ICI institute for chemical immunology

Interview

"THERE HAS TO BE SOME KIND OF PATTERN"

JOOST SNIJDER, PhD
Assistant Professor
Biomolecular Sciences
Utrecht Molecular Immunology Hub

Even though the interview with Joost Snijder was planned before SARS-CoV-2 managed to dominate the world, the fact that his main scientific interest concerns viruses makes the interview even more timely. Snijder holds an ICI Tenure Track position and is Assistant Professor in the department of Biomolecular Mass Spectrometry and Proteomics at Utrecht University. He wants to understand how antibodies manage to neutralize a virus and how we can use those insights to contribute to new therapeutic leads for combating viral infections.

The interactions between antibodies and viruses; that is quite a broad topic. What exactly are you studying?

"I am primarily interested in the role that glycans play in this process. Viral envelope proteins are heavily glycosylated and exhibit a wide variety of sugar residues. We know that these sugars can shield the virus from our immune system, but they can also function as specific epitopes that antibodies recognize and, in that capacity, activate the body's immune response. My aim is to unravel in detail how these glycans influence the interactions between antibodies and viral antigens with a particular focus on tropical viruses like dengue, zika and ebola, but I'm also interested in influenza."

Your expertise is in structural techniques, like mass spectrometry and electron microscopy. What is the role of structural biology here?

"We know that there are antibodies that can neutralize a ▶

Contents

virus. To really understand how they do that, we need to know their amino acid sequence, but that is not as straightforward as it seems. The problem is that antibody sequences are highly variable, they are not encoded as 'hard' in the genome as is the case for other proteins. The human genome sequence therefore offers little support when it comes to determining antibody sequences. Right now, the only way is to isolate the B-cell that expresses your antibody of interest, extract the mRNA and sequence that. However, the antibodies that are important in fighting infections are the ones that are secreted into the blood, meaning that they are no longer attached to their B-cell of origin. So, we need a new approach to determine the sequence of these secreted antibodies. That is where mass spectrometry comes in, we are developing MS-based methods as antibody sequencing tools."

How does that work?

"In short: we apply proteases to cut up the antibody, use MS to analyze the fragments and then the puzzle starts to connect all the fragments and reconstruct the original sequence. We use different proteases and because you know where each protease cuts, you can start looking for overlap and connections. The easiest way to understand this is to think of a sentence in which you use one protease to cut in all the blanks and another protease to cut everywhere where there is

"Antibody sequences are highly variable"

an 'e'. This will deliver fragments that completely overlap and that gives you a start to work backwards and find the original order of the words. We are currently still very much involved in technology development, for example on finding the best fragmentation methods, which proteases are the most useful and, of course, software development to handle the analysis."

Are you working on this because of the technical and methodological challenges or is there also a direct link to biological understanding and perhaps applications?

"It is a technical challenge and yes, that is something I like to work on. But developing new ways to sequence antibodies is definitely relevant from a biological perspective. Antibodies have become an increasingly important class of therapeutics, not only for infectious diseases, but also for cancer. For almost all important viral infections, antibodies are currently under development or are already applied as antiviral cocktails, for example in the treatment of rabies, respiratory syncytial virus and ebola. Being able to sequence antibodies is essential on two levels. First, there is the fundamental level of understanding how antibody and virus interact and what mutations might be useful to improve the antibody's antiviral properties. Second, large-scale production of antibodies requires knowledge of the sequence. Antibodies are mostly produced using recombinant technologies, so you need the amino acid sequence to deduce the genetic sequence to enable culturing cells that produce your antibody."

That is all still very focused on the antibody, how about the glycans that you mentioned earlier?

"The viral glycans play a big role in how an antigen is recognized. The mutations in a virus often introduce new sugar residues or remove existing ones, allowing it to escape

"No two copies of an antigen are alike"

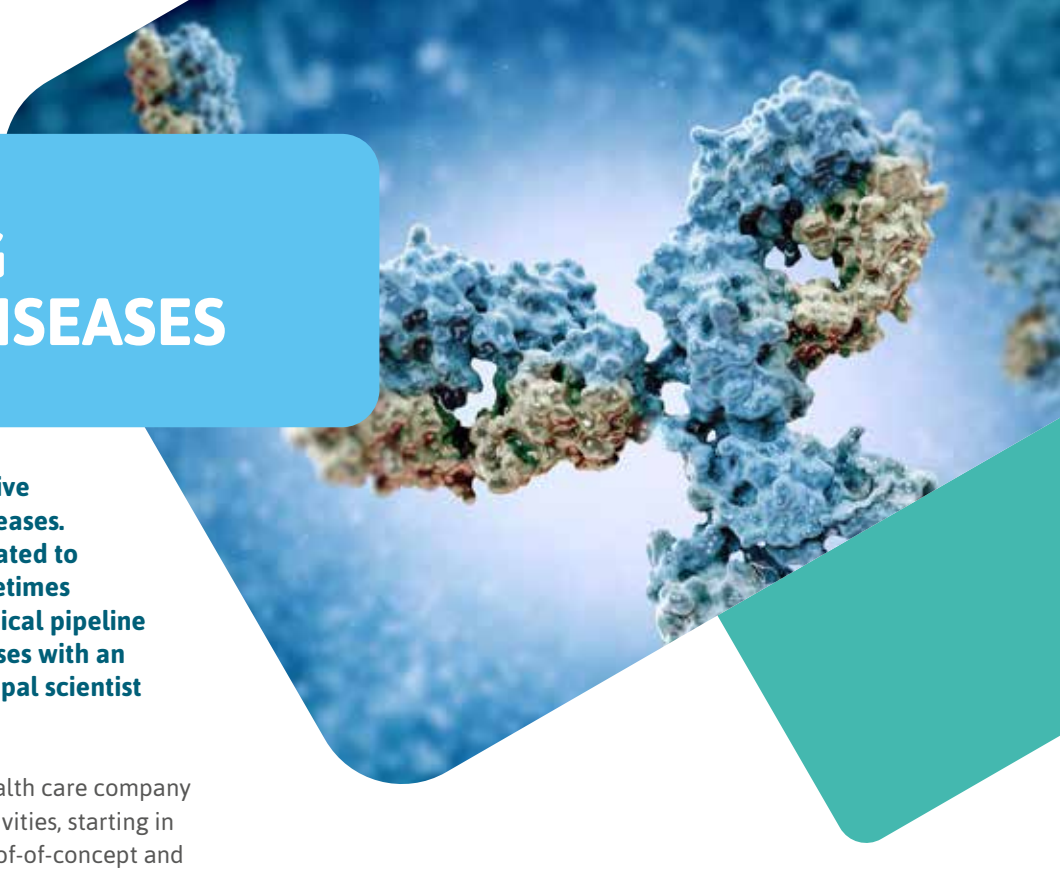
the immune system again. But antibodies are capable of recognizing sugars as well and I am interested to find out whether certain antibodies prefer a certain type of glycans. Even though the viral sugar coat contains a massive amount of different and complex sugars, using MS and glycoproteomics we can map the surface really well. We are doing experiments in which we use an antibody of interest to 'fish' for viral proteins and see what type of glycans, which glycoforms, are bound and which are not. That will give us an idea of the interactions, or the lack thereof, between the antibody and the virus. Again, this is interesting from a fundamental perspective to understand the nature of these interactions, but also for vaccine production because it tells you something about the host cell needed for vaccine production: which cell gives you the best glycan profile for immune recognition?"

Do you think that these more fundamental insights will also uncover general principles about immune recognition?

"If you consider that an antigen can easily have ten binding sites for a sugar and that each of those sites there are at least ten different sugar compositions possible, the complexity is overwhelming. No two copies of an antigen are alike. This poses a major obstacle to the immune system, but somehow, in the majority of cases, the immune system succeeds in creating a suitable antibody. So, there has to be some kind of a pattern and in spite of the complexity there are similarities as well. Those concern the residues that are located closest to the protein. The first five residues of a glycan are mostly the same, but how the branching and the residues attached there affect the binding of the antibody, that is what we aim for." ■

"Viral glycans play a big role in antigen recognition"

CONTROLLING INFECTIOUS DISEASES



Vaccination is one of the most effective methods of preventing infectious diseases. That's why Janssen Vaccines is dedicated to develop vaccines against these, sometimes life-threatening, pathogens. "Our clinical pipeline focuses on targeting infectious diseases with an unmet medical need," explains principal scientist Arjen Scholten.

Janssen Vaccines, which is part of the health care company Johnson and Johnson, covers all R&D activities, starting in discovery, going through pre-clinical proof-of-concept and clinical development. At the moment, the company employs approximately 1000 people at the site in Leiden. Most products in the pipeline are based on Janssen's innovative technology platforms: PER.C6® and AdVac®.
AdVac uses adenoviruses that have been made incompetent to replicate, but are still capable of penetrating cells and deliver their DNA for transcription. "When developing a new vaccine, we implement the DNA sequence of an immunogenic protein fragment of for instance Ebola or Covid in the adenovirus genome," Scholten explains. "Upon injection of the AdVac viral vector the Ebola or Covid DNA is delivered in the cells of vaccine recipients. The recipients will then express the immunogenic protein fragment and present this to the immune system to generate an appropriate response that can hopefully also be remembered in case the recipient encounters the real Ebola or Covid virus."
AdVac technology combined with the PER.C6® cell line allows the growth of the vaccine viral vectors up to very high densities in a bioreactor. "In this way we succeed to manufacture thousands of vaccine doses in a relatively small bioreactor volume. In our small-scale bioreactors of 2x10L we can manufacture approximately 100.000 doses."

Characterization tools

Scholten works for the product characterization group, which is part of analytical development. "We focus on figuring out what specific molecular characteristics of the adenovirus are critical for ensuring that the vaccine is safe and efficacious during manufacturing, storage and use." His team works on the relation between different stress conditions the product encounters during its lifecycle and the impact thereof on the molecular characteristics of the product. "For example, we are interested in the chemical and structural modifications that occur during exposure of our AdVac vector to high temperatures the product may encounter during manufacturing or during use in countries with a warmer climate."
The adenovirus vector is a very complex 'molecule' as it consists of about 3000 proteins (14 different ones ranging from 1 to 720 copies per virus capsid). This makes the study of molecular changes more challenging than for the typical antibody based biological therapeutics. Scholten: "As a consequence, the impurity profile is much more complex and requires advanced characterization tools to study. Many of these analytical tools we develop ourselves but we also collaborate with university labs to increase our knowledge and capabilities."

COVID-19 vaccine

Janssen Vaccines' development program focuses on many different infectious diseases such as, for example, Ebola, HIV, RSV and Flu. At the moment the company is also working very hard on the worldwide needed corona vaccine. "For Covid we are currently preparing for first in human trials by September 2020 at the latest. This means we are preparing the first GMP drug substance and drug product batches and are readying our analytical capabilities to release the batches as soon as possible." The company anticipates the first batches of a COVID-19 vaccine to be available for emergency use in early 2021—a substantially accelerated timeframe in comparison to the typical vaccine development process. "Our goal is to supply one billion doses of the vaccine globally," Scholten concludes. ■

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Key differences in anthracyclines

PhD project: Development anthracycline anti-cancer tools and drugs for chemoimmunotherapy

Anthracyclines and immunotherapy may strengthen each other's effect against cancer. A team of three combines their skills in an ICI project to find out why, in order to fully exploit the synergetic effect.

Chemist Dennis Wander and biomolecular scientist Sabina van der Zanden worked together in a joined ICI PhD project to investigate cardiotoxicity of anthracyclines (see ICI Bulletin 2, April 2016, p4). They discovered why doxorubicin and aclarubicin, two members of the group anthracyclines, differ in their toxic side effects. This started when Wander synthesized a range of 'in between' molecules to systematically explore the biological effects of the different functional groups present in the two anthracyclines. "That is easier said than done," admits Wander. "Anthracyclines are fragile, you need to treat them like babies in your round bottom flasks."

When 'a new baby' was born, Wander jumped on his bike to Van der Zandens laboratory nearby in Leiden. She explored its biological activity on living cells and subsequently in various mice models. Van der Zanden: "We discovered that analogues which contain a 'shielded' amine group like aclarubin do not induce DNA double strength breaks. They can still remain effective in killing cancer cells by inducing histone eviction. Doxorubicin has both activities." The almost 'forgotten' anthracycline aclarubin therefore doesn't cause heart damage, a common side-effect of the popular doxorubicin. "We've sent our results to various journals, but it was returned every time because reviewers want more proof. Yet, every additional experiment we have done confirms our findings," says Van der Zanden. Wander: "I understand the 'resistance', we challenge an established viewpoint in cancer treatment, it's antidogmatic. Yet, every rejection punches my belief in academic science a little."

Floortje van Haften
Tumor Immunology, LUMC
Ramon Arens group

Hands-on

Wander received his PhD in November last year and continues to work for the ICI project as a postdoctoral researcher. Van der Zanden is currently writing her thesis. "The corona crisis actually helps, it forces me to sit behind my computer, and not do extra experiments."

> *"Only together we all get the complete picture"*

Six months ago, the project team has been strengthened by another PhD student: Floortje van Haften. She has a background in biomedical sciences and will explore another aspect of the anthracyclines: their effect on the immune system. In first experiments by Van der Zanden the compounds show a synergetic effect when combined with cancer immunotherapy. Van Haften: "I started by studying the effects of doxorubicin and aclarubicin on T-cells, and will carry on to study the range of 'in-between compounds' that Dennis synthesized. He is also preparing labelled versions which I can use to trace their distribution in tissues, and hopefully in animal models." Van Haften hopes that clinical trials with a combination of an anthracycline and immunotherapy will also start during her PhD project. "I do realize that the chances are small that the work will go that fast, but it would be really amazing to be part of that."

Complete picture

Both Van der Zanden and Wander look back on a long, pleasant and instructive cooperation. Van der Zanden: "I definitely got more background in chemistry thanks to Dennis." Wander: "Once my compounds were ready, we started messaging a lot about the experiments, and soon also about other scientific stuff: Have you read that paper? What does this technical term mean? It's actually a pretty simple but logic combination. I can make compounds, Sabina, and now also Floortje, evaluate their effects. Only together we all get the complete picture." ■

A synthetic lymph node

PhD project: Tuneable synthetic immune niches

Local treatment may overcome important obstacles in immunotherapy. PhD students Lotte Gerrits and Lea Weiss will design, synthesize and test 'artificial lymph nodes' that must induce a strong immune response close to the tumor.

"It's really fun to try something really new," explains biologist and fresh PhD student Lea Weiss her reasons to start a PhD. "And when you succeed, it's very satisfactory," adds her ICI duo-partner chemist Lotte Gerrits. "After I finished my master, I started to work at a start-up company: really interesting work, very nice colleagues, but I missed freedom. As a PhD student, I can choose to make the new molecules or materials that I believe are the most interesting or useful."
Also, the reasons why they both chose for a PhD project in chemical immunology match. Gerrits: "That my work helps to cure cancer is key. Of course, I realize that actual application in the clinic is probably far away. Still, the goal is clear. Not only to me, but also to the general public. Many people have heard about the recent successes of immunotherapy and speak enthusiastically about the field." Weiss has the same experience: "There is so much attention for immunotherapy today. It's just cool to be part of that new wave and enthusiasm."

Corona times

Both PhD students only worked a few months at their laboratories before Covid-19 forced them to stay at home. Weiss now analyses data from first experiments and is making protocols for new tests. "When the lab opens, I can start immediately". She came to Radboud University because of its reputed research master 'Molecular Mechanisms of Disease' and applied for a PhD in the group she heard "only very positive stories" about. Gerrits works on a literature review. "I will be very well read into cancer immunology once the lockdown is over. I do miss the lab work a lot. That's what I like the most, but I consider myself lucky to be able to use the time at home well."

"I miss the lab work"

Tuneable

The ICI duo-project of chemist Gerrits and biologist Weiss focuses on tuneable, local delivery of immunotherapy. Weiss: "Immunosuppression by the tumor and systemic toxic side effects are important roadblocks in immunotherapy. Both may be diminished by local strategies." Gerrits will synthesize a 'switchable artificial lymph node'. "I start with experiments on cryogels that set in the body after injection and attract T-cells. We can load them with tumor antigens to activate T-cells. But that is one of the ideas initiated by my predecessor. We want to design and synthesize various other polymer scaffolds to induce a local immune response."
Once one of Gerrits' creations is ready, Weiss will test its activity and effects in *in vitro* experiments and, when successful, possibly in *in vivo* experiments. "The laboratory of Lotte is just across the road; she can bring the compounds over. I'm really happy to have a partner to discuss chemical aspects. Once a month we have a regular meeting with our supervisors, but when I start working with Lotte's materials, we will also have daily contact." Gerrits: "I need Lea's biological knowledge, for example for choosing which antigens we can use. I will stick to chemical experiments myself, but I'm really keen on learning the basics of the immunological tests she performs." ■

Lotte Gerrits (right)
Department Molecular Materials
Radboud University Nijmegen
Paul Kouwer group

Lea Weiss
Tumor Immunology Department
Radboudumc, Nijmegen
Carl Figdor group

Refining the repertoire: the ins and outs of TAPBPR

In the antigen presentation pathway, a variety of molecules is involved. One of them is TAPBPR, which is still the new kid on the block that we are not fully acquainted with. Louise Boyle is taking on the challenge to get more familiar the component she discovered.

Of course, we would all have preferred to meet up for the ICI Annual Conference, which was planned for March 13 in Amsterdam. One the speakers in the line-up was Louise Boyle, Reader in Molecular Immunology and Wellcome Trust Senior Research Fellow at the University of Cambridge. But the situation being as it is, the stage was exchanged for the living room and the big audience for just one reporter. Nevertheless, Boyle is still happy to share her research with the ICI community.

Her work focuses on the mechanisms that control peptide selection for antigen presentation. It all revolves around TAPBPR, a novel component in the antigen presenting pathway that Boyle discovered in 2013. TAPBPR is short for tapasin-related protein and like its close relative tapasin, it acts as an MHC class I-dedicated chaperone. "It has a role in selecting peptides on the MHC class I molecules to elicit a T-cell response. TAPBPR acts as a peptide exchange catalyst, but its specific role is still unknown," says Boyle. "MHC class I molecules get loaded with peptides and are then passed on to

▼ *Louise Boyle, Research Fellow at the University of Cambridge. Her research focus: exploring the molecular pathways controlling antigen presentation to the immune system.*

> *"A novel component in the antigen presenting pathway"*

TAPBPR for a kind of proofreading. If TAPBPR can dissociate the peptide, it would probably not have lasted long enough on the cell surface for recognition, so it looks like a form of quality control to narrow and refine the peptide repertoire."

Affinity

One of the main questions is how this selection process works, what are the criteria for TAPBPR to act and dissociate a peptide? "We don't yet know what it selects for. It could be related to affinity. Previous studies have shown that TAPBPR takes off peptides with low affinity. Tapasin, which also acts as a peptide exchange catalyst, loads peptides onto MHC class I and we know from studies in TAPBPR-deficient cells that the peptide repertoire changes and some lower affinity ones remain." Interestingly, in those cells that lack TAPBPR, the total levels of MHC class I molecules do not change, Boyle adds. "So, it does not seem to be needed for peptide loading as such, but we don't know what it is needed for. Why do we need TAPBPR, why did it evolve? We need more biological insight to understand its role in the broader immunological context."

Exploring these underlying biological mechanisms is one of the research lines in the Boyle lab, but she is also probing and pushing the properties of TAPBPR to find out what else it could do. "Our experiments have shown that TAPBPR can

> *"We need more biological insight to understand its role"*

work on surface expressed class I molecules, but that is not where it normally works. We can use TAPBPR in the 'wrong location', we have used it on tumor cells and showed that it can bind viral peptides. There is therapeutic aspect in this, if we can change what is naturally presented. TAPBPR could change the repertoire that is loaded onto class I molecules, we may be able to load new antigens onto tumor cell lines that might not express them naturally." ■

From chemical to clinical laboratory

"A perfect mix of chemistry and medicines". That's how Jolien Luimstra, former ICI PhD candidate, describes her new job as a trainee in clinical chemistry at Meander Medical Centre in Amersfoort. "As a clinical chemist you support doctors in making the right diagnoses."

It's all about bodily fluids, clinical chemistry. Blood samples, but also urine, sputum, spinal fluid and even sweat can provide essential information about someone's health. A modern hospital laboratory performs hundreds or even thousands tests every day. "My new laboratory looks very different from the chemistry lab at LUMC," tells Jolien Luimstra who recently received her PhD at Leiden University. "It is huge and fully automated; you see blood tubes moving around constantly. It's called 'the track'."

"Only one in five PhD students remains in academia"

Luimstra started as a trainee in clinical chemistry in September last year. A regular work day now begins at eight by attending a shift change meeting at one of the hospitals departments. "I need to brush up on my knowledge in medicines. These shift change meetings are very informative and instructive. I learn a lot about the clinical presentation of illnesses and about disease progression, but also about patients' personal medical histories, about co-morbidities and other characteristics relevant for treatment."

Jolien Luimstra, trainee in clinical chemistry and laboratory medicine, Meander Medical Centre, Amersfoort

Favourite option

Becoming a clinical chemist has been Luimstra's goal since a few years. "I started my PhD at the NKI where every employee gets a 'tour' around the associated hospital. I witnessed surgery, saw the emergency room, visited the children department and also the clinical laboratory." The visit at the clinical laboratory made an impression. Luimstra asked one of the clinical chemists if a personal tour was possible and started visiting other clinical laboratories too. "I just mailed or phoned to the head of the laboratory, and every time I was welcome. I would advise every PhD student to look and ask around for career possibilities, only one in five stays in academia."

There are 10-15 training vacancies for clinical chemists in the Netherlands every year. Luimstra considers herself lucky to be selected by Meander. "It was one of my two favourite options for a trainee position. Meander is a modern hospital with attention for sustainability and designed to provide a healing environment: all single rooms, lots of daylight, plants and trees, and views on the surrounding landscape. The only pity is that it is very unlikely that I can stay after I have become a registered clinical chemist. The team is quite young, so there is no chance someone will retire soon."

Luimstra started by using her research skills. "When there is blood in urine a common cause is a urinary tract infection, but another possibility is kidney failure. You can discern between the two by examining the shape of the red blood cells. The cells become deformed when pressed through damaged filtering membranes in the kidneys." Luimstra investigated new test options and is now preparing a new national guideline within a team consisting of nephrologists, internists and clinical chemists. "Quite cool that all laboratories will use 'my' guideline once it has been approved."

Your own track

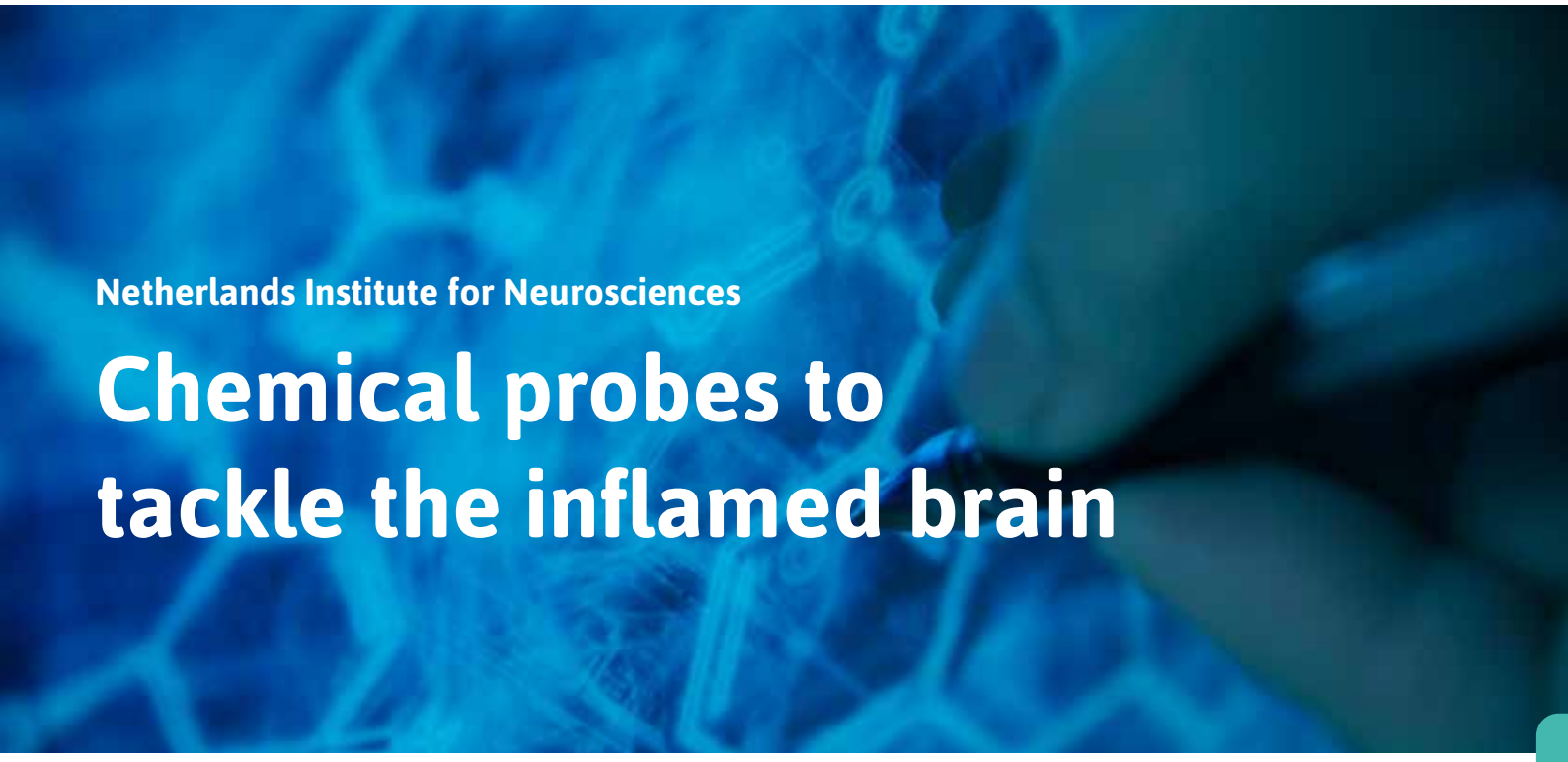
In four years time Luimstra will probably run her own 'track' with some decades in clinical chemistry ahead. No fear of repetition? Luimstra: "Not at all. The job has so many aspects and specialisations. You may focus on implementing new tests, on quality assurance, on management, on new guidelines. I won't get bored." ■

Reference

PhD project Jolien Luimstra: Mechanisms of action of the Ubiquitin-like modifier ISG15 in immune regulation (see ICI bulletin, issue 4 p4, May 2017)

Post PhD

ICI PhD projects from the first phase of the Chemical Immunology Institute are gradually being finished. Some PhD students have already defended their thesis and earned their PhD degree. In this section, *Career*, we follow the young scientists' first steps on their career ladder.



Netherlands Institute for Neurosciences

Chemical probes to tackle the inflamed brain

By combining chemical, biological and neurological expertise with an impressive collection of patient material and a set of advanced *in vivo* visualization techniques, the Netherlands Institute for Neuroscience and ICI are exploring new routes to understand multiple sclerosis, a devastating neurological disorder that, so far, remains untreatable.

Blurred vision, loss of muscle strength, problems with coordination, a tingling sensation in hands or feet - these are usually the first signs that point to multiple sclerosis, better known as MS. Later on, patients often develop additional symptoms, including cognitive problems, fatigue, memory loss and speech impairment. In the Netherlands, approximately 17,000 people suffer from MS and as the age of onset is usually between 20 - 40 years, this means that a substantial group of relatively young people is hit by a gradually debilitating disease for which effective treatment is lacking. And that is because, despite serious and meaningful progress in understanding the nature of MS, the disease is still surrounded by many questions. A new collaboration between the Netherlands Institute for Neuroscience (NIN) and ICI will use chemical tools in animal models and patient material to probe deeper into the underlying molecular mechanisms of nerve damage and inflammation. And perhaps, uncover new therapeutic leads.

Interrupted signals

One of the hallmarks of MS is the presence of focal inflammatory lesions with degradation of the myelin sheath that surrounds and insulates the axons - the long projections of the neurons that conduct the electrical impulses used by neurons in the central nervous system to communicate and control organs, glands and muscles throughout the body.

When, for reasons still unknown, the myelin sheath starts to degrade, the effect can be compared to what happens when the plastic cover of an electrical wire is damaged: signal transmission gets interrupted. The damaged axon can no longer properly conduct the nerve impulses, resulting in impairment of muscle control or organ function.

"In some lesions, inflammation is rapidly progressing whereas others show hardly any activity," says Inge Huitinga, director of the Netherlands Brain Bank (NBB) in the Institute for Neuroscience (NIN) and professor of neuroimmunology at the University of Amsterdam. "In my group, we study these lesions using our large collection of post-mortem brain tissue of MS patients. In the brain of an individual patient, we can view all stages of the disease from the first damaged sites to full-blown inflamed lesions and inactive scar tissue, but also remyelinated lesions. When we first started studying all this patient material, we were surprised to find so many highly

"This collaborating provides a promising opportunity to really move forward"

active lesions. Currently, we are characterizing the lesions in various stages of the disease and we are particularly interested in the role of microglia in these lesions." Microglia are immune cells that form the first line of defense in the brain and spinal cord. Their role in neurodegeneration is quickly gaining attention, says Maarten Kole, whose research group within NIN studies axon signaling in animal models of MS using advanced imaging, electrophysiological and

computational techniques. "We are currently focusing on a transgenic mouse line with fluorescent markers for microglia to study their role in disease development and progression. By inducing targeted inflammation leading to de-myelinization, we can study the disease at various stages in a living animal."

Perfect timing

Interestingly, microglia are not only involved the degradation of the myelin sheath, they can also initiate recovery, a process called re-myelination. Kole: "We know that certain endocannabinoid receptors play a role in re-myelination." More in general, the endocannabinoid system clearly is involved in MS as many patients benefit from medicinal marihuana, says Huitinga. "There is clearly an effect, but we don't understand the mechanisms involved." Teaming up with the chemistry group of Mario van der Stelt [see box] offers new ways untangle the complex interplay between microglia, the endocannabinoid system and MS pathology. "The timing of this collaboration is perfect. The role of microglia in the endocannabinoid system is a hot topic and the way we are now combining our expertise and techniques to study these mechanisms in detail is really innovative," Huitinga feels. "The MS community needs new approaches that address microglia. We can provide new insights on molecular targets that stimulate microglia towards re-myelinization." Kole agrees: "We will surely uncover new therapeutic leads. I know it doesn't sound very scientific, but I am really confident that the way we are together tackling the problem is the route we should take right now." ■

"The role of microglia in the endocannabinoid system is a hot topic"

NETHERLANDS INSTITUTE FOR NEUROSCIENCE
Master the mind

Adding MS to the portfolio

Cancer, auto-immune diseases, infections - those were the major disease categories within the ICI program. But Mario van der Stelt, ICI member and professor of molecular physiology at Leiden University, has now added multiple sclerosis (MS) to the consortium's portfolio.

"I have always been interested in neurodegenerative diseases and MS has a large immunological component," Van der Stelt explains. The idea for a collaboration with the Netherlands Institute for Neuroscience (NIN) first came up when he and Maarten Kole, department head at NIN and professor at Utrecht University met as members of an NWO committee. "We immediately recognized the interfaces between our research activities and saw opportunities for collaboration." So when a call for proposals was launched as part of ICI's second phase, Van der Stelt contacted Kole and Inge Huitinga, director of the Netherlands Brain Bank and professor of neuroimmunology at the University of Amsterdam, to submit a collaborative project on the development of activity-based chemical probes for lipases to study the dynamics of lipid metabolism in the inflammatory brain lesions that are characteristic of MS. "We know that MS patients have many lesions in their brain and that these lesions show a high variety in activity," says Van der Stelt. "We also know that inhibitors of monoacylglycerol lipases are promising compounds to modulate neuroinflammation. Our aim is to develop chemical probes that bind this class of lipases, allowing us to visualize activity of the lesions. Being able to distinguish between more and less active lesions will provide us with a better idea of the disease stage and how MS manifests itself in individual patients. It can also help to determine which patients are likely to respond to therapies based on inhibitors of these lipases, which are currently in preclinical development." Next to Van der Stelt's expertise in developing activity-based probes, he can contribute his knowledge of the endocannabinoid system. "The whole project evolves around that system," he says. "MS patients benefit from medicinal marihuana. From animal models, we know that THC, the active component of marihuana, diminishes MS symptoms and also slows the degeneration process. But we don't how that works on a molecular level. That is something we will be addressing as well." Collaborating with the NIN groups provides a promising opportunity to really move forward, he feels. "This project is really translational. We combine chemistry and visualization methods with studies in cells, in animal models and in patient material. All in one project. That is quite special." ■

In Memoriam Huib Ovaa

On the 19th of May 2020, our dear colleague and friend Professor Dr. Huib Ovaa passed away at the age of 46. In the past year, after being diagnosed with prostate cancer, Huib underwent a variety of treatments. Always with his usual optimism. He continued to work as much as possible and tried to keep the burden of his fight against cancer away from the people around him.

Huib was an excellent scientist who was able to look beyond the boundaries of his own field, chemistry, which allowed him to broaden his view. Add to this his fascination for biology and it is clear why he played such a prominent role in the development of a new and promising scientific field 'Chemical Biology'. His input was also invaluable for current status of the chemical immunology field. With his boundless enthusiasm, his inspiring creativity, his powerful sense of humor and his ability to raise funds, he was the silent driving force behind the position that ICI has achieved.

> ***"A highly gifted, motivated, productive and above all, a very creative scientist"***

Sjaak Neefjes, scientific director ICI: "Huib was a highly gifted, motivated, productive and above all, a very creative researcher who continuously and effortlessly crossed boundaries between chemistry and biology. He loved to collaborate and he flourished, as a synthetic organic chemist, in an environment, both at the Netherlands Cancer Institute and more recently at the LUMC, dominated by biochemists, molecular biologists, cell biologists and immunologists."

A top scientist, a friend, a prankster, an inspirer...and also a great mentor. Celia Berkers, his first PhD student, says: "For Huib, no idea was ever too crazy, no goal was ever out of reach. This led to exciting, pioneering, fun and elegant science. Being a PhD student in his lab, I learned so much from Huib. He completely changed my perception of what chemistry can do, taught me that you can use it to solve biological questions that you cannot even begin to answer without chemistry, and how this can open up completely novel fields. His fearlessness and way of thinking were truly inspirational and continue to inspire me almost every single day. But what was really special is that for all these years, he always made me feel like he was my biggest fan."

Huib lived for science and for his people, and was very proud of his group. Jolien Luimstra, formerly ICI PhD student, remembers the lab meetings. "The work discussions were sacred and he liked to speak about 'rocket science'. He also introduced the 'kick ass science' award comprising a super cool finding which would be rewarded with a bottle of champagne. Huib always did what he thought was best for the group. He liked to have fun and was averse to rules, bureaucracy and 'puppet show' ceremonies as he would call them. For example, at promotion ceremonies he was wearing a canary-yellow lined gown and he kept on postponing his own inaugural lecture for as long as possible, which was finally planned for November..."

We will miss his inspiration, his drive, his humor and his enthusiasm, but his ideas will live on within ICI and in the minds of everyone who worked with him. ■

News

ERC Consolidator Grant

Last December, Sander van Kasteren was one of the four Leiden scientists awarded with an ERC Consolidator Grant. These grants of up to 2 M euros will enable them to continue and expand their research. Van Kasteren aims to spend the grant for accurately mapping how our immune system responds to vaccines, particularly those aimed at curing diseases like cancer and chronic viral infections.

PhD Candidate of the year

Tomislav Caval was selected as 'PhD Candidate of the Year 2019' by the Scientific Advisory Board of the Bijvoet Centre for Biomolecular Research. His PhD work was part of the ICI Project 'Development of enrichment methods for intact n-glycopeptide profiling to identify interaction partners of tumor specific glycan-binding receptors.' Last November he defended his thesis at the Utrecht University

Multiple awards

In November last year Sjaak Neefjes won the Josephine Nefkens prize for his innovative and original work on a previously abandoned chemotherapeutic agent named Aclarubicin. The prize is awarded once every three years for outstanding cancer research. The prize money (100 K euros) will be used to revive Aclarubicin.
Last February Neefjes has been appointed to The Royal Holland Society of Sciences and Humanities: KNHMW. As of September 1, 2020, he will join the board of the Royal Netherlands Academy of Arts and Sciences (KNAW).

Recent publications

Iglesias-Guimarais V, Ahrends T, de Vries E, Knobeloch KP, Volkov A, Borst J.
IFN-stimulated gene 15 is an alarmin that boosts the CTL response via an innate, NK cell–dependent route.
J Immunol. 2020; 204:2110-2121; doi:10.4049/jimmunol.1901410

Maurits E, van de Graaff MJ, Maiorana S, Wander DPA., Dekker PM, van der Zanden SY, Florea BI, Neefjes JJC, Overkleeft HS, van Kasteren SI
Immunoproteasome inhibitor–doxorubicin conjugates target multiple myeloma cells and release doxorubicin upon low-dose photon irradiation.
J Am Chem Soc. 2020 Apr 22. 142(16): 7250-7253. doi: 10.1021/*jacs*.9b11969

van der Zanden SY, Luimstra JJ, Neefjes J, Borst J, Ovaa H.
Opportunities for small molecules in cancer immunotherapy.
Trends Immunol. 2020 May 4; S1471-4906(20)30069-7. doi: 10.1016/j.it.2020.04.004.

Wörner TP, Snijder J, Bennett A, Agbandje-McKenna M, Makarov AA1, Heck AJR.
Resolving heterogeneous macromolecular assemblies by Orbitrap-based single-particle charge detection mass spectrometry.
Nat Methods. 2020 Apr;17(4):395-398. doi: 10.1038/s41592-020-0770-7. Epub 2020 Mar 9.

Kissel T, *et al.*
Antibodies and B cells recognizing citrullinated proteins display a broad cross-reactivity towards other post-translational modifications.
Ann Rheum Dis. 2020 April 01; doi.org/10.1136/annrheumdis-2019-216499

Valente M, Dölen Y, van Dinther E, Vimeux L, Fallet M, Feuillet V, Figdor CG.
Cross-talk between iNKT cells and CD8 T cells in the spleen requires the IL-4/CCL17 axis for the generation of short-lived effector cells.
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Nat Chem Biol. 2020 May 11. doi: 10.1038/s41589-020-0528-7.

Koenders STA, *et al.*
Development of a retinal-based probe for the profiling of retinaldehyde dehydrogenases in cancer cells.
ACS Central Science. 2019 5(12), 1965-1974/ doi: org/10.1021/acscentsci.9b01022

Column

CHALLENGED BY SARS-COV-2 PANDEMIC

Expanding our knowledge of the immune system

SANDER VAN KASTEREN, PhD
ICI EXECUTIVE ADVISORY BOARD

Sander van Kasteren is associate professor at the Leiden Institute of Chemistry.

Over the past few months, the world ground to a halt under the pandemic clouds of the coronavirus' rapid spread. Our ICI did not stay out of the firing line either. It was a tough – but in hindsight correct – decision to cancel this year's Chemical Immunology Conference for the health of everybody involved. It turned out to be only the beginning of far-reaching measures that have kept many of us tied to our houses.

In the rare moments when I have not been trying to juggle a group, a family, the online-translation of my courses, and the lessons of my kids, I have found myself wondering what this pandemic will mean for our future. Not for the world in general, but more our future as immune scientists. For one, it has made me realize how pivotal a role the immune system plays in many diseases – both to prevent them and to aggravate them. What the pandemic has also exposed is the absence on some very fundamental knowledge; particularly on innate immunity in the anti-pathogen response. We don't seem to have answers to questions as basic as "why do some folk get sick and others not upon exposure to the virus?" and – perhaps even more acute – "why is the immune system of some patients actually killing them, whereas others suffer very little?"

Whilst a lot of research effort will be focused on the biology of viruses and other pandemic agents, the development of vaccines and drugs against these, I think the immunology of the anti-pathogen must not be forgotten. Particularly the study of the pathological role of the immune system in these infections. Questions, such as those above, but also regarding the mechanism of the near-mythical antibody-dependent disease enhancement, are perfect targets for teams of chemists and immunologist as we have set up over the past 6 years.

I therefore implore you all to look at this pandemic not only as a blight, but also as an opportunity for new research avenues in which chemistry and immunology, applied and fundamental science, can be beautifully bridged. Not a bridge of sighs but a bridge of hope so that we can meet the challenge of the current and of future pandemics. ■

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 Organization 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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