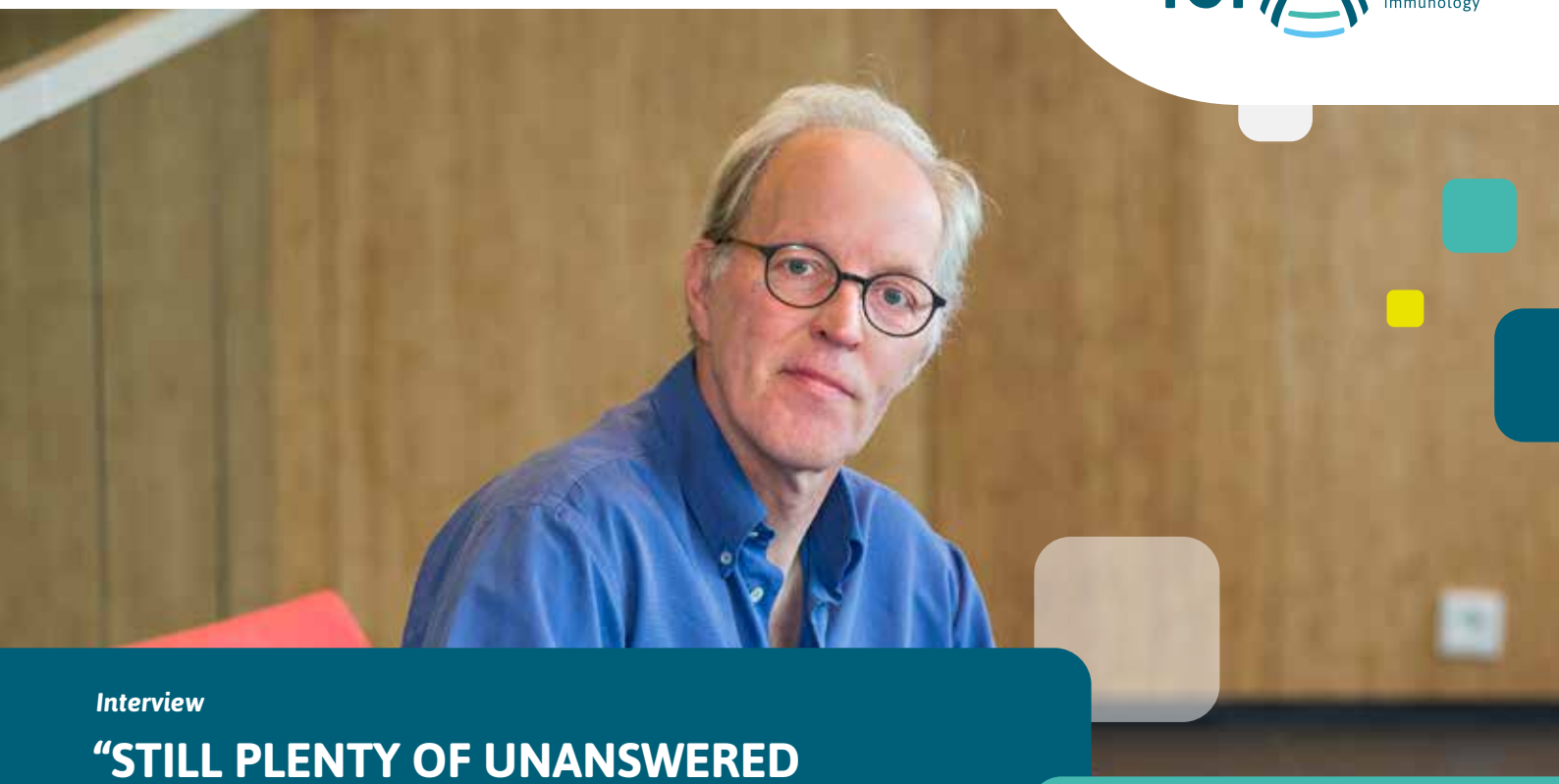
ICI institute for chemical immunology



Interview

"STILL PLENTY OF UNANSWERED QUESTIONS"

PIET GROS
Professor of Biomacromolecular Crystallography
Utrecht University

Boasting a history of almost 1.4 billion years, the complement system forms the most ancient part of the immune system. Throughout evolution it has developed into a large collection of protein complexes. Thanks to the work on elucidating the structures of these complexes by Piet Gros, professor of Biomacromolecular Crystallography at Utrecht University and member of ICI's executive board, the intricate molecular mechanisms that underlie this highly regulated system have been revealed. But there are still plenty of unanswered questions.

What sparked your interest in the complement system?

"During the nineties I was approached by a researcher who wanted to know the structure of a protein that activated the complement system against Neisseria, which causes meningitis. That was the first time I heard about that system. By that time it had already been extensively studied in terms of its biochemistry and its role in the immune system. It was known what it did and why, but how the system operated was still completely unclear. There was no mechanistic understanding, no insight into the molecular basis. This meant that there was unchartered territory waiting to be discovered if only we could manage to determine the structures of the proteins involved."

So, it was a pragmatic choice?

"Yes, in part it was. I am interested in recognition and regulation and how, on the molecular level, all these large ►

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protein complexes work together to create a finely tuned operational network. That my attention turned towards the complement system was also strategically motivated. Around the turn of the century, huge investments were made, especially in the US, to elucidate protein structures on a massive scale. It was obvious that our small group would never be able to keep up unless we concentrated on a well-defined system like the complement system. We quickly succeeded in getting the structure of the complement's central protein, called C3. This consists of thirteen domains, and once we had the structure we could immediately explain a whole lot about its properties and function on a molecular level. That gave us a head start in the field."

To what extent can we deduce generic principles on recognition and regulation from your work on the complement system?

"Each system has its own properties and mechanisms. Change one protein and the whole mechanism might change as well. However, detailed understanding of these mechanisms does offer valuable clues for studying other systems."

"My interest is in finding out what the complement system 'sees' when it is getting activated"

Throughout evolution the complement system has become more and more complex. You work on human complement; wouldn't it make more sense to first study the most basic system?

"Well, I think humans are fine model system for studying complement. In mammalians, we see the same level of complexity and moreover, the human system is the most studied in terms of its biochemistry and biological role."

What is the added value of understanding the molecular mechanisms of a system that was already well understood in terms of its role in human health?

"It has really boosted academic and industrial research into inhibitors of the complement system. Our work has opened doors to completely new approaches, and that is important because it has also become clear that the complement system is more than a line of defence against bacteria and viruses. The complement is also involved in cleaning up cellular garbage. When a cell is no longer able to defend itself against the complement's unyielding attacks, it will be destroyed. That results in a host of autoimmunity problems. For example, in rheumatoid arthritis, stroke, age-related macular degeneration and genetic defects in blood clotting factors, complement action against damaged cells leads to very serious, unwanted effects. Regeneration of healthy tissue cannot keep up with the destruction by the complement system and as result, the problems only get worse."

What does participating in ICI bring to the study of protein structures?

"I am just a protein chemist, I understand the molecular 'stuff', but when it comes to the bigger picture of a cell and an immune system, I need the help of immunologists and cell biologists."

Recently you received two important international awards: the 'Medal in Gold' by the European Complement Network and the Gegori Aminoff Prize. Signs of recognition?

"The European Complement Network consists mainly of medical and biomedical specialists, which makes me quite an outsider. That is why I really value this medal, because it shows that our work has resulted in breakthroughs that have become integrated in other research fields. The Aminoff Prize is a true crystallography award, and when I look at all the big names that have received this award, I am very honoured to be included in that list."

Do awards like these help in securing funding?

"They won't do any harm, but the real problem is the serious lack of funding for open calls and open competitions. In the Netherlands it is all about big proposals and large-scale collaborations. It is becoming tremendously difficult for young researchers to carve out their own niche. Of course, centres like ICI are very useful, but they are initiated and led by researchers who already have built a track record. It reduces the freedom for young researchers to get their own ideas off the ground. That worries me, because it will lead to a decreasing influx of fresh input. It is very important that young people get the opportunity to challenge the established order."

What about your own fresh ideas?

"Right now my interest is in finding out what the complement system 'sees' when it is getting activated. How does it distinguish healthy cells from sick or foreign cells? The complement system can only interact with the exterior of the cell, the membrane. A healthy cell has a healthy membrane that can defend itself against an attack by the complement. So, what happens on the membrane that weakens the cell's defensive capacity?"

The complement still holds your interest. What makes the research fun?

"The moment that you get it. The 'aha' moment when it all falls into place and you really understand how it works. And then you immediately move on to the next question." ■

Click to release:

USING *IN VIVO* CHEMISTRY TO EXPAND THE SCOPE OF ADCs

When it comes to developing treatments for cancer, Marc Robillard believes strongly in the power of chemistry to come up with innovative solutions. Robillard is co-founder and CEO of Tagworks Pharmaceuticals, a Philips Research spin-off based at Radboudumc in Nijmegen.

The focus on chemistry is not all that surprising, given that Robillard is a synthetic organic chemist who has been applying chemistry to solve biological problems for a long time. One of the most pressing problems his company is currently working on is releasing cytotoxic drugs in tumours that, for whatever reason, lack the capacity to internalise receptor-bound antibody-drug conjugates (ADCs).
ADCs are already successfully being applied in the treatment of lymphoma and metastasised breast cancer. But for many other types of cancer, the development of ADCs has proved to be more difficult. Robillard: "In contrast to lymphoma, in solid tumours typically only some of the cancer cells express suitable internalising receptors, or the desired receptor is present only in a subgroup of the patient population, or the number of receptors per cell is too low. The overall problem is that the cytotoxic drug is not sufficiently released from its antibody carrier. An approach that enables extracellular drug release would expand the number of potential ADC targets as there are sufficient non-internalising receptors and extracellular matrix targets selectively present in solid tumours."

Unclick

To this end Tagworks Pharmaceuticals has invented the 'click-to-release' concept, in which the well-established bioorthogonal click chemistry is used to 'unclick' the drug from the antibody in a highly controlled manner on the outside of the cells. Robillard explains: "First, we inject the ADC, which binds to the selected receptor on the tumour cells. After a day or two, we inject a second component, a small molecule, which 'clicks' onto the ADC. This click subsequently causes the instantaneous 'unclicking' of the drug, enabling it to engulf the cancer cells. We basically circumvent the biological obstacles by introducing a chemical trick."

All nice on paper and in glassware, but Robillard also has *in vivo* proof of the therapeutic power of his concept. "We have just published our preclinical data in Nature Communications. We treated mice with ovarian cancer and with an aggressive form of colon cancer with our two-step ADC method, and in both cases we were able to demonstrate a strong anti-tumour effect in our approach. In the control studies we used a 'traditional' ADC, without the second unclick-step. The therapy showed no effect here. Active release of the drug clearly is the way to expand the scope of ADC therapy to include more tumour types."

ICI expertise

Tagworks is already collaborating with several research groups within ICI, and Robillard foresees more opportunities for cross-overs in the near future. "Building on the expertise available within ICI, Tagworks is able to evaluate the click-to-release concept in applications ranging from the use of peptide targeting agents for the unclick drug delivery to other target types, as well as to the click-triggered activation of the immune system." ■

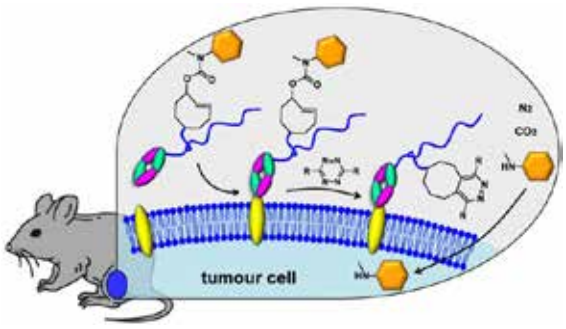

Image from: Rossin R., et al, Nat Comm (2018), CC 4.0 international

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Measuring the metabolome of T-cells

PhD project: Exploiting T cell metabolism as a target for therapeutic intervention

Differences in metabolism between certain types of T-cells might provide new clues on how to stimulate the immune system to attack tumours or stop attacking self-antigens. PhD student Anna Hoekstra uses advanced mass spectrometry and flux studies to discover these subtle differences in immunometabolism.

The immune system needs to outsmart cunning bacteria, viruses and other nasty intruders. That makes the system highly fascinating, according to biomedical scientist and mass spectrometry expert Anna Hoekstra. "But the system is also very complex with many cell types, subtypes and sub-subtypes."
Hoekstra focuses on the regulatory T-cells (Treg) in her PhD studies in metabolomics at Utrecht University. When intruders are discovered, the body drums up an army of T-cells to track down infected cells and mark them for destruction. However, the T-cells are halted by Treg when the defence is inadvertently directed against the body's own substances. "That means that people suffering from autoimmune diseases will likely benefit from upregulation of Treg." On the other hand, cancer patients may benefit from the downregulation of Treg, explains Hoekstra. "Tumour factors boost the production of Treg in order to circumvent the body's immune system."

Measuring the metabolome

Hoekstra measures the metabolome of Treg using advanced mass spectrometry and compares it with that of conventional T-cells (Tconv). She uses peripheral blood from human blood donors as the T-cell source. The cells are collected in cooperation with the Dutch blood bank Sanquin. "T-cells from donor blood are as close to *in vivo* cells as possible."
In so called flux studies, T-cells, for example, are fed with C^{13}-glucose. The carbon isotope is traced back in the metabolome after different time intervals to follow metabolism. Hoekstra: "It is quite unique to combine these biological experiments, mass spectrometry and bioinformatics. It suits me well; I like to be in control and prepare my own samples. I know exactly how I will perform my analyses, which makes it unlikely, for example, that I would forget to run a reference sample."

> *"I like to be in control and prepare my own samples"*

Hoekstra is currently analysing the first datasets. "The variation between donors in T-cell metabolome turned out to be quite large. That makes it difficult to filter out specific differences between Tconv and Treg. You might say there is a lot of 'noise' on the signals we are looking for. That also meant that we needed a lot of cells from multiple donors for our experiments, which unfortunately also take quite some time to culture." Ultimately, Hoekstra hopes to get "an as realistic as possible picture of the physiology of Treg and Tconv."

Special cooperation

ICI PhD students work in pairs. A chemist is matched up with a biologist to perform interdisciplinary research in chemical immunology. PhD student Anna Hoekstra, however, is paired with Sander de Kivit, a *postdoc* in immunology at the NKI, the Netherlands Cancer Institute. He takes care of the sorting (and partly the culturing) of the T-cells Hoekstra analyses. He also performs transcriptomics and proteomics experiments and functional analyses. De Kivit: "The cooperation offered me a quick start. We combine insights from Anna's metabolome analyses with the proteome. That provides clues for biological experiments on influencing Treg functions." De Kivit stresses that they are real research partners. "I may have spent more years in research and can provide a tip or two in doing a PhD, but we have our own expertise." ■

Anna Hoekstra (photo)
Utrecht University, Metabolomics
Celia Berkers group

Sander de Kivit
NKI Amsterdam, Tumour Biology&Immunology
Jannie Borst group

Following an antigen throughout the immune system

PhD project: *In vivo* tracking of T cell epitopes from synthetic tumour vaccines

Tracking an antigen from its first detection by the immune system to the final presentation of an epitope to T-cells to initiate a specific defence. That's the ambition of PhD students Brett Hos and Alexi Sarris. Sarris puzzles out the chemistry; Hos turns it into an immunological tool.

Cancer vaccines are based on a peptide fragment from a tumour cell. In cancer patients the fragment elicits an immune reaction, but not one strong enough to overcome the disease. By using a few 'tricks', such a fragment can be turned into a vaccine that gives the necessary extra boost to the immune system. One relatively new trick is coupling the fragment to a TLR ligand, a compound that binds to receptors known to recognise common structures in microbes. Why the combination works is still unknown.
PhD students Brett Hos and Alexi Sarris want to clarify the issue by following a synthetic vaccine in cell lines and in mice. To do so they first need to find a suitable labelling strategy. That consists of a small non-disturbing chemical group (bioorthogonal group) on to the epitope and a substance that, when added, selectively attaches to this group and initiates fluorescence. Then the peptide may be followed all the way through the immune system using a light microscope. Their first goal is visualising the epitope on the surface of an antigen presenting cell.

Parallel projects

"We already have such a labelling technique," affirms immunologist Hos, "which was recently developed here in Leiden. However, the coupling of the fluorophore requires copper ions which are toxic to the cell." The requirements for the new labelling system are crystal clear, according to organic chemist Sarris, but non-toxicity is just one of the many obstacles. The fluorophore needs to attach to the bioorthogonal group with high selectivity, and the fluorescence signal should be strong because the epitope is present in very low concentrations. "But I've always loved solving a complicated puzzle. To me this is an ambitious chemistry riddle." The chemist already synthesised several combinations which were tested by Hos. Sarris: "The signal was unfortunately either too low or the fluorophore was not selective enough. I'm working on a new candidate now."
Both Hos and Sarris also work on parallel projects. Sarris, for example, has published on deprotection strategies using tetrazine groups. Hos is searching for realistic epitopes they may use instead of the ovalbumin-derived model epitope.

"To me this is an ambitious chemistry puzzle"

"We have sequenced a cancer cell line and determined all mutations. Using an algorithm we selected the potentially best presented epitopes and tested them for their immunogenity in the laboratory. I actually found a previous unknown epitope that consistently induces immunoreaction."

Sharing experiences

The two are in touch most frequently when Hos is testing Sarris' chemistry and during the ICI courses. It's not only science they discuss; both Hos and Sarris are young fathers. Hos: "We talk a lot about how to divide your time and attention equitably between work and home, and also about how to get some sleep." Sarris: "For many PhD students science is everything. We both have a family that is highly important too. It's nice to share our experiences, since for PhD students this is still quite an uncommon situation." Because of their family lives, they both consider pursuing a career outside academia after finishing their PhDs. Sarris: "A career in academia is an elimination race, while I'm looking for stability." ■

Brett Hos (left)
LUMC, Immunohematology and Blood Transfusion
Ferry Ossendorp group

Alexi Sarris
Leiden Institute of Chemistry, Bio-organic Synthesis
Sander van Kasteren group

Single cell analysis is quickly gaining ground

New technologies enable the study of molecules at the single cell level. The field of immunology was the first to conduct single cell studies, and other fields are now rapidly following. Frits Koning and Ahmed Mahfouz of LUMC share the latest developments on this hot topic.

"In the past twenty years, we have come to realise that the immune system is far more complex than we previously thought," says Frits Koning, professor of Immunology at Leiden University Medical Centre (LUMC). In 2016, Koning published the results of a large study on the immune cell composition of the intestines of patients with inflammatory intestinal diseases (see also ICI Bulletin #3, November 2016). "When comparing intestinal biopsies of patients and controls, we discovered that the complexity of intestinal immune cell composition was much larger than we anticipated: we identified as many as 120 subsets of cells! We could identify subsets of immune cells that distinguished celiac disease patients from controls. And patients with Crohn's disease in turn had another immune cell composition."

"Various exciting new developments are emerging"

Mass cytometry

Koning and co-workers could take a much closer look at the variety of immune cells because of the development of a powerful new technology, mass cytometry, which offers a huge increase in resolution compared to conventional flow cytometry. "With flow cytometry you can only incorporate a maximum of sixteen markers in one experiment. This means that we can only distinguish coarse subsets of immune cells in a sample. With mass cytometry we can simultaneously analyse 39 markers, and this will rise to 100 in the near future. This is a gigantic leap forward. It allows us to identify subsets within the coarse subgroups."

▼ By applying powerful data analysis techniques peaks and valleys emerge from the big blob of dots. In that way biological knowledge is deduced from the infinite quantity of data points.

Such studies produce immense datasets. "We measured 32 markers in 102 biological samples, each consisting of many cells. To analyse the data, we collaborate intensively with computational biologists from TU Delft. They developed an algorithm to analyse complex multidimensional data.

"Providing a very close look at the variety of immune cells"

Frontrunner position

"The Delft algorithm can simultaneously analyse all markers for millions of cells, resulting in an unbiased analysis and system-wide data-driven conclusions," Dr Ahmed Mahfouz explains. He is an assistant professor at the Computational Biology Centre of LUMC and a guest researcher at the Delft Bioinformatics Lab. "The field of immunology has a frontrunner position in single cell studies because they use cell surface markers to characterise cells," says Mahfouz. "Many other fields are more interested in intracellular molecules such as RNA. Early experiments used microarrays to measure gene expression in single cells. Thanks to the advent of high-throughput next-generation sequencing technologies, we have been able to scale up our gene expression experiments to measure hundreds of thousands of cells at the single cell level at a reduced cost. Hence, fields such as neurology, oncology and developmental biology have now also picked up single cell studies."
According to Mahfouz, various exciting new developments are emerging. "Enabling multiple measurements from the same cell is a hot topic. And the upcoming techniques for imaging mass cytometry on histology sections allow scientists to perform single cell measurements while knowing a cell's original location in the tissue. I am also intrigued by the Human Cell Atlas Project, which aims to build a collection of maps that will describe and define the cellular basis of health and disease. Projects like this are likely to impact biology and medicine, leading to a richer understanding of life's most fundamental principles." ■

Acknowledgement: summarised interview from DTL Newsletter (December 2017)

Unravelling the endocannabinoid system at the molecular level

"The endocannabinoid system is a leitmotiv in my scientific career," newly appointed professor Mario van der Stelt begins. His research group is currently focusing on the design, synthesis and application of small molecules as chemical tools to control and visualise proteins of the endocannabinoid system in physiological and disease processes.

▲ Professor Mario van der Stelt is head of the department of Molecular Physiology at Leiden Institute of Chemistry.

Extracts of the plant *Cannabis sativa*, also known as marijuana, have been used for recreational and medical purposes for thousands of years. Extensive research on the active substances and their mechanisms of action eventually resulted in revealing the endocannabinoid system. This major neuromodulatory system consists of cannabinoid receptors (CB1 and CB2), their endogenous lipid ligands (endocannabinoids) and the enzymatic machinery for their synthesis, release and degradation.
The two main endocannabinoids are N-arachidonoylethanolamine (AEA) and 2-arachidonoylglycerol (2-AG). "They modulate neurotransmitter release and regulate many physiological processes, including pain perception, learning and memory, energy balance, emotional states (anxiety, fear), and reward-related behaviour," van der Stelt explains. Furthermore, endocannabinoids have proven to play an important role during neurodegeneration and inflammation, all of which are major risk factors for illness and death. His research group is trying to come to grips with underlying (patho) physiological processes. "My current research interests are focused on the detection and modulation of endocannabinoid biosynthesis/metabolism and kinase signalling."

Multidisciplinary approach

In a multidisciplinary line of research, van der Stelt and his team combine organic and medicinal chemistry with molecular biology and chemical biology. They use computational chemistry together with activity-based probes for compound profiling and optimisation. "In (inter)national collaborations with biologists and pharmacologists we test our molecules in preclinical models of disease. For instance, my group discovered the first inhibitors of endocannabinoid biosynthesis in the brain. Key to the discovery of these compounds was the development of tailored activity-based probes that could be used to determine the activity and selectivity of the compounds in complex brain proteomes using chemical proteomics." Van der Stelt also is involved in ICI. In a collaborative effort with Reina Mebius' group Molecular Biology and Immunology (VUmc), he guides the duo PhD project 'Visualisation of vitamin A metabolism.' Recently his group coordinated an international team that discovered the off-targets of the experimental drug BIA 10-2474, a fatty acid amide hydrolase inhibitor, which caused severe neurological symptoms and killed a patient in a first-into-human study in France. He also led a multinational joint venture that reported an extensive cannabinoid CB2 receptor ligand profiling.

Gaining momentum

Van der Stelt's career has gained momentum in recent years. He was awarded the Galenus Research Prize in 2017 for his ability to translate knowledge of endocannabinoids into therapeutic applications. Furthermore, last year he received the Young Investigator Award from the International Cannabinoid Research Society. Last but not least, as of November 2017 he was appointed Professor of Molecular Physiology at Leiden Institute of Chemistry, where he guides as many as 15 AIOs, including organic chemists as well as molecular biologists. Last February he secured an NWO Vici grant (€ 1.5M) which will allow his groups to add two AIOs and two postdocs. The grant will enable them to take new directions, focusing principally on selectivity. "We want to develop inhibitors against enzymes that are responsible for the production of endocannabinoids in selected cell types. We want to ensure that our inhibitors are active in a given cell type, so we can find out where exactly in the brain which endocannabinoids are responsible for what function. In the end we want to understand how our brains work at the molecular level," van der Stelt concludes. ■

“I really enjoy the experimental side of science”

Annemarthe van der Veen has been awarded ICI’s second Tenure Track Fellowship

In 2019, Annemarthe van der Veen will join the Chemical Immunology department at the Leiden University Medical Centre as assistant professor. She was a speaker at ICI’s Annual Conference and we talked to her there about trading London for Leiden, the joy of performing experiments and the importance of not focusing too narrowly.

One moment you’re just thinking about new steps in your career, and the next moment you’ve secured yourself a tenure track position. A bit simplified perhaps, but this is essentially how it happened for Annemarthe van der Veen. She is currently a postdoc in the group of Caetano Reis e Sousa at the Francis Crick Institute in London. There was no vacancy at the Neefjes lab, says Van der Veen. “I contacted Sjaak [Neefjes], whom I already knew, to learn more about the research in his department and then one thing led to another. What I like about his approach is that he combines immunology with cell biology, biochemistry and molecular biology. That combination fits very well with my background and research interests.”

Why did she decide to look around, albeit informally, for new opportunities? “Well, I have been a postdoc for quite a while now and the time has come to take up an independent research position.” Van der Veen is Dutch. After doing her PhD research in Boston and being a postdoc in London, was it time to head back to The Netherlands? “London is a great city, but it is so expensive, it’s practically impossible to live there as a researcher. That is why my husband and I decided to move elsewhere, but we did not specifically focus on The Netherlands. Because I knew Sjaak, I just got in touch very informally and then it turned out that his group was looking for someone with experience in molecular immunology. It sounds corny, but it really was a case of being in the right place at the right time.”

“Understanding the biological process behind a clinical problem”

From different perspectives

Van der Veen is primarily interested in innate immunity and specifically in sterile inflammation: the process in which an inflammatory response is generated, but there is no infectious agent involved. Inflammation without infection. “This is seen, for example, in autoinflammatory diseases, but also in the tumour micro-environment. Tumour tissue is often inflamed, but there is no infection. I want to unravel the molecular mechanisms that underlie such a sterile response. Which molecules trigger this response and how does that work?”

That is the main line of research that she will bring to Leiden, but her precise plans are still open. “In my experience you first have to be embedded in a group to really get a good idea of what everybody is doing and who is an expert in what. And then ideas will start to flow.”

“In the right place at the right time”

That is exactly the way she likes to work. “I did my PhD research with Hidde Ploegh at the Whitehead Institute, a very multidisciplinary environment where I got the chance to participate in different projects and to learn how to look at these projects from completely different perspectives. Also in Caetano Reis e Sousa’s lab, where I went next, I worked on a variety of topics. I like to team up with other researchers. I find it refreshing to think about different projects and about how we can solve a biological question together. Sometimes I get criticised for not focusing, but this is how it works best for me.”

Inspired by experiments

For Van der Veen it all starts with the experiments. “I really enjoy the experimental side of science. Designing the best set-up, with the best controls, performing the measurements, testing your hypothesis: all this done in such a way that you can draw sound conclusions in the end. My inspiration comes from my experiments. What I observe there always provides me with new clues and ideas. For me the fun of science is in the experiments, and I think it is very important to enjoy that part. As a molecular scientist, it is about taking small steps. But when such small steps help you solve a bigger piece of a puzzle and contribute to a new treatment, that is of course fantastic.” ■

Sterile inflammation

Unwanted triggering of the inflammatory response

Inflammation is the body’s normal reaction to intrusion by pathogens. It is how the innate immune system deals with foreign threats. The inflammatory response is triggered by so-called pattern recognition receptors (PRRs) that sense microbial molecules, such as viral nucleic acids. This stimulates the production type I interferons (IFNs), which activate the proper defence pathways. However, PRRs can be activated by the body’s own nucleic acids as well. This unwanted triggering of the inflammatory response is known as sterile inflammation. Continuous and excessive production of type I IFNs can result in various severe auto-inflammatory disorders and is also associated with several autoimmune diseases, including systemic lupus erythematosus and type 1 diabetes.
Interestingly, sterile inflammation is also a hallmark of the tumour microenvironment. Here, high levels of type I IFNs may help to recruit intratumoural immune cells, and they can increase the effectiveness of both chemo- and immunotherapies. The sterile inflammatory response is, however, not as strong as that invoked by microbial nucleic acids. Understanding how type I IFN-mediated inflammation is induced in a sterile environment could perhaps shed light on new ways to boost the body’s anti-tumour immune response.

Key question

How does the innate immune system discriminate between the body’s own molecules and microbial ones? That is the key question in Annemarthe van der Veen’s research. As this is still a very broad question, she will specifically focus on nucleic acid sensing and type I IFN-dependent autoinflammation. Van der Veen will be studying the nature of the endogenous ligands that initiate a sterile inflammatory response; the molecular mechanisms that suppress unwanted activation of the innate immune system; the cause of failure of these mechanisms; how type I IFN production is triggered in the tumour microenvironment and how enhancement of type I IFN-related sterile inflammation can be used to boost anti-tumour immune responses. By combining these different viewpoints on the sterile inflammatory response, Van der Veen aims to generate a deeper understanding of the molecular mechanisms that underlie autoinflammatory pathogenesis, which may lead to the identification of new therapeutic targets. ■

“What I like about the ICI approach is that the research combines immunology with cell biology, biochemistry and molecular biology. That combination fits very well with my background and research interests.”

From PhD student to professional

In 2015 ICI launched a special course for PhD students focused on soft skills to complement their scientific core. Working with Louise Mennen (Mennen Training and Consultancy), ICI put together a tailored programme which the first group of ICI PhD students recently finished. Participants respond very positively and share their experiences of the various course components.

1. Time management and project management

The first module focused on coping with time. You don't earn the title of 'doctor' simply by arriving at the lab on time! Jorieke Weiden (Tumour Immunology Lab at Radboudumc, Nijmegen) explains the obstacles: "The most difficult challenge is how to manage and oversee the huge project you embark on when you start your PhD. We learned about discovering what works for you as an individual. There was a lot of attention on the personal struggles in your project." In her case, she found out how to prioritise less urgent tasks like updating the lab journal and reading literature, and how to explore strategies such as time blocking and taking a break from emails.

▼ *Completing a PhD study comprises an exciting scientific goal, but comes with plenty of unpredictable challenges. How can you get the most out of your busy supervisor? How do you plan four years in advance? Where do you want your career to go next? The ICI PhD course endeavours to answer these questions.*

2. Communication in science

The second module dealt with successful networking, giving convincing presentations, poster design and styles of communication. Anna Hoekstra (Biomolecular Mass Spectrometry, Utrecht University) learned how to improve her ability to summarise. "I am aware that I like to put too much text and details on slides and posters." She brought in her first poster with 'far too much text' and got feedback on how to improve it. Furthermore, participants were instructed on giving oral presentations. Anna: "Standing and speaking in front of a quiet room full of your peers is the kind of thing that strikes fear into your heart. You are nervous and afraid of forgetting things." The course taught several useful tips and tricks. With respect to the structure, for instance, Anna learned: "You should first connect with your audience by telling a story that leads to your key message, then support your key message with examples and arguments, and conclude with a persuasive ending, leaving enough time for questions and feedback."

3. Personal leadership

Participants highly appreciated this third module, which addressed personal qualities and success stories. They are eager to learn more on topics like approaches to difficult situations, self-assessment and ethics in science. Jorieke Weiden explains: "I think this gives clear insight into my own strength and weaknesses. It will certainly help me to exploit specific skills that I have and help me become aware of the things that I need to work on in order to successfully finish my project."

4. PhD, what next?

During this fourth and final module participants were confronted with the need for career planning. Laurent Paardekooper (Tumour Immunology Lab, Radboud University, Nijmegen). "Time 'after PhD' seems far away for most of us, but we were encouraged to think seriously about the future." Much attention was focused on the importance of taking pleasure in your job. "To me it seemed simple, because my ambitions are in science, and so I am contemplating becoming a scientific researcher. During the course, however, I realised that I have to substantiate such a choice. It would be wise to formulate pros and cons." Participants were furthermore advised to consider several different careers. "I was surprised with respect to alternative professions such as being a consultant, a journalist or a policy maker. These possibilities may be an eye opener for some of us! On the whole it was a very useful session, challenging us to start considering the future early." ■

News

Second ERC for Piet Gros

The European Research Council has awarded Prof. Piet Gros of Utrecht University his second ERC Advanced Grant. The grant of almost 2.5 million Euros enables him to take his research into our immune system in a new direction. Gros studies how proteins in our blood determine whether a cell is healthy or not, and should therefore be protected or cleared from our body. Problems with the clearance of injured cells appear to play a role in more and more diseases, but scientists know little as yet about the crucial first step in this process, how are injured cells distinguished from healthy ones.

Berkers and Van der Stelt appointed as Professor

On 1 February Utrecht University has appointed Celia Berkers as Professor of Metabolomics at the Faculty of Veterinary Medicine and Science (Department of Chemistry). Berkers will mainly focus on metabolism research in order to better understand the role of metabolic processes in health and disease. Mario van der Stelt has been appointed Professor of Molecular Physiology at the Leiden Institute of Chemistry with effect from 1 November 2017.

VICI grant for Mario van der Stelt

ICI researcher Mario van der Stelt (Leiden University) has been awarded a prestigious Vici grant by the Netherlands Organisation for Scientific Research (NWO). He receives 1.5 million Euro to develop his own research project (The body's own marijuana) in the coming 5 years.

Recent publications

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ortho-Quinones and Analogues Thereof: Highly Reactive Intermediates for Fast and Selective Biofunctionalization.
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Column

THE FUTURE OF CHEMICAL IMMUNOLOGY IS NOW

MARTIJN VERDOES (LEFT) AND SANDER VAN KASTEREN

ICI EXECUTIVE ADVISORY BOARD

Van Kasteren is associate professor at the Leiden Institute of Chemistry. Verdoes is assistant professor at the Radboud Institute for Molecular Life Sciences.

The previous editions alike, the 4th Chemical Immunology Conference was a great success. The program was exciting, spanning the whole range of chemical immunology, from mechanistic immunology to synthetic organic chemistry. The feedback received from the attendants and the guest speakers was very positive. The one thing which is always positively highlighted is the concept of the ICI duo-projects, in which a chemistry oriented PhD student is working together with a PhD student with a background in immunology.

The conference came at a pivotal point in the history of the ICI: the first couples of PhD students are currently approaching the writing up-stages of their theses. And it was with the presentation of their duo-projects – both as oral presentations and during the poster session – that the strength of the ICI became apparent: their fluency in each other's discipline fostered by these close collaborations really highlighted the fact that a new generation of true chemical immunologists are being trained within the framework of ICI.

The ICI has proven its value for the next generation: it has created a generation of strong monodisciplinarians that have no fear of approaching and collaborating with other disciplines on an equal footing. The ICI network has further proven its value in being at the basis of several new collaborative projects and successful grant applications. This was all highlighted during the recent midterm evaluation of the ICI. This has resulted in the continuation of the funding for another five years of ICI.

It is now time to consider what the shape of the ICI will be for the next few years to ensure that the end of the Gravitation funding does not mean the end of chemical immunology as a nascent discipline. In order to let this budding new discipline reach maturity, we need to further strengthen the cross-disciplinary collaborations; to allow rapid identification of new opportunities for all parties and to establish new collaborative, cross-disciplinary projects that can attract both national and international funding.

The future of chemical immunology is now, and it is our collaborative task to make ICI a true consortium and secure its future. ■

About ICI

The Institute for Chemical Immunology (ICI) is a Gravitation project, made possible by the Ministry of Education, Culture and Science, in collaboration with the Netherlands Organisation for Scientific Research (NWO). ICI will define and exploit a new field termed chemical immunology and train a novel generation of interdisciplinary scientists. It aims to promote academic excellence. The ICI publishes twice-yearly the 'ICI Bulletin' featuring ICI research, education and other relevant developments. To (un)subscribe please send an mail to info@chemicalimmunology.nl.

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