ICI institute for chemical immunology

Interview

BEING AT THE RIGHT PLACE AT THE RIGHT TIME

MARTIJN VERDOES, PhD
Assistant Professor at the Department of Tumor Immunology
Radboud UMC Nijmegen

Always on the lookout to learn something new, Martijn Verdoes has steadily expanded his horizons. Working from a basis in organic synthesis, he has gradually added a whole array of biological techniques to his portfolio. With a recent ERC Starting Grant and the first ICI Tenure Track under his belt, he is now all set to tackle a range of interesting research ideas. "I don't believe in a magic bullet when it comes to a complex disease like cancer. We need multiple lines of attack."

When you started in early 2013 as a postdoc in Carl Figdor's group in Nijmegen, the ICI was just getting off the ground. Did that influence where you decided to do your research?

It did, but not as you might think. Before moving to Nijmegen, I was a postdoc at the Stanford School of Medicine with Matt Bogyo. After almost four years there, my girlfriend and I decided to move back to the Netherlands. She interviewed for a position at the chemistry department in Nijmegen, so I started orienting myself there as well. The research in Carl Figdor's Tumor Immunology department got me interested and Carl granted me thirty minutes of his time. That turned into a two hour conversation. Anticipating the possibility of the ICI being funded, Carl was looking for a chemist to expand the group. I happened to be in the right place at the right time. It really was lucky timing.

You started out as a chemist with a classic focus: organic synthesis. Now, you're working in an immunology group within a medical center. How did biology cross your scientific path?

During my studies, I hugely enjoyed puzzling around with chemistry and trying new things, but most of the time, your ▶

Contents

compounds end up in a freezer and that's the end of the story. But then I went to Hidde Ploegh's group at Harvard Medical School for a student internship. That was my first experience of applying chemistry to biological study. From that moment on, I knew I wanted to work on biological questions. Back in Leiden, I started my PhD research in Hermen Overkleeft's bioorganic synthesis group. I was one of the first to bring biology into the lab there - doing cell cultures and all that. But I wanted to explore further and also test my compounds in preclinical models. My move towards biology has been a gradual process of discovering new possibilities and trying to take new steps.

And the move to Stanford was motivated by further expanding the biological part of your research?

(Laughs) When I was reviewing my options for my NWO Rubicon application to go abroad, I wasn't only focusing on the science to be honest. From my time with the Ploegh-lab, I knew that the East Coast environment was pretty competitive and that the weather didn't really suit me – with very hot summers and really cold winters. So, spending a few years with a renowned research group at one of the best universities in the US in relaxed and comfortable Northern California sounded very attractive.

"The ICI community clearly has a collaborative attitude"

Was it a good move?

Yes, it was a great environment to work and live.

What did you work on?

I focused on quenched fluorescent activity-based probes (qABPs) to investigate a specific group of proteases, the cysteine cathepsins. These are linked to the regulation of antigen presentation, matrix degradation and cell motility. In tumors (as well as in inflamed tissues) protease activity is high, making the cysteine cathepsins useful targets for our probes. The probes mimic the cathepsins' substrates, but instead of the usual peptide bond, they contain an electrophilic trap. As a result, the cathepsin gets stuck. By ensuring that the quenching group is also the leaving group, binding the cathepsin makes the fluorescent dye visible. You get to see the trapped cathepsin. The approach worked out really well, but it immediately got me thinking about the underlying biology. What caused all that protease activity in the tumor?

...and what did you discover?

Measurements with FACS (fluorescent activity-based cell sorting) revealed that our probe was specifically switched on one type of macrophage called M2. We know that tumors can recruit immune cells to work on their behalf. One of the tumor's strategies is to lure macrophage precursor cells, manipulate them and then put them to work, for example in degradation of cellular matrices to create room for new blood vessels. Tumors are very good at creating their own beneficial microenvironment with immunosuppressive conditions.

"We need multiple lines of attack"

2015 was a very successful year; you obtained an ERC Starting Grant and were selected as the first ICI Tenure Track recipient. What are your plans now?

I strongly believe in a combined strategy of stimulating and evoking a tumor-specific immune response while simultaneously breaking down the tumor's immunosuppressive barrier. We are working, for example, on targeting tumor antigens at dendritic cells as a vaccine approach. Another important topic is the checkpoint inhibitors. These compounds interfere with the communication lines that tumors use to inhibit T-cells. The checkpoint inhibitors reactivate T-cells to do their proper job. Checkpoint inhibitors are already used in the clinic, but often they generate autoimmune responses as well. What if we were able to make the checkpoint inhibitor work only in a very specific manner? Then, we might avoid autoimmunity. Furthermore, I plan to continue my work on the 'bad' macrophages; can we find a way to manipulate them and turn them into the good guys again?

That's a lot of work on a range of topics.

I don't believe we'll find a magic bullet for treating a complex disease like cancer. We'll need multiple lines of attack. After a year spent largely on writing proposals, I now have the time and, most importantly, the resources to really get going with all these ideas.

Finally, about the ICI - can a large initiative like this, involving multiple parties, really be effective?

When large sums are at stake you often see that on paper a proposal sounds fantastic, revolutionary and innovative. However, as soon as the money is secured, everyone just goes back to minding their own business. But with the ICI I don't see that at all. This community clearly has a collaborative attitude, and the combined PhD projects are a great example. We are now training true chemical-immunologists. This exchange between disciplines is very fruitful and we can all stimulate it. We must push chemists towards doing biological experiments and motivate biologists to dive into the chemistry. ■

PROMISING RESULTS WITH ITS FRONT-RUNNING ADC PROGRAMME

Synthon Biopharmaceuticals is a prominent player in the field of antibody-drug conjugate (ADC) technology. "We strongly believe that our second generation ADCs will become a new class of effective, targeted medicines in oncology," says programme leader Gijs Verheijden.

Synthon was founded in 1991. Within two years the young enterprise succeeded to launch its first generic product, dobutamine. This drug, used in the treatment of heart failure and cardiogenic shock, was a success and gave a solid basis for further development. The small Nijmegen-based local company, employing less than a hundred people, steadily grew to its present form: an international – still privately-owned – company with laboratories, offices and production plants all around the world, employing 1.600 highly educated people. "Research and development are vital components of the overall value chain and essential to our company," Verheijden explains. The products are mainly marketed through a business-to-business model. "Our strategy is to develop robust partnerships which enable us to share knowledge with and draw upon specialist skills of partner companies."

Science-driven innovation

Innovation and continuous improvement are the heartbeat of the company. Verheijden: "We are aware that most of the ideas that will take us forward originate in the laboratory with our scientists. They are continuously challenged by finding new promising leads or technologies that may lead in time to new drugs." After established successes in the field of complex small molecule generics, in 2007 the company extended its activities to the field of biopharmaceuticals, starting with the successful development of a biosimilar to trastuzumab. The biotech activities were built out and transferred to subsidiary Synthon Biopharmaceuticals. "The R&D team now employs more than 250 staff. We completely focus on research into new molecular entities in the therapeutic areas oncology and autoimmune diseases." The acquisition of Syntarga and its proprietary antibody-drug conjugate (ADC) technology in 2011 had been a significant strengthening of Synthon´s biopharmaceutical capabilities.

Synthon

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Second generation

The ADC approach provides a new class of drugs in cancer treatment. Highly toxic molecules are attached to tumor-targeted antibodies. The antibody delivers the cell-killing agent directly to the tumor site and healthy tissue is protected against the devastating effects of the agent, since the ADC only binds to tumor cells. "Typically, an ADC binds to the tumor-associated target, is internalized and subsequently releases the potent drug," Verheijden summarises. Synthon's lead ADC programme uses the HER2-binding antibody trastuzumab linked to a duocarmycin analog, a strong cytotoxic drug. "The differentiating design of our linker connecting the antibody to the duocarmycin drug, leads to high stability in circulation and also induces efficient release of the cytotoxin in the tumor cell." Initial results in clinical studies with this second generation ADC are promising. "Our approach may provide an additional treatment option for patients refractory to the established HER2-targeting drugs and may broaden the patient population eligible for HER2-targeted treatment," he concludes.

Collaborative partnerships

Synthon believes in a collaborative model, based upon strong partnerships with leading scientists, research institutes and partner companies. Verheijden: "ICI perfectly fits in this strategy. We know the consortium and we highly appreciate the scientific qualities of the partners. I feel honoured being invited for a lecture at ICI's second Chemical Immunology Conference, where I will explain our ADC technology in more detail. Taking part in the conference and the accompanying discussions may lead to new and fruitful cooperation." ■

Foto: Broekbakema/Menno Emmink

Tackling the cardiotoxicity of anthracyclines

PhD project: Understanding and modulating anthracyclin-induced immunogenic death

Anthracyclines are very potent chemotherapeutics, but they are also notorious for their damage to the heart. Dennis Wander and Sabina van der Zanden combine their respective expertise in organic synthesis and cell biology to devise and apply modifications to the sugar side chains of these drugs. Their goal is to reduce side effects while increasing therapeutic efficacy.

We like to think that every drug that is administered to us is completely understood. However, that isn't always the case. Sabina van der Zanden is a PhD student in Sjaak Neefjes' group at the Netherlands Cancer Institute in Amsterdam. Her research focuses on an important group of chemotherapeutics called anthracyclines, of which doxorubicin is the most prominent member. "Anthracyclines are widely used, but there is still a lot we don't know about them. For example, we don't understand why these drugs exhibit such severe cardiotoxicity and other side-effects. That really surprised me, considering the long and strictly regulated track for new drugs entering the market." Anthracyclines all contain a central element of four coupled rings that each consist of six carbon atoms and various side groups. The key to understanding the severe side effects seems to lie in the composition of the sugars coupled to this central element.

Dennis Wander, MsC
Leiden University, Bio-Organic Synthesis
Hermen Overkleeft-group

Sabina van der Zanden, MsC
Netherlands Cancer Institute, Cell Biology II
Sjaak Neefjes-group

"The four-ring element of the topoisomerase II inhibitor wedges itself into the tumor DNA, thereby blocking translation and replication," says Dennis Wander, PhD student at Leiden University in Hermen Overkleeft's group. "Most likely, the sugar side chains invoke all kinds of reactions that result in severe cardiotoxicity. This is a serious dose-limiting factor in the use of doxorubicin. That is unfortunate, because doxorubicin is a very potent anticancer drug."

Biological effect

All the more reason for Van der Zanden and Wander to see if they can come up with ideas to modify doxorubicin's sugar composition in such a way that the cardiotoxicity is decreased without affecting its potency. Van der Zanden's background in cell biology helps give her a detailed view of the effect of various anthracyclines on cells. "This has resulted in discovering possible connections between anthracycline

"Cardiotoxicity is a seriously dose-limiting factor"

structure and its effect on cell survival, DNA damage and other parameters. These results provide hints on how we can try to adapt the structure of doxorubicin," she explains. Working from a completely different area of expertise, Wander is using his skills as a synthetic organic chemist to synthesize new sugar side chains. It is a serious challenge, but that's exactly what he likes about the project. "I really like to tackle difficult syntheses, but not only for the sake of making a new molecule. The driver is to generate a biological effect, and by collaborating with Sabina I quickly get feedback on the performance of new compounds." He welcomes input from someone with a completely different area of expertise. "Sabina knows a lot about cell biology and I know how to synthesize the compounds. It is a good combination."

WhatsApp

Van der Zanden and Wander communicate regularly on an informal basis. Wander says, "We started out by using e-mail, but that was a bit static. Now we use WhatsApp and that works really well." Van der Zanden admits that she had to get used to the timelines and 'language' of chemistry. "When Dennis would say that he was starting up an experiment, I had no idea of how much time that would take and when I could expect a first result, unlike in biology." This is no longer the case and they both are pleased with the way the collaboration is working out. Van der Zanden: "It is about communication. Sometimes daily, depending on what there is to share. Even though we don't see each other very often, it feels like a close collaboration." ■

How low oxygen conditions sustain themselves

PhD project: Novel optogenetics approach to study systemic sclerosis etiology

Laurent Paardekooper and Andrea Ottria try to unravel the mechanisms behind systemic sclerosis, one of the most devastating rheumatic disorders. They come from different scientific backgrounds and thus employ different strategies. The result: a broader perspective. "We both observe different things. So when we collaborate, we see more."

Systemic sclerosis (SSc) is an extremely severe autoimmune disorder that leads to excessive fibrosis – formation of connective tissue – in blood vessels and various organs. The mortality risk is high and adequate therapeutic options are lacking. Although the underlying causes of SSc are still unclear, there are some good clues as to the mechanisms involved. "We know that hypoxia, a lack of oxygen, plays a role on the cellular level," says Laurent Paardekooper, PhD student in Carl Figdor and Geert van den Bogaart's group at the Radboud University Medical Centre in Nijmegen. Distortion of the cellular oxygen balance leads for example to vascular damage, because certain parts of the vessel walls do not receive enough oxygen. "We also know that dendritic cells from SSc patients contain high levels of reactive oxygen species (ROS) and of hypoxia-induced factor (HIF), a protein associated with hypoxia. An increase in ROS creates hypoxic conditions that drive the development of SSc."

Feedback loop

Another important clue is the overproduction of the chemokine CXCL4. Andrea Ottria, PhD student in Timothy Radstake and Wioleta Marut's group at the University Medical Centre Utrecht, explains. "CXCL4 induces the transformation of endothelial cells into myofibroblasts leading to the formation of fibrotic tissue, which is a hallmark of SSc." And there seems to be a positive feedback loop. Ottria: "The formation of ROS is the starting point, but the resulting hypoxic conditions in turn favour the formation of ROS. So, hypoxia is both a consequence and a cause. Moreover, fibrotic tissue is low in oxygen as well, which also stimulates the production of ROS, leading to hypoxia and so on. This whole system is really like a dog chasing its tail."

Cytokine profile

So, where to start looking for answers? Paardekooper concentrates on the subcellular level and on mapping relevant pathways. "Currently, I am studying the effects of ROS on different elements of the cell, in particular mitochondria and membranes, and on the regulation of hypoxia-induced factor (HIF). Another area of interest is the cytokine profile of cells under hypoxic conditions. I have observed that healthy and hypoxic cells generate different cytokine profiles in response to infection, which corresponds to clinical observations in patients." Ottria tackles the problem on the level of a model system. "We are now trying to bring all the discoveries into a mouse model that is a CXCL4 knock-out. As chemokine CXCL4 triggers the formation of fibroblasts, we want to know what happens when we create hypoxia in mice. Will that also induce fibrosis? As there is no cure for fibrosis, it is important that we learn what precedes the fibrotic process, so we can generate leads to stop progression or even prevent disease onset."

"This disease is like a dog chasing its tail"

Sharing knowledge pays off

Tackling a problem from different angles and exchanging results and ideas is very valuable, according to both Paardekooper and Ottria. "We have already come to similar conclusions, which is a confirmation that we are doing the right thing," says Ottria. "What I really like about this duo set-up is that Laurent can see things that I cannot and vice versa. Together, we see more." Paardekooper agrees: "Collaboration is essential. Both groups have different knowledge and expertise and by sharing, everyone benefits. With these kind of complex problems, you can't get anywhere on your own." ■

Laurent Paardekooper, MSc
Radboud UMC, Tumor Immunology
Carl Figdor/Geert van den Bogaart-group

Andrea Ottria, MSc (not on picture)
UMC Utrecht, Clinical Immunology
Timothy Radstake-group

Science across borders

If we join forces we can double the speed of progress

In recent years, as medical and scientific research has become increasingly specialised, it's become crucial for researchers to share knowledge and expertise. They must broaden their perspectives and hunt for answers further from their research areas. "Innovation can be found at the interface of different disciplines," argues Reina Mebius, "and that is certainly true in the field of immunology."

Our immune system is a network of cells, tissues and organs that work together to defend the body against 'foreign' invaders. The system can recognise and remember millions of different enemies, and produce secretions and cells to match up with and wipe out each of them. "The immune system is amazingly complex," says Reina Mebius, professor of Molecular Cell Biology at VUmc and chairwoman of the Dutch Society for Immunology (NVVI). Her research focuses on studying immune reactions and unravelling the underlying defence mechanisms. "It would be a near-impossible mission without cooperation and contributions from different disciplines."

Vitamin A

The relationship between immunology and nutrition is one of the areas that Mebius' research group focuses on. "'We are what we eat' is not just a slogan," she laughs, "there's a lot of evidence too." Vitamin A has proven to be indispensable for the function of the intestinal immune system. "We are studying the role of vitamin A in regulating gut-associated immune response. We are particularly interested in its metabolic breakdown product, retinoic acid, which is crucial for safeguarding homeostasis within the intestine and providing protection against disorders like inflammatory bowel disease (IBD), coeliac disease or food allergy." She takes a piece of paper and sketches the proposed mechanism, elucidating the importance of food in regulating the enzymatic conversion of vitamin A into retinoic acid. "We have shown that retinoic acid derived from intestinal epithelial cells mediates the differentiation of tolerogenic dendritic cells, which are needed to control the immune system as well as the composition of the intestinal flora. Importantly, we have recently found that a high fibre diet can enhance the metabolism of vitamin A through induced expression of the vitamin A-converting enzyme retinal dehyrogenase (ALDH1), within the intestine of mice. This is important, as higher levels of vitamin A conversion in epithelial cells will lead to more tolerogenic dendritic cells and thus more immune regulatory responses, when compared to lower levels of vitamin A conversion."

> ***"The immune system is amazingly complex"***

Cross-pollination

Mebius is very pleased about her recent cooperation with Hermen Overkleeft's group. Together they develop methods and tools to follow vitamin A conversion within cells in order to identify dietary products able to influence the levels of vitamin A-converting enzymes. "These tools will enable us to dissect the various immune cells within the mucosal immune system which rely on retinoic acid-dependent signalling for their functions." The cooperation takes shape through a joint ICI PhD project (Visualization of Vitamin A metabolism) including a chemical arm and an immunological arm. This

approach leads to cross-pollination. "It works wonderfully. The chemists continually surprise me with their original and daring ideas. From our side, we can enrich the study with our immunological know-how. Together, we can make 1+1 = 3!"

Disease-transcendent concept

The concept of multidisciplinary cooperation has also become the strategic mission within the NVVI. It aims to create alliances to combat chronic diseases. "Diseases like diabetes, rheumatoid arthritis, psoriasis, MS and BDI seem to be unrelated, yet they share the same underlying mechanism: an immune system gone haywire," says Mebius. Unlike cancer, immune-mediated diseases lack a common denominator. We don't say: 'he or she has a chronic immune-mediated disease', and in hospitals there aren't 'immune system disease' departments."
Within cancer research we focus on the general mechanism of uncontrolled cell growth. Similarly, inflammatory disease research should be aimed at the underlying process of immunological imbalance. Therefore, the NVVI proposes a disease-transcendent approach, including an integrated research programme and participating of all involved parties. "It is vital that we exchange information about the underlying immunological processes in different chronic diseases and learn from each other. That way we can double the speed of progress and improve our knowledge of the basis functioning of the immune system. This will lead to [more] effective therapies that may benefit patients suffering from chronic diseases."
The first step in realising cooperation is allocating financial funds. "Unfortunately, getting funds is not easy nowadays. An NWO gravity grant would be wonderful. The ICI has shown how this can lead to fruitful cooperation between different disciplines." ■

"Walls between disciplines should be broken down"

Natura docet

Jon van Rood has been a pioneer in bridging sciences. He was trained to become an internist, but combined being an MD with heading the blood bank where he ended up in transplantation research. Combining two worlds has been instructive and has opened new insights. "However, nature is our most important teacher: natura docet," argues emeritus professor van Rood.

At 89 years-old Jon van Rood doesn't see his age as an excuse to take it any easier. The immune-haematologist and transplant medicine specialist remains curious. Occupying an unpaid workplace at the Dutch stem cell donor registry, the Matchis Foundation, and the Leiden University Medical Centre, he continues to work. Since his retirement in 1991 he has focused on the intriguing immunologic dialogue between mother and child during pregnancy.

HLA tissue types

After studying medicine in Leiden Van Rood became, during his internist resident training, head of the blood bank at the University Hospital. From the beginning he's been intrigued by immune reactions and the mechanisms at work in transplantation and procreation, with a central role for the human leukocyte antigen (HLA) system. His group was the first to start unravelling the complexities of the HLA system through collaborative studies that used panels of sera and leukocyte samples. Their research not only contributed significantly to the discovery of the HLA system, they also succeeded to classify the HLA tissue types including more than a hundred million different combinations. No mean feat! How did he manage it?
"First of all, I was assisted by a fantastic team of highly competent employees," Van Rood answers. Furthermore, he is of the firm opinion that coincidence always plays a main role. "I happened to meet a woman who had just given birth to twins and who responded extremely violently to a blood transfusion. Although it was her first blood transfusion, she seemed to have antibodies against the donor blood. This incident set us thinking and became the key to realising the importance of the HLA system and its role in the complex immunological balancing act during pregnancy."

Miraculous cooperation

Bridging disciplines sounds easy but "it's bloody difficult," says Van Rood. "It isn't easy to be considered as a full colleague in both worlds. You definitely have to speak both languages." However, if managed, it surely yields profits. Combining chemistry and immunology, like ICI aims, may lead to surprising findings. Van Rood, however, would like to make one comment: "Chemists want to understand nature by dissecting the different molecular processes. I recommend chemists to be challenged by nature. Try to learn from it and to understand the miraculous cooperation in natural processes."
"In the course of evolution, nature even has learned to cure cancer," Van Rood concludes. He hopes to find out more about the underlying mechanisms from a joint project with Sjaak Neefjes aimed to unravel the immunology of pregnancy at a molecular level. ■

Geert-Jan Boons wants to turn biological problems into technological innovations

After 25 successful years in England and the United States, Prof. Geert-Jan Boons has chosen Utrecht University as the place where he will realise his next ambition. Last month, he and several members of his research group moved from the University of Georgia (USA) to Utrecht. As department head and Professor of Chemical Pharmacology, he wants to take his pioneering work in the field of complex cellular carbohydrates, called glycans, to the next level. Boons wants to know what the complex structures of the glycans says about their biological functions to uncover the roles they play in disease and to open new avenues for the development of therapeutics and vaccines.

"Every cell of every living organism is covered by a layer of complex carbohydrates, known as glycans, which are critical for life and play vital roles in health and disease," Boons explains. For example, a defect in a specific complex carbohydrate structure can cause cellular migration, which in turn can result in tumor metastasis. This implies that tumor cells can be recognised by a specific glycan that is not present on healthy cells. With this knowledge, Boons and his colleagues have developed a therapeutic cancer vaccine that allows the immune system to recognise this glycan and spring into action. That is Boons' driving motivation: turning biological problems into technological innovation.

Utrecht University

This is also a reason why he decided to move, after 18 years, his large and successful research group at the University of Georgia to start afresh in Utrecht. "The University of Georgia doesn't have a University Medical Centre. In addition, Utrecht University has a Department of Pharmaceutical Sciences and

What the complex glycan structures tell about their biological functions

a Faculty of Veterinary Medicine. The research group led by Frank van Kuppeveld, for example, has a lot of expertise in pathogens such as the flu virus that use glycans to penetrate cells. I love the opportunity to work with them to understand viral cell entry and help develop the next generation of diagnostic and therapeutic."

Homecoming

After 25 years speaking English on a daily basis, Boons occasionally has to search for the correct word in Dutch, but he says that the return to Utrecht feels like coming home. But even Russian, Indian and Chinese researchers in his group who followed him from the US are enjoying the move to Utrecht. "They've been offered great living accommodation in Utrecht, and they've found that the Dutch are very open and

Opening new avenues for the development of therapeutics and vaccines

welcoming people. I hope that their positive experiences will encourage other members of the group to come over soon. Because the chemistry of cellular glycans requires quite a bit of specialist knowledge and their expertise is needed in Utrecht."

Thousands of different types

Boons is a pioneer in the synthesis of the complex glycans, which perform a wide range of biological functions on the outer cell surface. There are thousands of different types of these molecules on every single cell in the body. They are compiled from a known set of building blocks, but they are not linear like DNA and proteins. The innumerable branches of these molecules create enormous structural diversity, which makes their analysis and synthesis in the laboratory much more complex than that of DNA or proteins. "For now every glycan is basically a research project of its own," explains Boons.

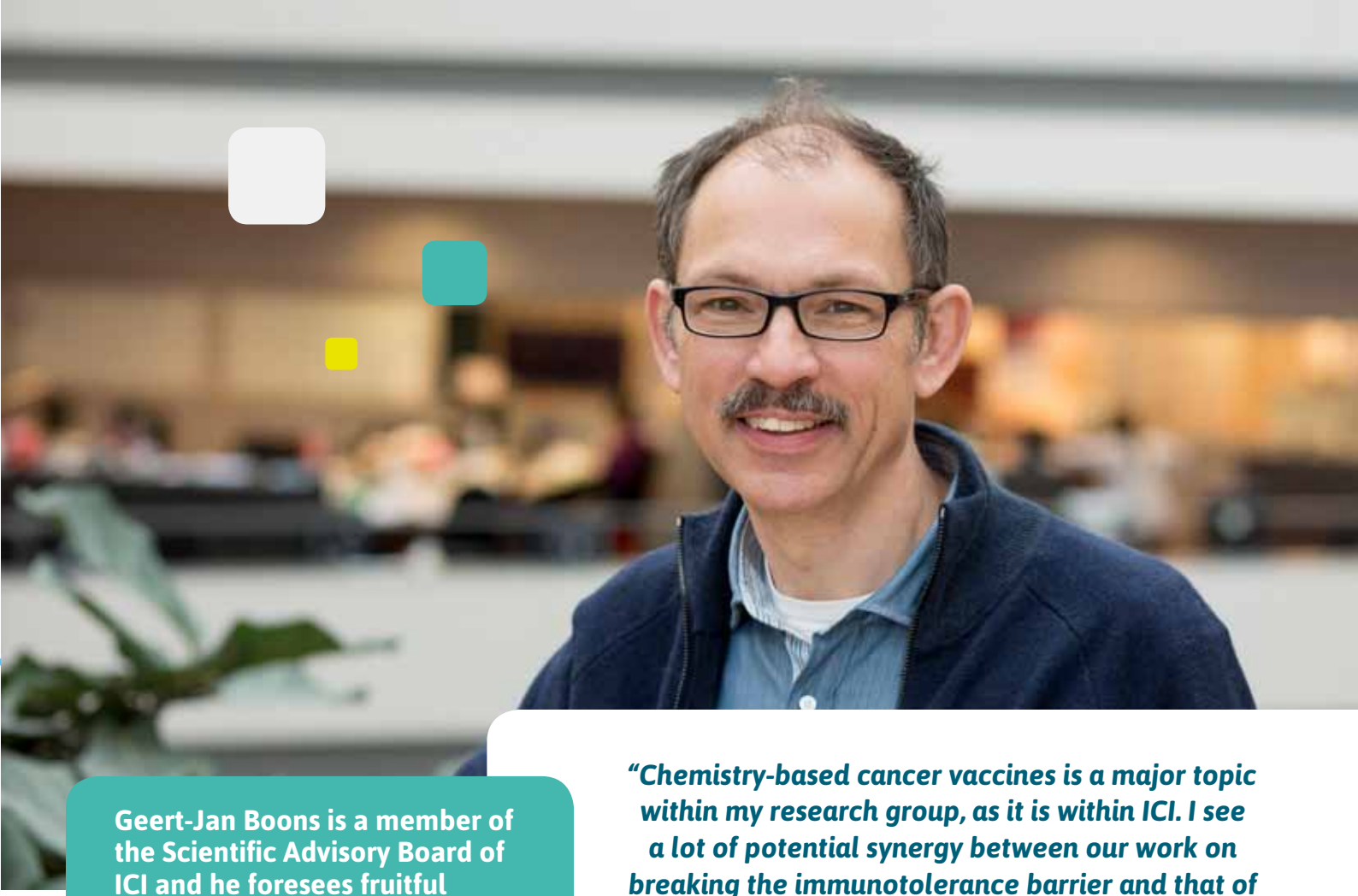
Complex for a reason

Boons finds the complexity of the glycans intriguing: "Nature makes these molecules complex for a reason. I want to understand why, by discovering the relationship between their structures and biological functions at the molecular level." But to do so, the glycans must be analysed and synthesized much faster than is currently the case.

'Glyco-omics'

In order to realise his ambition, last year Boons was awarded an NWO TOP-PUNT subsidy of two million Euros together with Albert Heck who is the Professor of Biomolecular Mass Spectrometry and Proteomics at Utrecht University. Boons expects that glycans will eventually be able to be analysed and produced fully automatically, as is now the case with DNA and proteins, so 'glyco-omics' may be able to provide a major impulse to biomedical research the way that 'genomics' and 'proteomics' have done in the past. ■

Interview Utrecht University, 29 February 2016



Geert-Jan Boons is a member of the Scientific Advisory Board of ICI and he foresees fruitful interaction between his research topics and the special research area within ICI.

"Chemistry-based cancer vaccines is a major topic within my research group, as it is within ICI. I see a lot of potential synergy between our work on breaking the immunotolerance barrier and that of the ICI immunology groups, for example the group of Yvette van Kooyk. Working with ICI offers us the opportunity to further evaluate and refine our technologies in a wide range of applications."

Reaching a broader audience through Kennislink.nl

The Dutch website 'Kennislink.nl' provides well-informed stories on developments in science and technology that appeal to the inquisitive minds of its broad readership. With more than 3 million unique visitors per year, Kennislink is the best visited popular science website of the Dutch language area. Kennislink covers science from two angles: by discussing the latest news from the world of science and technology and by offering a scientific perspective on topical issues in society. Through its large team of editors and their network of correspondents, Kennislink offers news, background and expert opinions on all scientific areas from natural sciences to linguistics, from medicine to history and from mathematics to social sciences.

In 2015, Kennislink discussed ICI research several times. Examples are an interview in May with Carl Figdor (Radboud UMC) on developing cancer vaccines, a news item in April on a Angewandte Chemie paper by the group of Sander van Kasteren (Leiden University) and a news item in November following a paper in Chemical Science by Daphne van Elsland (Leiden University) on imaging of degraded bacteria.

Chemical immunology is a research field that is highly interesting and relevant to a non-expert audience. The Kennislink editors that specialize in medicine, chemistry and biology respectively all have backgrounds in the field they cover and are always interested in new developments and results from their areas. For those ICI researchers who like the idea of discussing their research with an audience outside their peer group, please contact ICI's communication manager Martje Ebberink on info@chemicalimmunology.nl ■

www.kennislink.nl

How to communicate more effectively

The second module of the Institute for Chemical Immunology's soft skills PhD programme has just concluded. It was on Communication in Science, and we spoke to one of the students to find out what she learned.

Having a great idea is hard. Turning that idea into a scientific discovery is even harder. The days of researchers making solo breakthroughs after toiling away in isolation are long gone. Scientists work in teams by necessity, and get better work done together. However, group work isn't always entirely frictionless. Balancing workloads, sharing results, leading effectively – it all takes experience. Rather than let that impede scientific progress, the ICI has organised a PhD programme to help researchers improve their soft skills and thus work together more efficiently.

The programme, focused on augmenting scientific expertise with organisational and communication skills, has been organised by leadership and communication coach Louise Mennen. After the first module in September on personal effectiveness, the second took place in February and March on Communication in Science. Anna Hoekstra, Utrecht University, Biomolecular Mass Spectrometry Group, was on the course. She studies the metabolism of various T cell subsets in order to find targets to manipulate the immune balance in cancer and autoimmune diseases.

Less text, more pictures

A key area that Anna was looking to improve was her ability to summarise. "I am aware that I like to put too much text and details on slides and poster, and I was hoping to get some feedback on how to slim that down." So as part of the two-day programme, students brought in posters they'd made previously to analyse. Anna brought the first poster she'd made, from the beginning of her PhD. She had felt that the concepts were fairly digestible from the pictures and captions alone, so filled the rest of the poster with information. The feedback she received was that there was "far too much text" however. Anna is keen to learn from this, and said, "Next time I will try to reduce the amount of text to 20%, use 40% for pictures and also leave plenty of empty space. Furthermore I will make sure the take home message is highlighted so it cannot be missed."

Another key academic skill the module focused on was how to present properly. Standing and speaking in front of a quiet room full of your peers is the kind of thing that strikes fear into many people's hearts, including Anna's, who says she's, "very nervous [and] often afraid of forgetting things". So she was pleased to learn about a different method of presenting, one that breaks up the usual 'wall of information'. "They suggested that you should first connect with your audience by telling a story which leads to your key message, then support your key message with examples and arguments and end with a convincing ending, leaving enough time for questions and feedback."

Communication style

The way we talk, write and express ourselves is often such an unconscious act that we don't really think too much about how we do it. Anna was surprised to learn that there is a name for the way she prefers to communicate – she is apparently a 'Thinker'. Having completed a questionnaire based on the Myers-Brigg personality test, all attendees were grouped into one of four different styles. It turns out that Anna's style tends towards the verbose – and she says, "It explains why I like to write very long emails/blogs with a lot of details, and posters with a lot of text". She acknowledges that she communicates this way because it reflects how she prefers to receive information, but having learned about other possibilities, she feels better equipped to adapt her style to her recipients.

Learning how to communicate more effectively has a lot to do with understanding yourself, and understanding others. It's something we often take for granted, and don't see as something we can change. But a little self-reflection and analysis can be hugely helpful in working more successfully with others. ■

ICI Modules

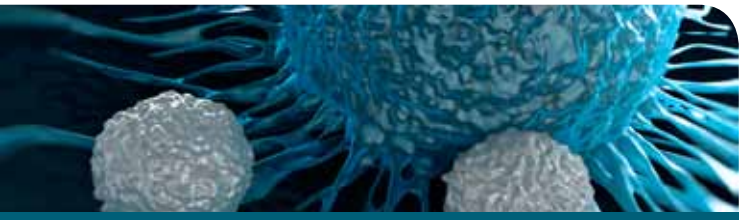
Module 1
Personal Effectiveness: time and project management
Autumn 2015

Module 2
Communication in Science
Successful networking, presenting convincingly, poster design, communication styles
Spring 2016

Module 3
Personal Leadership
Personal qualities & success stories
Spring 2017

Module 4
A PhD, what next?
Desires and qualities, create your future (vision, action plan)
Spring 2018

News



Collaboration Neon Therapeutics and NKI

The Netherlands Cancer Institute (NKI) together with the Amsterdam Biotherapeutics Unit has entered into a collaborative reseach agreement with Neon Therapeutics, an immuno-oncology company developing neoantigen-based therapeutic vaccines and T cell therapies to treat cancer. The work will leverage the research by Prof. John Haanen (NKI) and Neon co-founder Ton Schumacher (NKI, ICI executive board member).

2016 Award of the ESMI to Peter Friedl

Peter Friedl (RIMLS) has been awarded the European Society for Molecular Imaging 2016 Award for his work of preclinical imaging of cancer and immune cell function in live tissues and therapy responses, using advanced and intravital microscopy. The ESMI Award is given yearly to an excellent scientist for her/his outstanding contribution to the interdisciplinary research field of Imaging Science.

Albert Heck partner in EU programme MSmed

Within five years, the first hospitals should be able to completely analyse all of the proteins in a patient's blood and urine in order to provide more individualised treatment. That is the ambition of the Heck group at Utrecht University and the four European partners. The researchers have received a 3.7 million Euro grant for their MSmed research proposal as part of the Future and Emerging Technologies programme within the Horizon 2020 project.

Recent publications

Banno A, Garcia DA, van Baarsel ED, Metz PJ, Fisch K, Widjaja CE, Kim SH, Lopez J, Chang AN, Geurink PP, Florea BI, Overkleeft HS, Ovaa H, Bui JD, Yang J, Chang JT

Downregulation of 26S proteasome catalytic activity promotes epithelial-mesenchymal transition.

Oncotarget. 2016 Feb 22. doi: 10.18632/oncotarget.7596. [Epub ahead of print] PubMed PMID: 26930717.

Unanue ER, Turk V, Neefjes J

Variations in MHC Class II Antigen Processing and Presentation in Health and Disease.

Annu Rev Immunol. 2016 Feb 22; In press

de Bruin G, Mock ED, Hoogendoorn S, van den Nieuwendijk AM, Mazurek J, van der Marel GA, Florea BI, Overkleeft HS

Enantioselective synthesis of adamantylalanine and carboranylalanine and their incorporation into the proteasome inhibitor bortezomib.

Chem Commun (Camb). 2016 Mar 3; 52(21):4064-7.

Mommen GP, Marino F, Meiring HD, Poelen MC, van Gaans-van den Brink JA, Mohammed S, Heck AJ, van Els CA.

Sampling from the proteome to the HLA-DR ligandome proceeds via high specificity.

Mol Cell Proteomics. 2016 Jan 13; In press

van der Kant R, Jonker CT, Wijdeven RH, Bakker J, Janssen L, Klumperman J, Neefjes J

Characterization of the Mammalian CORVET and HOPS Complexes and Their Modular Restructuring for Endosome Specificity.

J Biol Chem. 2015 Dec 18; 290(51):30280-90.

Wijdeven RH, Jongsma ML, Neefjes J, Berlin I

ER contact sites direct late endosome transport.

Bioessays. 2015 Dec; 37(12):1298-302.

Poolman JM, Maity C, Boekhoven J, van der Mee L, le Sage VAA, Groenewold GJM, van Kasteren SI, Versluis F, van Esch JH, Eelkema R

A toolbox for controlling the properties and functionalisation of hydrazone-based supramolecular hydrogels

Journal of Materials Chemistry B 2015 Dec; 4, 852-858

Wijdeven RH, Pang B, van der Zanden SY, Qiao X, Blomen V, Hoogstraat M, Lips EH, Janssen L, Wessels L, Brummelkamp TR, Neefjes J

Genome-Wide Identification and Characterization of Novel Factors Conferring Resistance to Topoisomerase II Poisons in Cancer.

Cancer Res. 2015 Oct 1; 75(19):4176-87.

Column

CHEMICAL IMMUNOLOGY IS THE PLACE TO BE

For years, immunologists have employed molecular approaches as well as cell biological tools to grasp how our immensely complex immune system operates. It has been fascinating to observe how immune cells are able to communicate, both by intimate contact in the lymphoid organs as well as over greater distances when residing in peripheral tissues.

Based on our current extensive knowledge of how immune cells communicate and exert effector functions, we are now able to start manipulating the system effectively in patients. This has resulted in recent breakthrough immunotherapies finding their way into the clinic. These techniques hold potential both for tackling autoimmune diseases such as rheumatoid arthritis, as well as for grappling with cancer, where oncologists are beginning to recognise immunotherapy as a serious treatment modality.

These novel immunotherapies are based on the use of antibodies as well as on cellular approaches, such as the use of expanded tumor-infiltrating lymphocytes (TILs), chimeric antigen receptor carrying T cells (CARs), and dendritic cell (DC) vaccines. A major disadvantage of these cellular therapies is the immense GMP-compliant culturing requirements and patient-specific designs, which results in very labour-intensive and expensive therapies.

I believe that 'cross-talk' between chemists and immunologists will revolutionise our molecular understanding of the immune system. By exploiting chemistry – as we aim to within the Institute for Chemical Immunology – we will become able to mimic immune functions by designing and producing fully synthetic supramolecular structures as off-the-shelf immunomodulators. We are just beginning to scratch the surface, and I am convinced that within a few years we will be able to design structures for a wide range of applications. I foresee that we will be able to replicate diverse immunological functions ranging from antigen presentation to boosting T cell proliferation and skewing immune responses. Furthermore, these advances may also contribute to the design of lymphoid structures such as lymph node-like structures at sites where we want them to develop or expand.

Although this might sound like science fiction right now, I believe we are closer than many of us expect – we can already produce polymers decorated with antibodies, and antigens that effectively activate T cells. These truly are exciting times for chemical immunologists!

CARL FIGDOR
EXECUTIVE BOARD ICI

He is professor of Immunology (in particular Tumor Immunology) and head of the Tumor Immunology Department at Radboud UMC, Nijmegen.

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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