Take cats, for example. Not only are they murderous carnivores that kill 40-80 million birds and small mammals every year[8,9], but also the perfect example to highlight this problem. Every time I come near one, my eyes will redden, and I will start sniffling and sneezing. This is the result of my immune cells having once mistaken a cat hair coated in the saliva protein FelD1 for a worm. And every time I inhale another saliva-coated hair or skin flake, the anti-cat memory cells reactivate and begin this pointless attack all over again. Until the day I die.

And I am still quite lucky: my symptoms are mild, and I quite like avoiding cats anyway. Sadly, these misguided immune responses also exist against things found in food, against the bacteria on your skin and in your gut, and even against your very own cells. These events underlie diseases like Coeliac's disease, Crohn's disease, psoriasis, rheumatoid arthritis and multiple sclerosis. As many of you know on a personal level, these are highly debilitating, and increasingly prevalent.[10] They are also chronic and the first ways to cure them are only now emerging. Understanding how the T-cells are activated, leading to these immune responses, both the right and wrong ones, is therefore essential in understanding, preventing and treating disease.

So how are these T-cells activated?

This is done by my favourite of all immune cells: the dendritic cell, or DC as I will call them from now on. If you imagine the helper T-cell being the James Bond, then the dendritic cell is Q and M, and the rest of MI6 all rolled into one. DCs live all over your body where they spend their lives sitting around. That is until the point that they sense – using the most sophisticated sensor array in the body – the presence of a pathogen. This sensor array is so sensitive, that 1 millionth of a gram of a bacterial cell wall component in your blood activates them so hard, that the resulting immune reaction will kill you.[11]

The sensing in only the beginning. If they find a pathogen, they will eat it, kill it and cut it into small chunks that they then show to T-cells to select and train them to kill that specific pathogen. They on what the pathogen looks like, what type of pathogen it is, and how they need to organise the attack. Like James Bond getting briefed by M and given the tools by Q before going out on a mission. Except a DC does not use words, it teaches the T-cell all these chemical signals and touches to convey the message. A bit like the way ants talk.

My research field, my broken piano if you will, has been to study this process of a DC eating a pathogen – or a vaccine for that matter – and communicates this danger to a T-cell. In particular, how subtle changes in the things that the DC eats, lead to changes in the activation of the T-cell. To understand this, I have tried to zoom in on single DCs, but even look inside these DCs, to its organelles, (which are organs of a cell), and even at individual molecules inside these organelles.

Sounds like a pretty complicated piano right? True, and I have not even mentioned the worst of it. DCs are so sensitive to external threats, that any prodding and probing you do as part of their experiment can trigger their sensory array and put them in attack mode. A mundane example: slamming the door of the stove in which we grow these cells, can lead to them activating before even doing a single experiment. This sensory array has also forced me to come up with new ways to study them without changing their behaviour. Which feels a bit like being a spy for Mr Blofeld infiltrating the MI6 headquarters.

Many other people have worked and are working to understand this process as well. And learning from these ancestors and my contemporaries is one of the most fun aspects of this job. Ralph Steinman, the discoverer of DCs and their function, of course meriting specific mention.[12]

Two historical giants, that I want to mention here too as they shaped the way I look at cells, are Antoni van Leeuwenhoek and Paul Ehrlich. Antoni van Leeuwenhoek, a cloth salesman from Delft, is important to me, because he was the first person to see and describe a cell.[13] He was also the first person to use chemistry to make a cell visible under the microscope. He did this by dipping samples in saffron[14], which turned the walls of the cells yellow. And for those of you, who sometimes accidentally swear in the lab, you are not the only one. Van Leeuwenhoek referred to these cells as 'klootjens', which roughly translates as 'little testicles.[15]

Paul Ehrlich was the first to use dyes to visualize the immune system.[16] In the late 19th century, he started staining tissues and blood and found that different dyes stuck to different cells in the blood. Even to structures *within* those cells, those organelles I mentioned. This led to him identifying different types of immune cells in the blood. T-cells were also found in the blood but deemed too boring to study further. Their role as chief orchestrators and memory of other immune cells and the downstream immune response was not discovered until the nineteen sixties and seventies.[17,18]

He is not just my hero for this reason. After also finding that dyes could selectively label certain disease-causing pathogens, he reasoned that '*we must kill these bacteria with magic bullets*'. If these dyes could selectively colour bacteria, maybe toxic

versions of them could also kill the bacteria without killing us. Indeed, one of the dyes he studied, methylene blue, became the first ever synthetic antibiotic.[19] Although it was not a success: the soldiers receiving it didn't like it as it (being a dye and all) turned their urine and the whites of their eyes blue. The approach did pay off and formed the basis for the first ever curative antibiotic, the drug Salvarsan for the treatment of syphilis. An event that marked the birth of the pharmaceutical industry.

These molecular dyes were hugely important and when we discovered how to attach light-emitting dyes to individual proteins in the cell, immunology was revolutionised: we could see where and how these molecules were moving in immune cells and what they did. We learned, for example, how DCs give T-cells a 'kiss' during which they passed on all the information about the pathogen.[20] But here again, the sensory array of the DCs throws spanners in the works: many of these colouring methods change and activate the DC. If you attach dyes to a vaccine molecule for example, the immune cells will eat it, and cut it up, but the way in which they do is so different that they show other parts of the vaccine to the T-cells. So, a visible vaccine does not behave like a normal vaccine at all! This makes studying this process to make better vaccines very difficult.

The year 2000 brought a new solution to this problem, when Carolyn Bertozzi introduced a new concept for looking at cells.[21] One that could potentially bypass the sensory array of immune cells.

The idea is quite complex, so I will try to explain it with a metaphor. If you think about building a house. Not just any house, but a house for a highly overpaid football player with an ostentatious taste, who wants a giant chandelier in their living room. This chandelier represents the dye that we want to use to study how living room ceilings are made in houses. The pre-Bertozzi approach would be to attach the chandelier to the ceiling plate first, and then try to build the house like that. You do not have to be a builder to appreciate, that doing this is far harder than building a house with ceiling plate without a chandelier attached. You will have to build the house in a completely different manner: add special wrapping to the chandelier, use a special crane and extra care to put the ceiling plate with chandelier in place. Prof. Bertozzi's solution was different. What she proposed, was to – rather than hanging a chandelier from a ceiling and then studying house building – to attach a small hook to the ceiling plate *and only after the house was built* to put in the chandelier so we could see where the ceiling plate had gone. In chemical terms, rather than attaching a fluorescent dye or protein to the molecule of interest, she chose to attach tiny chemical groups to them, some as small as two atoms.

The second stroke of genius was that she picked chemical hooks for which she found chemical reactions that only reacted with the hooks and not with any other feature of the house. This allowed her to have only the place where the hook, and therefore her ceiling plate, had gone light up. The rest of the house stayed dark. This technique that we now call 'bioorthogonal' or 'click chemistry' won her, together with Morten Meldal and Barry Sharpless, the Nobel Prize in 2022.

This is where my story starts. I learned how to do this click chemistry during my PhD with Ben Davis in Oxford.[22, 23] Then, during my postdocs with Colin Watts in Dundee and Huib Ovaa at the NKI, I learned how exquisite the sensory array of dendritic cells is.[24, 25] I decided to put 2 and 2 together and study whether click chemistry, with its tiny chemical hooks, would be a good method to study DCs without activating their sensory arrays and changing them. My idea was that – after Bertozzi and others had shown how stealthy these click-hooks behaved when cells were being built – that they could also be great to study how dendritic cells broke things down when activating T-cells.

As I mentioned earlier, the main role of DCs is in activating T-cells by showing them partially digested bits of pathogens and vaccines. The big question in the field was, and is, how they make these bits.[26] From the outside it looks like they destroy the 'house' that they eat with brute force: with over forty different types of wrecking ball leaving, it a smoking wreck. Yet, it turns out they are good at preserving specific parts of the house to show to the T-cells, whilst never showing other parts. To stick to our example of the footballer's house. They can blow up the house – perhaps after the player has moved to Saudi Arabia for their next career move – yet every time they do this, the leave the leopard-print sofa intact. Which they show this to the T-cell that can then go on and arrange the destruction of every other house in the neighbourhood that has such a sofa. At the same time, the marble statue of the player himself that stood next to the sofa, is never shown to a T-cell. So likely the house is dismantled with a high degree of subtlety.

What you can also imagine is that a house filled with giant chandeliers is dismantled differently from a house that does not. And indeed, if we decorate a vaccine with molecular chandeliers, and then see how a DC chews it up, it is chewed up completely different than the non-decorated vaccine.[27] My first research line was therefore to see if click chemistry would serve as a better way of looking at how vaccines and pathogens are dismantled by dcs.[28, 29] The hypothesis, or better 'the hope', was that the tiny click-hooks that we built into the pathogens and vaccines would not change the way that the DCs degraded the vaccines and that the parts they showed to T-cells remained the same. And – after about 10 years of hard work – we got it to work! We can now use the approach to see how vaccines, bacteria[30], but also our own cells and proteins that can cause auto-immune disease[31-34], are degraded by the DCs. We are even beginning to see the steps of the dismantling process; order in which they are taking the house apart. My first PhD student Joanna Pawlak, followed by Linda Pieper, Dimitrios Poulcharidis, Mirjam Groenewold, Tyrza van Leeuwen Thijmen Mostert and Kristine Bertheussen, Ward Doelman, Eva Carmen Del George Matlalcuatzi and the postdoctoral workers Can Araman and Diana Torres-García have all been instrumental in getting this concept from thought to reality. Collaborations with René Toes, Bert 't Hart, Wia Baron, and Bobby Florea were instrumental in using the approach to learn about the emergence of rheumatoid arthritis and multiple sclerosis with this approach.

We also wanted to these clickable vaccines and bacteria being broken down inside the cell. I am deeply grateful to Daphne van Elsland and Thomas Bakkum who made this a reality, in collaboratioin with Bram Koster, Erik Bos, Lorenzo Albertazzi, and Roman Koning. The details of this approach are exquisite, and I am still amazed every time I talk about it: they first slice cells in slices of about a 10 millionth of a centimetre. They then do click chemistry on these ultra-fragile wafers, before firing electrons at them. This lets us see both the lights we attach, but also the parts of the cell that normally remain dark. We have used this to see bacteria being destroyed[30, 35], but then also see the organelles of the cell where this destruction takes place. To take a peek inside the wrecking yards, if you will. Thijmen Mostert, Diana Torres-García, and Kristine Bertheussen are now using it to figure this out for vaccines and how this correlates to how well a vaccine triggers the immune response.

These are two of our tools that helped us make a route map of the dismantling process in DCs. What this click chemistry did not let us do yet, was to let us time these processes. The next challenge we took up, was to figure out how fast DCs could dismantle a vaccine. And whether this played any role in how they activated T-cells.

To do this we needed a 'molecular stopwatch' and the chemistry we use for it, came to us by mistake. Joanna Pawlak found that in very rare cases, the small click-hooks of 2 atoms in size that we attached to vaccines could make a T-cell completely ignore our vaccine.[36] It was as subtle as adding an

extra pillow to our leopard print sofa, and suddenly our T-cell ignoring it as a sofa. Our click chemistry hook acted like an invisibility cloak. Not what we were looking for, but when we found that we could remove this cloak chemically, *after* the entire dismantling process, we suddenly had our stopwatch to time how fast the DCs did this. The chemistry we use for this is called '*unclick*' chemistry or '*click-2-release*'. Our chemistry to do this was quite bad, but luckily, Marc Robillard had developed some beautiful chemistry to do this very fast and in a way that was not toxic to cells. Applying his chemistry has even allowed us to do timing reactions inside a mouse[37], or in a specific organelle of a DC.[38] Marc, in the meantime is taking this chemistry to the clinic and coming up with ways to use it to treat cancer with fewer side-effects.[39]

We have had so much fun with this chemistry. It felt a bit like Harry Potter and his Cloak of Invisibility sneaking around Hogwarts. We cloaked different types of molecules and let them sneak up on DCs, or to T-cells unnoticed. Ten, using this unclick chemistry, or even using light, we could rip of the cloak and make them sound 'boo!' causing the near-instant activation of the cell. Joanna Pawlak, Anouk van der Gracht, Timo Oosenbrug, Amber Barendrecht and Nina Ligthart used these reagents to measure how fast different immune cells responded after we scared them.[40] Alexi Sarris, Mark de Geus, Michel van de Graaff, Merel van de Plassche, Yixuan Wang, Luuk Reinalda made the beautiful molecules that allowed us to do this.[41-43]

These two types of chemistries, click and unclick, have allowed me to study the process of T-cell activation in new ways, with a new level of detail. However, both my chemical and my immunological scopes have been expanding of late. On the one hand, Kas Steuten, Ward Doelman and Hans Bakker in collaboration with Lorenzo Albertazzi and Jeroen Codée, are zooming in on the single molecules.[44] They are now able to see individual molecules interacting with dendritic cells just before they get eaten, essentially seeing how the sensory array of the DC picks out dangers. Thijmen and Diana are doing the same after the destruction is complete and are trying to visualise the individual bits are being shown to T-cells, mapping the topology of how single peptides are presented on the dendritic cell surface.

I am also beginning to look at what happens after the T-cells are activated. What happens to them during the briefing-meeting by the DC. In an exciting collaboration with two old friends, Linda Sinclair and David Finlay, with the experiments done by Leonard Pelgrom[45], we are measuring what food T-cells need to eat to get activated. As it turns out, this is a lot, and putting them on a diet, or over-feeding them, restricts their activation. In fact, it is a trick that many tumours use to stop the immune system from killing the tumour. This project is growing very hard, supported by Luuk Reinalda, Yixuan Wang making reagents for many collaborators, such as Sander Kooijman, Henk Schipper, Bart Everts, Kristina Ganzinger, Patrick Rensen, and Sophie Janssens, and many more, who are using it to study these cells in living immune systems. The approach I was taught by Hermen Overkleeft, of freely giving out reagents to collaborators being a great driver of this.

And that brings me to my vision of the future of Molecular Immunology as a whole. I think as chemists working on biological problems three things are important to make the approach successful: the first of these is to listen to immunologists/biologists to figure out what their questions are. We can design beautiful molecules, but if they are no use for answering a relevant question, they are pointless. I also think that we, as chemists working on immune cells or other biological systems, need to do better biology. Over the past two decades, we have been guilty of publishing papers focussing on building the molecule and not paying enough attention on how well it can address what problems. Much like the way a director thinks of a story line for an action movie. We need to up our game, either alone or in collaboration with specialised labs, address the questions for which we have designed our

tools. Rather than hoping that our papers get picked up and someone else will do it for us. I think the big interdisciplinary consortia, such as the Institute for Chemical Immunology of Hermen Overkleeft and Jacques Neefjes, and the institute for Chemical Neuroscience that Mario van der Stelt and Inge Huitenga and others are trying to set up, are essential for fostering such collaborations.

Finally, we need to make our click chemistry better, and be more honest about what works and does not work. Because like a real hook, sometimes our chemical hooks get bent out of shape when we put the in the cell, stopping them from reacting. Or they get caught behind something and do something in a cell we do not expect. We, as the field of click chemistry, need to make our chemical hooks stronger and smaller and the reactions to find them more selective. These are the ingredients for a future where Molecular Immunology no longer exists but has simply become 'immunology'.

But enough about my science, let us get back to Keith, Vera and the broken piano. Creativity through limitation is not the only reason the story resonated with me. Other characters in the story also symbolise some aspects of my scientific journey. Like the staff of the opera house that wheeled in the mini-piano. Comparing them to inappropriate incentive system in Dutch academia is crass. However, I do think certain keys of the Dutch funding system are a little out of tune. The 'PhD-premium' for example, where research institutes get paid per PhD that completes their degree, sends out the wrong message. By making it a numbers game, in which we are rewarded to churn out as many people as possible. This makes the degree loses its value. What is shriller, is that we make those students for whom quitting is the better for them, suffer by keeping them in a program that does not fit their talents, just because we are incentivised to have them finish. What I propose instead is to pay out this premium at the start of someone's PhD. That way it can be spent on the student earning this money. And for those people for whom a PhD does not work out, we can create a degree that honours the effort that they have put in, but that is not a PhD. The British version of the *MPhil*-degree serves this purpose.[46]

And Vera Brandis. Her bravery and audacity to stage this gig at seventeen, I find deeply impressive! She is such a great example of the energy, creativity and resilience of the young people, that I work with. It is the working with all these PhDs, postdocs, masters and bachelors, that makes my job so rich. I want to thank all of them for the energy you have put in working on my, sometimes a little esoteric, ideas. Unlike Keith, alone at his piano, my career has been a team effort. -

And not just a team of scientists working in my research group. My collaborators, colleagues and mentors have been essential in shaping my ideas and turning them into reality. I cherish these connections, and the friendships that have grown from them. The lessons from the people that trained me, like Colin Watts, Jacques Neefjes, Benjamin Davis, and the late and great Huib Ovaa, formed me into the scientist I am today. Collaborators outside, but also the faculty, like Nathaniel Martin, Ariane Briegel, and Alexander Kros keep the work fun. And of course, Daniel Rozen: It is funny how chatting during our running and climbing sessions, run has resulted in actual collaborations, where we are now doing click chemistry even in sponges!

Being so reliant on teamwork for the success of my science, I find it complicated that science does so poorly at rewarding this. The prestigious grants and prizes are all for the individual, not the teams. And the more of these prizes and grants you win, the more of these prizes and grants you win. This creates a gap between the haves and have-nots, the so-called Mattheus Effect.

The best example is probably someone you have never heard of before, a man called Douglas Prasher.[47]

Whilst a tenure tracker at Woods Hole, he conceived the idea to use the gene from a fluorescent jellyfish to study biology, yet he struggled to make it work, so faced with a tenure committee that wasn't appreciative of this ultra-high risk-high gain research he was conducting, he quit before he got fired. As a last act of keeping his ideas alive, he sent all his samples to Martin Chalfie and Roger Tsien, so they could hopefully continue his struggle and make his dream a reality.

They did.

In 2008, listening to the radio of the minibus he was driving for a car dealership in Alabama, he heard the announcement that they had won the Nobel prize for their work with the fluorescent jellyfish protein that he had sent them.

Fair? Of course not, but science is full of stories like this. People whose area of research is not popular at the time, or whose writing style is such that grant committees do not like them enough to be part of the top 10% of the grants submitted. Because this is the reality. Out of every ten grants we write as scientists, about nine get rejected. The personal grants that determine whether you are seen as a 'successful young scientist' are particularly hard to get. I therefore propose to step away from this personal fellowship culture. How? By making it a lottery. The panel of scientists that decide on funding allocations are notoriously bad at deciding whether some research idea is going to be important in the future. So why not just make the fact that it is a lottery official and let fate decide? That way, no misplaced prestige can be drawn from getting such a grant, nor can they play a role in whether someone gets hired for a faculty position or not.

That brings me to my own hiring. I would not have been here, if it were not for the support of my institute, faculty, and my colleagues. The trust that Jaap Brouwer, who was the head of department when I started, put in me and the trust of the subsequent directors, Hermen Overkleeft and Marcellus Ubbink have placed in me, is essential for me to do my work. I am also grateful to the Board of the University, the Faculty and all the people that have contributed to my appointment as professor. And of course, Hermen Overkleeft who as the head of my division when I started and later also my director, made all his resources available to this young upstart, and was a great mentor in my transition from researcher to group leader. Teaching me basic things, like 'when is a paper complete' and 'how do you deal with a stressed-out student'. You have been instrumental in my development as a scientist.

I also want to mention the fantastic support staff of the LIC. Lian Olsthoorn, Jeannette de Wolf, Christina Schlupen, Ineke Hoef, Inge Rietveld, and Astrid Vrieling, you have been, and are so valuable in helping me navigate the oceans of grants, forms and admin. Floor Stevens, Thierry Shema, Nico Meeuwenoord, Hans van den Elst, and Rian Nieuwendijk. Thank you for helping me with the running of the lab. Without you the wheels would have come off a long time ago. And of course, Jessica van Krimpen. I would be wandering lost in the forest without you.

Mario van der Stelt. You have been my partner in crime since starting all these years ago. It has been amazing to see your research line soar. It is amazing to see how you have transcended the field of chemical biology and that – with stellar paper after stellar paper – you have become one of the leaders in the field of lipid signalling. I am so excited that, after 10 years of trying to find research overlap, we are finally working together. Noelle van Egmond and Jeroen Punt being the great students making this research come to life.

I have now reached the end of this oratie, but not before thanking all of you here. Many of you in this room have known me for large part of my life and have witnessed first-hand that this has been a journey of ups and downs. Your friendship, support and enthusiasm was often what got me through the tough times. I want to also thank Mirjam, for having been so

supportive as a co-parent in navigating the chaos of combining a family life with the academic career.

That is perhaps the most important message I want to give to the administrators here today. Support your academic staff. The demands on us in terms of publishing, getting funding, teaching, student management, and creating the paper trail to prove we do all this, has this job bursting at the seams, and has made it unworkable in the 36 hours of our contract. Every new policy and plan results in more workload. Often without proven result. I think, being a single dad, that this leads to you are losing many of the family-minded people, that you really want as part of your faculty. Only by aiming to reduce our workload will you make this job attractive for those people too.

Finally, my family. Jur, thanks for having my back. From when I was young, and I could draft you in when I feared things real or imagined. To now, where we talk about how to handle pointless admin and managerial issues. I am proud to have you as my brother.

And my parents, Joost and Lucy. Joost, I am not exaggerating that quite a few people in this room, whilst being interviewed by you, have heard the phrase 'my son is in this field too, he is working on….'. Lucy (and Joost too). This unwavering support, not to mention the endless proof-reading of my grants, often at scandalously short notice, have helped me so much. Lucy, from teaching me not to be scared of my school tests, to helping me deal with the failures that marked the first three years of my PhD, and to teaching me that even when something has been a struggle to achieve, that you should be proud of it and celebrate it. These are all huge lessons you have taught me. I owe you so much.

And Kari. Thank you for showing me that life is not all about science, and that two people as different as us can be so awesome together. You brighten up my day, every day.

Lieve Taran en Eleah, ik ben zo trots dat ik jullie vader ben en ik hou zo ontzettend veel van jullie. Jullie snappen waarschijnlijk niet al te veel van al dat geblaat van me de afgelopen drie kwartier. En dat geeft niet. Ik wil dat jullie weten is dat het leven wat we samen hebben, jullie zien groeien, het belangrijkste is in mijn leven. Véél belangrijker dan alle wetenschappelijke dingen die ik doe. Ik kijk uit naar alles wat nog komen gaat.

Ik heb gezegd.

References

(1) https://www.udiscovermusic.com/stories/koln-concert-keith-jarrett/

(2) For a detailed telling of this, and other related, stories, I highly recommend the episode 'Bowie, jazz and the unplayable piano' by Tim Harford.

(3) It has since been overtaken by 'Kind of Blue' by Miles Davis, which has sold over 5 million copies.

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Prof.dr. Sander Izaäk van Kasteren

Research Positions

2021-present	Professor in Molecular Immunology at Leiden University
2018-2021	Associate Professor Molecular Immunology at Leiden University
2012-2018	Assistant Professor Chemical Chemical Biology at Leiden University
2010-2012	NWO-Veni Postdoctoral fellow at the Netherlands Cancer Institute
2007-2010	Henry Wellcome Postdoctoral fellow at the University of Dundee, Scotland
2007-2002	PhD Candidate at the University of Oxford, St. Catherine's College
1996-2001	Master of Chemistry at the University of Edinburgh

The research of Sander van Kasteren bridges the fields of chemistry and immunology. In this oratie, he highlights the chemical approaches he has developed to study the processes of antigen presentation in the immune system.

Sander van Kasteren (Roosendaal 1978) trained as an organic chemist in Edinburgh. He performed his PhD research under the tutelage of Prof. Benjamin G. Davis in Oxford, where he worked on carbohydrate total synthesis and its application to the development of MRI- and histological probes for the detection of early brain inflammation. This was followed by a period in the lab of Prof. Colin Watts at the University of Dundee. Here he worked on the development of protease inhibitors to improve antigen cross-presentation in dendritic cells. A second postdoctoral position in the groups of Huib Ovaa brought him back to the Netherlands. In this lab he continued his development of the field of chemical immunology, and worked on the development of highly selective deubiquitinase inhibitors.
In 2012, he started his own group at Leiden University. In 2014 he joined the institute of chemical immunology of which he is now a board member and in 2018 was promoted to associate professor, and in 2021 he was promoted to full professor. For his work he has received the Wellcome Trust Sir Henry Wellcome Fellowship, an NWO-Veni fellowship, as well as two ERC Grants (Starting/Consolidator), and funding from the Reumafonds and MS Motion. In 2012, he was awarded the 2012 Early Career Investigator Award by the British Biochemical Society.

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