Interview

"I REALLY ENJOY DEVELOPING NEW METHODS"

KIM BONGER, PHD
Assistant Professor Biomolecular Chemistry at Radboud University Nijmegen

With an ERC Starting Grant and an ICI Tenure Track position secured, Kim Bonger, Assistant Professor at Radboud University Nijmegen, is all set to go and explore new lines of research. Understanding the role of citrullination and PAD enzymes in auto-immunity is high on her wish list, as is selective targeting of memory B-cells. The common element is Bonger's focus on method development using chemical biology approaches.

Congratulations on your ERC Starting Grant. Obvious question: what will you be studying using this €1.5 million grant?

"The focus is on citrullination, a post-translational modification that is linked to various auto-immune diseases. For example, in rheumatoid arthritis, 70% of the patients express so-called ACPAs, anti-citrullinated protein specific antibodies, that recognize citrullinated epitopes. A key role in this process is played by a class of enzymes called PADs, peptidyl arginine deiminases, which convert arginine into citrulline, also an amino acid. So, PADs are responsible for creating the epitopes that illicit an auto-immunity response, but apart from that we know very little about these enzymes. We don't know what their substrates are and how PADs are regulated. We also don't know whether citrullination is reversible and if it is a specific or a more general post-translational modification. I want to use this grant to study how, when and where PADs become activated and what the major players in this process are. We need to know which proteins are involved and therefore, a large part of the work ▶

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will be dedicated to developing new chemical biology-based methods that enable us to capture PAD substrates and to measure PAD activity."

Citrulline is also a 'normal' metabolite as part of the urea cycle. Is there also a normal role for PADs and for citrullination?

"We have theories on that, but we want to develop probes that allow us to study the role of PAD enzymes and citrullination in healthy cells. The conversion of arginine into citrulline is not something trivial, it means a huge change. Arginine is positively charged, whereas citrulline is neutral. We know for example that histones can get citrullinated, which means that their capacity for binding the negatively charged DNA decreases. That could point to a regulatory role for citrullination in transcription and translation, but this is still just theory. But I do think that PADs have a rather general function in the cell and that they are regulated through protein-protein interactions. And identifying those interactions is one of my main objectives."

And how is all this related to the role of PADs in auto-immunity?

"We know that PAD is activated by calcium, but under normal conditions the intracellular calcium level is too low to be relevant. However, outside the cell, calcium is the leading activator. We also know that extracellular PAD is not very specific. One theory suggests an important role for neutrophils, which are part of the immune system's first line of defense. Neutrophils can initiate the formation of so-called neutrophil extracellular traps, the NETs, which lead to cell damage and cell death. It has been demonstrated that this causes the release of intracellular PADs, which then get activated by the extracellular calcium. In rheumatoid arthritis, this leads to unchecked citrullination of matrix proteins such as fibrinogen, which in turn are recognised by the anti-citrulline protein specific antibodies. Interestingly, these ACPAs can already be detected as early as ten years before the first symptoms of rheumatoid arthritis emerge."

"We know very little about these enzymes"

Is citrullination only a problem in rheumatoid arthritis or is it involved in other auto-immune diseases as well?

"Citrullinated epitopes have also been identified in multiple sclerosis and Alzheimer's disease. I think this points to a more general process of neo-epitope formation in which the body's own proteins undergo a transformation that leads to an unwanted immune response."

You want to unravel the protein-protein interactions involved in PAD regulation. How do you plan to do that?

"By developing new methods. We need new approaches to study how PADs operate. We have just developed a new method for mapping such interactions using enzyme fusion. In short, we fuse PAD to another enzyme and this fusion product reacts with a small molecule to a highly reactive intermediate that will covalently bind to anything in the near vicinity. Next, you isolate and characterise the complexes."

"It is really satisfying when you manage to control processes in a living cell"

Would that be applicable to other proteins as well?

"That is what you always hope when you work on a new method. It is also a reason why I enjoy method development so much. You can unleash all your creativity and it is really satisfying when you manage to control processes in a living cell. Moreover, by coming up with good methods you enable a big leap forward in biological research. That is the best part, you not only take your own project to the next level, but you can help other projects ahead as well."

Is the research related to your ICI Tenure Track appointment also focused on citrullination and PADs?

"In part. We are also interested in more translational projects to treat auto-immune diseases. For example, together with the group of rheumatoid arthritis-expert René Toes at the Leiden University Medical Center, we plan to selectively target and inhibit memory B-cells. The current therapy against rheumatoid arthritis, rituximab, shuts down the whole B-cell system. That includes the useful, protective ones. We want to develop a more fine-tuned method, but there are not many targets available. One of the few possibilities is the B-cell receptor that we hope to use to create specificity. We need to identify which epitopes are recognised by the B-cells we want to target and then develop a system that can bind those receptors and deliver an inhibitory signal. So, this again involves method development and it will surely lead to yet new research ideas in the future." ■

"This points to a more general process of neo-epitope formation"

T CELL THERAPY MEETS METABOLOMICS

▲ Jürgen Kabull, cofounder Gadeta

New insights into the biology of cancer pave the way to new promising treatment strategies. Gadeta focusses on novel cancer immunotherapies based on selectively sensing metabolic changes in cancer cells.

"From a therapeutic point of view, this may be a good thing, because metabolic changes in a cell occur very early in cancer and don't seem to be dependent on the genetic changes that are typical for tumour cells," explains Jürgen Kuball, professor of haematology at the UMC Utrecht. He chairs the section applied tumour-immunology within the laboratory of translational immunology. He is also CSO and cofounder of Gadeta which is located in the Bio Incubator next to the UMC Utrecht. The company develops immunotherapy strategies based on Kuball's ground-breaking discoveries regarding the role of gamma delta T cell receptors (γδ TCRs) in the broad recognition of both haematological and solid tumours whilst leaving healthy tissue unharmed.

T cell engineering

The immune system can detect early metabolic changes in cancer cells that have only very few genetic abnormalities. Kuball's research group has identified and characterised a new sensor that is instrumental in this process. The sensor is a γδ TCR that scouts for altered lipid metabolism in cancer cells. Unfortunately, the replication capacity of the immune cells that carry this sensor is low, making it difficult to generate adequate amounts for therapy or resulting in a quick elimination of cells once stimulated or transferred in human.

Gadeta developed a new technology platform to overcome this major weakness of γδ T cells, but also to use their powerful tumour-sensing receptors. The technology is based on engineering αβ T cells, which have good proliferation capacity but lack appropriate tumour reactivity, to express a well-defined γδ Receptor with strong anti-cancer reactivity. These new type of immune cells, so called TEGs, combines the strengths of both original cell types. "It has the ability to specifically recognise malignant transformation of a cell; it has the ability to proliferate well; and even more importantly, it can effectively target a broad range of tumour cells," summarizes Kuball. "In 2015, we established the UMCU-spinoff company Gadeta, based on this innovative immunotherapy."

Molecular Immunology Hub

TEGs seem to have strong therapeutic potential for combatting and eradicating both haematological and solid tumours. "Exploring this novel type of receptor is just the tip of the iceberg," says Kuball. "Because utilising the γδ TCR mode of recognition for cancer detecting is so novel, many other subtypes may also be of value in the near future." This is where the Molecular Immunology Hub comes into play. Recently Utrecht University invested in thirteen so-called hubs. The four Life Sciences hubs aim to bring excellent researchers from different disciplines together to work on societal relevant issues and scientific breakthroughs, within the framework of Utrecht Life Sciences. The Molecular Immunology Hub is a bridging platform that can mitigate many risks of early drug developments. Through the hub, it will be able to move γδ TCR science forward quickly into translational application, thereby supporting early and late stage development of clinical compounds, which will create new funding sources and stronger connections with biotech and pharmaceutical industry. "Together, we can develop technologies and inventions so that we can target more specifically broader patient populations and translate these findings into daily clinical practice. The recent success of our spin off company Gadeta nicely illustrates how excellent science and entrepreneurship creates true impact," Kuball concludes. ■

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Creating pluribodies

PhD project: Design and construction of multipurpose pluribodies

Immunotherapy may gain specificity by conjugating multiple antibodies in a 'pluribody'. The design and construction is a true challenge, experienced PhD students Elko Peterse and Angela el Hebieshy. Now the proof-of-the-pudding-moment is approaching, the excitement is rising in Leiden.

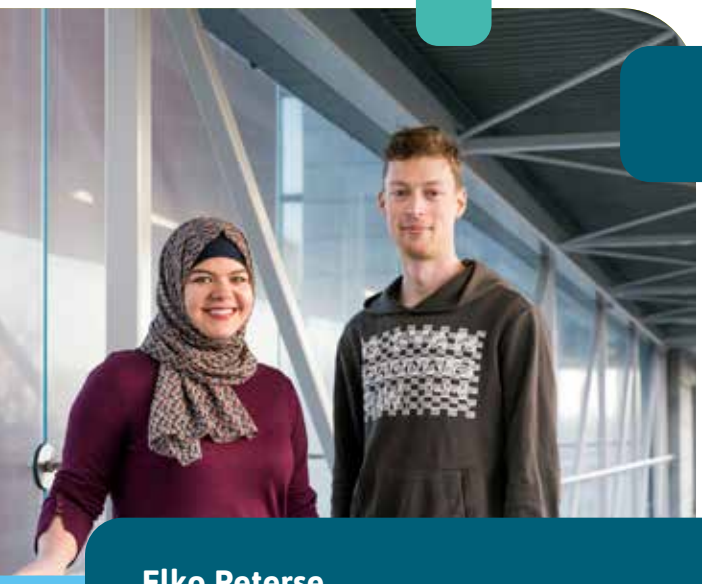
"It took a lot of trial and error to find the right combinations of reactive groups and coupling strategies," tells chemist Elko Peterse. "Actually, that took far more time and effort than I expected, but that also made it a truly challenging chemical puzzle." Despite the setbacks, Peterse sounds cheerful. That's because he recently succeeded in solving a complicated chemistry puzzle. He synthesised a scaffold carrying two different reactive groups on which two antibodies or antibody fragments can be attached in subsequent steps. "You can 'click' an antibody or antibody fragment on the scaffold, one by one."

Testing the total construction

The latter is exactly what his PhD partner at ICI, Angela el Hebieshy is doing. She is 'decorating' the scaffold with different antibody fragments which she isolated and purified while Peterse was synthesizing the scaffold. She also showed proof-of-principle that the proteins can be clicked onto the scaffold without disturbing their natural conformation. "It's the first time I'm doing these more chemical experiments, but I have a lot of support from within the group. In the beginning it was quite exciting being more biologically trained, but it went just fine."

By attaching antibody fragments to the scaffold, el Hebieshy is constructing a 'pluribody'. Although there are very successful examples of antibody therapies, the number of proteins that can be targeted safely is limited due to a lack of tumour-specific proteins. Moreover, infiltration of tumour cells with activated regulatory T-cells often hampers the immune attack. Pluribodies, therapeutics combining several antibodies or antibody fragments, are designed to overcome these problems by binding to a combination of cell markers that is specific to the target cells.

"If it works, it is for both of us the icing on the cake!"



Elko Peterse
Leiden University, Bio-organic Synthesis
Hermen Overkleeft group

Angela el Hebieshy
Leiden University Medical Center, Chemical Immunology
Huib Ovaa group

El Hebieshy received a BSc in clinical pharmacy in Egypt. "I've always been very interested in how the body works. At eight, I enjoyed watching medical and surgical documentaries." She continued her education in Amsterdam studying molecular pharmacology. "The differences in work culture aren't big in academia worldwide, and I speak Dutch as my mother is from the Netherlands."

A highpoint for both PhD students is testing the total construction, the scaffold carrying two antibody fragments. Will it indeed bind to target cells as expected? El Hebieshy is planning and will perform the crucial experiment. "I'm looking forward to it. Experiments are anyhow my favourite part of the work. You do something new. That is certainly true for this key experiment." Peterse: "The experiment is Angela's first responsibility, but I hope I have time to be there. If it works, it is the icing on the cake for both of us!" Currently, Peterse is building an even more complex scaffold that carries three different reactive groups. Peterse: "I've learned a lot assembling the first scaffold. The step from two to three reactive groups should be smaller."

Strong partnership

The PhD students are very pleased with their partnership. Peterse: "Without Angela, I would probably be waiting for months for test results coming in by email. Instead, I'm fully involved in the preparations. We confer about the design of the experiments and the best conditions." Also the contacts with other ICI PhD students are very valuable to him. "Sharing your ups and downs is very comforting, and it gets you out of the bubble of your lab-life." ■

The secret power of omega-3 fatty acids

PhD project: Specialized pro-resolving lipid mediators in acute and chronic inflammation

Omega-3 fatty acids are healthy. Your brains but also your immune system benefits from these compounds in fish oil. But why and how? PhD-students Joost von Hegedus and Berend Gagestein try to follow the fatty acid metabolites and pinpoint them in action, thereby unravelling their role in immunology.

"We know that omega-3-poly-unsaturated fatty acids are essential and beneficial to the immune system," tells biomedical scientist Joost von Hegedus. "Active lipid metabolites are formed that are known to contribute to the final process in acute inflammation: the return to the normal situation." The active metabolites are known as SPMs: specialized pro-resolving lipid mediators. However, which cells produce SPMs and which proteins and receptors bind them is largely unknown, tells Von Hegedus explaining the focus of his PhD-studies. "My PhD-partner has just succeeded in making awesome tools for visualizing and detecting SPMs based on ω3-fatty acids. SPMs are so small that detection using classical techniques such as antibodies fail. The probes are a really unique, new opportunity to study these lipids in detail."

Eagerly awaiting

Von Hegedus regrets that he has only a few months left to do experiments with the probes. He started half a year before his PhD-partner, chemist Berend Gagestein. Gagestein: "It would have been more logical if I had started first." On the other hand the chemist is happy that somebody was eagerly awaiting his molecules. "Often the work of an organic chemist ends up in a freezer for months or even years, my probes are immediately tested. Moreover, I'm also closely involved in the experiments. That is really great. After all, that's why the compounds were made." Synthesizing the photo-reactive probe turned out to be quite a tough exercise. Gagestein: "Some of the compounds I needed to work with are highly unstable; they are sensitive to oxygen, light and elevated temperatures. I took some time to learn all tricks to handle them."

"The probes are a really unique, new opportunity to study these lipids in detail"

While Gagestein was busy synthesizing the probes, Von Hegedus was involved in biological studies on SPMs. He followed a clinical trial with osteoarthritis patients to see if SPMs are less or more present compared to healthy people, and studied the influence of the therapy. Von Hegedus: "In the lab, I also studied patient material, blood and synovial fluid, and I did experiments using cell cultures obtained from surgery. I added, for example, SPMs to cell cultures to study their effects." In this way Von Hegedus traced the likely source cells of the lipids: macrophages. "Upon sensing intruders macrophages first produce inflammatory molecules, but later also anti-inflammatory compounds."

Different mind-set

After handing over his probes for ω3-fatty acids, Gagestein is pursuing some ideas that "popped up during the synthesis". For example synthesizing a probes based om ω6-fatty acids. He is also closely following the experiments of Von Hegedus. "In biology, experiments require a different mind-set than in organic chemistry. I try to assist Joost by thinking along about all control experiments we need to interpret the results correctly. In doing so, I'm picking up a lot of interesting knowledge on immunology and biology in general."
The end of Von Hegedus' PhD-period is approaching. Does he often think about the next step in his career? "I should, but I'm actually busier setting up experiments," sniggers Von Hegedus. "I certainly want to spend the coming years in research, possibly abroad. Seeing things happening for the first time right before your own eyes is really cool. My curiosity hasn't disappeared." ■

Berend Gagestein (left)
Molecular Physiology, Leiden Institute of Chemistry
Mario van der Stelt group

Joost von Hegedus
Rheumatology, Leiden University Medical Center
René Toes / Andreea Ioan-Facsinay group

Expected and justified: Cancer immunotherapy gains Nobel-status

Carl Figdor and Ton Schumacher on the 2018 Nobel Prize to Allison and Honjo

The rise of immunotherapy has been (and still is) nothing short of spectacular. In less than two decades we went from fundamental discoveries that changed our perception of how the immune system operates and how we can manipulate its actions to multiple, commercially available drugs that have revolutionised cancer treatment.

Looking at the astonishing number of ongoing drug development programmes and clinical trials, the end of the immunotherapy pipeline is nowhere in sight. So when the Nobel Prize in Physiology or Medicine 2018 was awarded to James Allison and Tasuku Honjo for 'their disWcovery of cancer therapy by inhibition of negative immune regulation', nobody in the field was truly surprised. "To be honest, this was to be expected," says Carl Figdor (Radboud University Medical Center). "For several years, I have nominated Jim Allison for the Nobel Prize and I am very glad that it worked out now. It is also really important for the whole field of immunotherapy, because we all still have lot of work to do." Similar views are voiced by Ton Schumacher (Netherlands Cancer Institute). "This prize is highly justified and definitely in line of expectation. When Allison and Honjo were gathering the first evidence for the potential of inhibiting CTLA-4 and PD-1 in cancer immunotherapy, there was basically no confidence in the field that immunotherapy could be relevant to cancer treatment. But Allison and Honjo were right! The clinical impact of checkpoint inhibitors is exceptionally large, not only for melanoma, but also for, for instance, lung cancer and bladder cancer. And I'm convinced that this impact will only increase in the coming years."

"The end of the immunotherapy pipeline is nowhere in sight"

The success of immunotherapy is however not only due to the scientific discoveries, but also to the tenacity of the laureates. Figdor: "I know that Jim Allison has put a lot of effort in getting checkpoint inhibitors to the clinic. It took him years, because at first the pharmaceutical industry was extremely reluctant."

Limited presence vs. inhibition

Allison and Honjo published their groundbreaking results in the early 1990s. For Figdor, their findings were not immediately relevant to his research at the time. "But the importance of the proteins they discovered to the regulation of the immune system was immediately clear," he says. For Schumacher, the papers had a more direct impact, because these elucidated an important question concerning the lack of T-cell recognition of cancer. "There were two lines of thought," Schumacher explains. "Was lack of tumor control by the immune system due to a limited presence of tumor-reactive T-cells or was inhibition by proteins such as CTLA-4 the main reason? When the results from the first clinical trials with checkpoint inhibitors were published, as well as the clinical results from the TIL therapy developed by Steven Rosenberg, it became clear that in at least a part of the patients cancer-recognising T-cells were present. And upon the right stimulation, these T-cells could destroy tumor

"Plenty of interesting questions ahead"

cells. These findings got my group interested in studying how these reactive T-cells recognise tumor cells as non-self. Our subsequent work, together with work by scientists such as Ugur Sahin and Bob Schreiber, contributed to the insight that tumors with substantial DNA damage produce the neoantigens that are a leading trigger for the immune system."

Immune deserts

Despite the clinical success so far, immunotherapy is far from perfect. What are currently the main obstacles and problems and what are the most promising approaches to tackle them? Both Schumacher and Figdor have no problem in coming up with a list of challenges that require scientific attention. "PD-1 and CTLA-4 are not the only checkpoints," says Schumacher. "There are many more and we need to understand which combination of checkpoints should be inhibited in individual patients. We need tailored immunotherapy."

Another problem arises when there is no dormant immune response to trigger. Schumacher: "In some cases, the endogenous immune response is just too weak. Especially in tumors that have very little DNA damage, this can be a problem. For these tumor types, we must find new ways to create an immune response, for example through genetically modified T-cells."

And then there are also tumor types that remain completely out of reach of the immune system, Figdor adds. "These are the 'cold' tumors that are surrounded by an 'immune desert'. These tumors have no immune cells in their vicinity, so even if you manage to activate an immune response, the immune cells are unable to reach the tumor. We know that tumors are able to silence the immune system, but it will take a lot of research to understand how this works and what we can do to solve it."

▲ Carl Figdor (left), Ton Schumacher

Deploying chemistry

Finally, there is a problem that is not scientific in nature, but poses an important challenge nonetheless. "Right now, there are so many clinical trials ongoing, that we face a 'shortage' of suitable patients," says Figdor. "The sheer number of trials also makes it difficult to combine and process all the results in a meaningful way, especially because patients tend to 'shop' at different trials. That makes it really difficult to determine which trial actually generated the outcome."

Plenty of interesting questions ahead. How can ICI contribute most effectively? The Figdor-group aims for synthetic analogues of the immune system. "Think of synthetic antigen-presenting cells of even synthetic, tailor-made lymph nodes that we can administer wherever they are needed," he explains. "That sounds very futuristic, but the first experiments are already running. I think that ICI, with its chemical knowledge, will play an important role in these developments. The same goes for developing really novel vaccines."

Chemistry is also on Schumacher's mind. "A student in my group, Meike Logtenberg, has recently identified an enzyme that is essential to the maturation of the CD47 checkpoint on myeloid cells. Developing small molecule inhibitors for that enzyme is a logical next step. I also see opportunities for ICI in the development of chemical probes to study and measure pathways of interest. Lastly, we can deploy chemistry to come up with 'smart' molecules, which can be activated or deactivated on demand." The breakthrough that Allison and Honjo created will no doubt keep on fueling the cancer immunotherapy field in the coming years. ■

Nobel Prizes 2018

Engineering technologies in the spotlight. Connection between two awarded disciplines: Physiology or Medicine and Chemistry.

It is no surprise that the clinical success of cancer immunotherapy took up most of the attention during the Nobel Prize 2018 aftermath. But there is another aspect to the work of James Allison and Tasuku Honjo, which interestingly creates a direct connection to the 2018 Nobel Prize in Chemistry to Frances Arnold, George Smith and Gregory Winter. And that link is formed by the engineering technologies to generate antibodies and enzymes with novel properties. These technologies have proven their relevance in a wide range of research fields and industrial and medical applications. An editorial in the January 2019 volume of *Nature Materials* provides an interesting read on the connection between the two Nobel Prizes. It was published online on 12 December 2018 and can be found here: doi.org/10.1038/s41563-018-264-5 ■

ICI Conference 15 March 2019

On 15 March 2019 we will host the annual ICI Conference in Amsterdam. This will be the 5th edition, at the end of the first term of the Gravitation grant. We are happy to celebrate the continuation of the Gravitation grant and another 5 years of chemical immunology projects within the Institute for Chemical Immunology. Just as our previous editions of the ICI Conference we will deliver a broad programme, filled with contributions by national and international speakers. In addition, there will be presentations by our own ICI PhD students and by the newest addition to our tenure track team, Kim Bonger.

Multidisciplinary design

This year's conference will again cover a broad spectrum of research areas at the forefront of both immunology and chemistry. You can expect to hear the latest research about diverse subjects, ranging from autoimmune pathogenesis to chemical reporters and materials science for vaccine development. We aim to not only welcome researchers, but also clinicians, biotech companies, charity funds and other stakeholders.

PhD day: What's next?

A pre-conference day will be organized for and PhD students. Now that the first term is coming to an end the first generation ICI PhD students are rounding up and will soon start looking for jobs outside the ICI. The workshops planned for this day will help prepare for the future. ■

Confirmed speakers

Darrell Irvine

Professor of Materials Science & Engineering and Biological Engineering at MIT

Prof. Irvine holds a Bachelor's Degree in Engineering Physics from the University of Pittsburgh. After completing his PhD at MIT in Polymer Science, he continued his postdoctoral research in Immunology at Stanford University. Darrell Irvine joined MIT in 2002 as Assistant Professor of Biomedical Engineering, Department of Material Science and Engineering and the then Biological Engineering Division.

Shoba Amarnath

Research Fellow at Newcastle University

Dr. Amarnath obtained a Bachelor's Degree in Biochemistry from the University of Madras, Chennai, India, a Master's Degree in Biotechnology and Molecular Biology from the University of Hull. She stayed on in Hull on an Overseas Research Scholarship (ORS) award to continue her PhD with Prof. John Greenman. In 2005, she moved to the National Institute of Dental and Craniofacial Institute at the NIH, to pursue a post-doctoral fellowship with Dr. Wanjun Chen. In 2007, she joined Dr. Daniel H. Fowler's laboratory at the Experimental Transplantation Immunology Branch, NCI, NIH.

Howard Hang

Associate Professor at the Rockefeller University

Dr. Hang obtained his Bachelor's degree in Chemistry from the University of California, Santa Cruz in 1998, and his PhD in chemistry from the University of California, Berkeley in 2003. He was a postdoctoral researcher at Harvard Medical School and Whitehead Institute for Biomedical Research from 2004-2006. He set up his own lab at the Rockefeller University in 2007.

Bert 't Hart

Professor in Neuroimmunology at University Medical Center Groningen

Prof. 't Hart obtained his Master's Degree in Biological Siences from the University of Utrecht in 1981. After completing his PhD in Immunology in 1986, also in Utrecht, he stayed as a postdoctoral fellow until 1989. He has since then been chairman at the department of Immunobiology at the Biomedical Primate Research Center in Rijswijk. In 2010 he became professor in Neuroimmunology at the UMC Groningen.

Kim Bonger

Assistant Professor Biomolecular Chemistry at the Radboud University

Dr. Bonger studied organic chemistry at the University of Applied Sciences Leiden and graduated from the Vrije Universiteit Amsterdam in 2002. After roughly a year of research experience at the University College Stavanger in Norway, she began her PhD research in organic chemistry at Leiden University in 2004, where she received her PhD in 2008. She was a postdoctoral researcher at Stanford from 2009-2012 and then returned to The Netherlands to start her own group in 2013.

Ton Logtenberg

Co-Founder, CEO and Executive Director of Merus N.V., and part-time Professor and Staff Member of the Department of Immunology at the University Medical Center Utrecht

Dr. Logtenberg has a Masters in Biology and a PhD from the University of Utrecht. From 1987 to 1989, Dr. Logtenberg was a post-doctoral fellow at the Howard Hughes Institute, Department of Biochemistry at Columbia University in New York. From 1989 to 1995 he was a Senior Researcher on a fellowship from the Royal Dutch Academy of Arts and Sciences. From 1994 to 1995 he served as a Visiting Scientist at Becton Dickinson Immunocytometry Systems. He is a Professor of immuno-biotechnology at the University of Utrecht since 1996. He Co-founded U-BiSys and served as its General Manager and Chief Scientific Officer. Dr. Logtenberg served at the U-BiSys Management Board in June 2000, in connection with the merger between IntroGene and U-BiSys. Dr. Logtenberg served as Chief Scientific Officer of Crucell NV, until September 9, 2002, also served as its External Advisor and Member of Management Board. He co-founded Merus N.V. in June 2003 and has been its Chief Executive Officer since June 2003 and Executive Director since June 5, 2017.

A new way to control T cells

The search for new ways to treat autoimmune diseases or cancer (or both) has delivered an unexpected target called BH4. In Nature, Shane Cronin (IMBA, Vienna) and co-workers describe the role of BH4 in T cell proliferation as well as a potential therapeutic lead to either block autoimmunity or stimulate anticancer immunity.

In neurobiology, the compound tetrahydrobiopterin (BH4) has been known for years. BH4 is an enzyme co-factor involved in the production of important neurotransmitters like dopamine and serotonin, as well as of hormones including adrenalin and melatonin. It also has a role in processes related to pain. But there is more to this small aromatic molecule. A broad international collaboration, led by Clifford Woolf (Harvard Medical School/Boston Children's Hospital) and Josef Penninger (Institute of Molecular Biotechnology IMBA, Vienna) found that BH4 is also of fundamental importance to T cells.

"Well known metabolite in neurobiology turns out to be a key player in T cell proliferation"

Iron metabolism

Starting point was the enzyme GTP cyclohydrolase 1 (GCH1), which is known to be expressed in activated T cells. GCH1 is also the first enzyme, and the rate-limiting one, of the BH4 biosynthesis pathway. The team generated Gch1 knock-out mouse models to study the role of the GCH1-BH4 pathway and activated T cells. They found that TCR-stimulated Gch1-deficient CD4+ and CD8+ T cells showed markedly reduced proliferation. As it turned out, inactivation of BH4 synthesis negatively impacts iron metabolism and mitochondrial metabolism, which in turn results in impaired proliferation of mature T cells.

In an article on the IMBA website (www.imba.at), Josef Penninger shares his excitement about this completely unexpected role of BH4. "This finding links to two completely different systems in our body and is unlike previously known immune checkpoints. It was truly amazing to find such a critical new player in T cell biology. Since it not regulates early activation but how T cells grow, the possibilities for medical applications are extremely varied: from controlling autoimmune diseases, asthma and allergies to having a new way to trigger anti-cancer immunity."

Promising antagonist

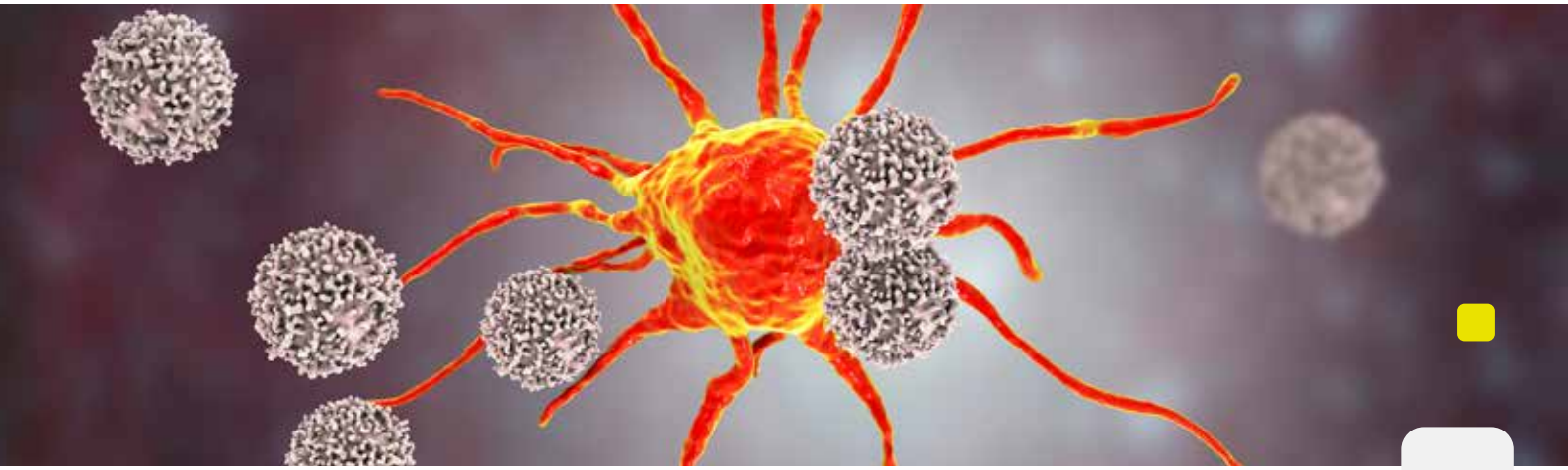
To support the claim for clinical potential of BH4, the team explored the effect of blocking and stimulating BH4 synthesis. Both approaches sorted effect in mouse models. Blockade of BH4 synthesis halts T cell mediated autoimmunity and allergic inflammation, while stimulating BH4 production results in increased antitumor activity of CD4+ and CD8+ T cells. Markedly reduced tumor growth was seen in mice after administration BH4, as well as an expanded population of intratumoral effector T cells. Taking first steps towards potential drug leads, the team developed a potent antagonist to sepiapterin reductase (SPR), which is the terminal enzyme in BH4 biosynthesis.

Clifford Woolf is very optimistic about the potential of blocking BH4 synthesis as a way to treat autoimmune diseases and allergies. "The beauty of the approach is that instead of targeting a singly cytokine or class of T cells, we halt proliferation in all disease related T cells and this could translate into activity across multiple, diverse clinical conditions." ■

Nature publication

Shane J.F. Cronin, et al., The metabolite BH4 controls T cell proliferation in autoimmunity and cancer, *Nature* volume 563, pages 564–568 (2018)

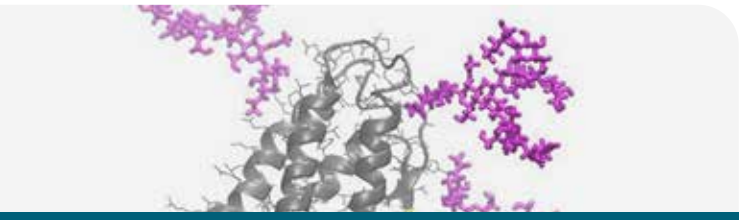
▼ *T cells attacking cancer cell.*



News

Hidde Ploegh appointed as professor Chemical Immunology at LUMC

As of September 1st Prof. Hidde Ploegh has been appointed professor Chemical Immunology, in particular biochemistry of the immune system, at the LUMC. He will take on the Jon J. van Rood Chair. Ploegh is already a professor of Immunology at the Children's Hospital of Harvard Medical School in the United States. In the first instance, he will therefore have an advisory role for the LUMC research.



Design and control of biobetter EPO

Apart from its illicit usage by top athletes, EPO is a medicine for patients who suffer from anemia. The production of this therapeutically-used EPO and similar biological medicines can now be taken to the next level through a method developed by researchers from Utrecht University, the Netherlands, and Copenhagen University, Denmark.

Utrecht Molecular Immunology Hub kicks off

Utrecht University invested in thirteen so-called hubs. The Utrecht Molecular Immunology Hub kicked off this autumn. Newly appointed researchers will start exciting new research projects. The hub will have a strong basis in fundamental research. Co-coordinator Albert Heck stresses: "We aim to unravel molecular details of our highly complex immune response to diseases and pathogens. This knowledge makes it possible to steer the system in a healthy direction. Societal impact will come from innovative vaccines and immunotherapies that can only be developed upon new discoveries."

Recent publications

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Column

CHAINS HOLDS A MARRIAGE TOGETHER

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.

Last December saw the Dutch chemical community descend on the Conference Centre Koningshof. Under the smoke of Eindhoven, an exciting range of topics was discussed; ranging from the hijacking of stop codons to introduce additional functionality into proteins (Jason Chin), *in vivo* sensing of biomolecules (Kevin Plaxco) to bio-inspired materials systems (Thomas Speck).

Because the Institute for Chemical Immunology (ICI) represents a "marriage" between chemistry and immunology, CHAINS also marked an exciting time for the ICI, as it really highlighted how immunology has become a mainstream biological problem for the chemists to ply their trait on. This already became apparent in the poster sessions, in which various posters were presented by chemists – both from the ICI and elsewhere – making compounds for probing the immune system.

The talks alike covered the whole breadth of the immune system. There was even a focus session on chemical immunology for which the venue was packed. Michel van de Graaff, special guest Aaron Esser-Kahn and Niels Reintjens all showed excellent work in controlling the activation of innate immune receptors using new chemical tools. Kimberly Bonger and Anouk van der Gracht focused on temporal manipulation of the adaptive immune response through the use *in vivo* compatible chemistry. Frans Bianchi (Nijmegen/Groningen) took a different approach and talked about how protein structure affects antigen cross-presentation efficiency.

A final theme throughout the conference was the new chemistries that are being developed for antibody manipulation. The former ICI-conference speaker Marc Robillard (Tagworks Pharmaceuticals) showed his latest work in using chemical triggers to locally release cytotoxic payloads at sites of tumours. ICI PhD student Jorick Bruins (Wageningen UR) too showed some great work in using tyrosine oxidation to site-specifically modify antibodies with drugs. ICI PhD student Angela el Hebieshy (LUMC) demonstrated a ubiquitin-Fab conjugate to ligate different antibody fragments together to generate bi- and maybe even tri-specific antibodies.

In conclusion, this year's edition of CHAINS really showed the impact of immunology on chemistry and vice versa. The increased awareness that the field represents a unique set of problems requiring interplay between chemistry and immunology will aid the mission of the ICI to mature the exciting field of Chemical Immunology. ■

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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