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ICI institute for chemical immunology

Interview

"TWENTY YEARS AGO, NOBODY BELIEVED IN IMMUNOTHERAPY"

TON SCHUMACHER
Professor of Immune Technology
Netherlands Cancer Institute

No fewer than 800 clinical trials are currently underway to evaluate some form of immunotherapy against cancer. A remarkable number, since just two decades ago most oncologists did not acknowledge any relationship between the immune system and cancer. Ton Schumacher, group leader Molecular Oncology & Immunology at the Netherlands Cancer Institute, chief scientific officer at Kite EU and member of ICI's Executive Board, was one of the early believers.

You are not trained as an immunologist or as a chemist. How did you get involved in immunotherapy?

"It took some time. I studied biology, and just before graduating, I met Hidde Ploegh, who back then was still here at the Netherlands Cancer Institute. I was immediately taken by the lively atmosphere in his group, and when Hidde offered me a PhD position on an immunology-related topic, I didn't hesitate a moment, even though I did not find the project I started off with all that exciting."

What made working in the Ploegh lab attractive?

"The people in that group all had what I still look for now when interviewing candidates: drive and enthusiasm. People whose eyes start to shine when they talk about their research; people who really want to create something new and interesting. The Ploegh group was filled with that kind of motivated individuals, and that is why I wanted to work there. Studying the immune system just happened because the group worked on that." ▶

Contents

But at a certain point the immune system and its potential therapeutic use got your attention. When and why was that?

"After my postdoctoral research in the US, I returned to the Netherlands Cancer Institute and started collaborating with John Haanen, now head of Medical Oncology. This was around '96, '97 and at that time the idea that immunotherapy could become something real was forming very slowly. John was looking for ways to measure whether T-cells in cancer patients could recognise cancer cells. My work focused on developing technologies to measure immune responses. John's idea to measure immune responses in cancer patients sounded intriguing, and my feeling was that there was something to be discovered."

But the idea of an immune response against tumour cells was a niche opinion?

"Oh yes, the idea that such a response would be relevant to patient outcome was still highly controversial. If we had organised a survey of the staff here to ask if they thought the immune system played a role in tumour development, roughly

"The key is to understand what makes tumour cells 'strange' to the immune system"

95 percent would have answered 'no'. The general opinion was that the immune system was very interesting, but had nothing to do with cancer."

Then what made you think that measuring immune responses in cancer patients would lead you somewhere?

"There were for instance some intriguing results from clinical studies by Steve Rosenberg at the NIH. He had isolated T-cells from metastases of melanoma patients, cultured them to high numbers and administered them back to the patient. In a small fraction of the patients this resulted in tumour regression. That had to imply the occurrence of a clinically relevant T-cell response in at least some patients. Rosenberg's results affirmed our idea that it would be worthwhile to try to see if we could unravel this whole process and find out what was really happening.

Our approach was to develop technologies that allowed us to determine what the T-cells actually recognise on tumour cells. Together with Huib Ovaa we developed a ground-breaking technology using so-called placeholder peptides bound to MHC-molecules. This placeholder peptide is UV-sensitive. You distribute the complex over many wells and then simply add a different, non-UV responsive peptide, to each well. Turn on the UV light, the placeholder peptide gets destroyed and the other peptide binds to the MHC molecules. The result is a large array of different MHC-peptide complexes that you can then use for screening. This technology gave us the means to really measure in a high-throughput manner what makes a T-cell respond."

And what did you find?

"The answer lies to a large extent in the amount of DNA damage a tumour cell carries. These mutations result in all kinds of new and unique peptides that are non-self. T-cells recognise these mutant epitopes or neo-antigens thereby triggering a tumour-specific immune response. The more DNA damage, the stranger a tumour appears to the immune system you can say. We now know that many human tumours are not ignored by the immune system. Rather, the T-cell response is just not strong enough to keep the tumour under control, or the response is rendered ineffective by inhibitory receptors on the tumour surface. And with this being established, a logical strategy is to look for ways to stimulate this T-cell response or to block the inhibitory signals, which is exactly what all the currently registered immunotherapies do."

Your shift from basic research to therapeutic applications even went as far as starting a company. Why did you take that step?

"There is a transition point in the development of knowledge. From the free, explorative phase up to proof-of-concept, academia is the best place to be. But once proof-of-concept has been established, the next phase is about further testing, refining, improving and more standardised operations. This type of work just doesn't fit well within academia. When this phase starts, you better move to an industrial setting where everything is focused on that one particular product. So far I have been involved in founding three companies, and each time it has been an exciting and fun experience."

But industry is not exciting enough to get your full attention?

"Big companies are not interesting to me: they are too far removed from the science. Start-up companies are interesting and really fun to work in because that is where the truly creative part of the work is still centre stage. Combining the freedom of academia with the creative excitement of a small company, like I do now, to me is an ideal situation. It offers the best of both worlds." ■

"Start-up companies are interesting and really fun to work in"

FROM CHEMISTRY TO DRUG CANDIDATE

Mercachem is an innovative chemistry service provider in the fields of Discovery Chemistry, Parallel Chemistry, Medicinal Chemistry, Process Research and GMP Manufacturing. "Through our specialised business areas, we can support projects from early discovery chemistry up to phase 2A clinical trials," asserts managing director Eelco Ebbers.

The independent, privately held company was founded in 1997 by Eelco Ebbers and Frank Leemhuis, who are the present managing directors. At that time the two entrepreneurs, originally organic chemists, detected a rapidly growing demand for special chemical substances, usually complex compounds and commercially unavailable, a market that perfectly aligned with their organic synthesis skills. "We wrote a business plan and started Mercachem as a spin-off of the Radboud University," Ebbers explains. The company currently employs 175 highly skilled individuals who work in modern, state-of-the-art laboratories equipped with advanced research facilities.

Four pillars

Mercachem is a contract research company that initially focused on chemistry services. This activity grew into the current division of 'Discovery Chemistry.' "It still is one of our main pillars," Ebbers says. "Quality, creativity and innovation are our major strengths." At the same time, Mercachem responded to the growing trend of outsourcing. Over the course of time adjoining services were set up. It began in 2002 with the division 'Parallel Chemistry' offering library synthesis and combinatorial chemistry technology. In 2005 'Process Research' service was formed, focusing on early scale-up processes and GMP production for clinical trials. Finally, in 2008 tailored research facilities paved the way for starting 'Medicinal Chemistry' and striking out in the area of hit and lead optimisation, and innovative drug design. "Enhancing our company with the GMP production facility in Prague (CZ) strongly strengthened our chemistry services by service solutions from early discovery chemistry to GMP production," Ebbers tells.

Customer-related service

Steady growth has now led to a broad range of services to support R&D for pharmaceutical companies, especially in Europe, USA and Japan. In addition, Mercachem also works for agriculture, the food sector and material sciences. The Mercachem business model is fully based on customer-related service that often results in long-standing partnerships, in which different activities may be involved. Ebbers illustrates by describing a recent project targeting the development of novel K agonists. "Three of our business areas took part in a joint effort: first, Medicinal Chemistry by performing hit and lead optimisation, in parallel Discovery Chemistry by cracking the challenging chiral synthesis of different isomers, and finally Process Chemistry by optimising the synthetic route and delivering the first GMP batches for clinical studies. This is what we mean by seamless integration of our chemistry services!"

Projects are always exclusively for customers and all new intellectual property is owned by the customers involved. "Mercachem's company ethos of open communication and shared knowledge requires transparent policy. It is reflected in the design of our buildings, which facilitates close working relationships," Ebbers adds.

Joining forces

Recently, Mercachem and Syncom announced they were joining forces. The two companies belong to Europe's leading drug discovery CROs serving large and mid-size pharmaceutical, life sciences and innovative chemistry customers worldwide. Today's merger enables the Mercachem-Syncom Group to broaden its offering of integrated drug discovery services and to invest in a state-of-the-art knowledge base and facilities. The group has enough critical mass to address clients' growing demand for outsourcing solutions and to continue a high-quality pallet of services. "Large enough to matter, small enough to care," Ebbers concludes. ■

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Identifying suspicious sugars

PhD project: Turning tumour glycans into anticancer vaccines

Glioblastoma, aggressive brain tumours, are masters at immune system evasion. Glycans on their surface are thought to be important in tricking the defence. PhD candidates Sophie Dusoswa and Tomislav Caval unravel which glycans are crucial to the camouflage.

Sophie Dusoswa has always been intrigued by the biology of cancer. That is why she holds a master's degree in both medicine and biomedical sciences. "My greatest ambition is to become a neurosurgeon." Yet at the moment she is studying the role of glioblastoma glycosylation on immune escape, very fundamental research. "I believe medical doctors with a strong background in research will speed up the development of new therapies. I am hoping that future employers will appreciate my 'detour' into fundamental research."
Dusoswa compares the 'sugar decorations' of highly aggressive brain tumours with those of the most healthy available human brain tissue: cells taken from patients with severe epilepsy. "I'm searching for tumour specific glycoproteins." Those glycoproteins often carry truncated O-glycans. Dusoswa just spent half of a year at Harvard studying their effect on the immune system in mouse brains. "The difficulty is that there are many variations in the glycosylation of tumour cells, in O- and N-glycans. The main challenge therefore is to unravel if and how each of these variations or combinations thereof sabotages the immune system." Knowledge on immune evasion may help reach the ultimate goal of developing glycan-based anticancer vaccines.

Sophie Dusoswa
VUmc, Molecular Cell Biology and Immunology
Yvette van Kooyk & Juan J. Garcia Vallejo-group

Tomislav Caval
Utrecht University, Biomolecular Mass Spectrometry & Proteomics
Albert Heck-group

Epo

Glycan identification is where her PhD partner Tomislav Caval comes in. He is an analytical chemist, a specialist in mass spectrometry on glycoproteins. Caval: "At the moment Sophie and I are working out a purification protocol together. Sophie will use it in preparing the samples she sends me. These need to be very clean as we analyse the total native glycoprotein." That is a necessity. Glycans often shield glycoproteins from proteases which would provide smaller and therefore easier to analyse glycopeptides. "Using orbitrap technology we can get a high quality spectrum of the complete glycoprotein.

> *"That is of course a highly complicated puzzle"*

That is of course a highly complicated puzzle showing hundreds of peaks. But we are able to solve it, including the glycan structures. My best days in the lab are the days when I am able to identify the last peaks and complete such a puzzle."
"The methodology for identifying N-glycans has been developed by studying spectra of known variants of the glycoprotein erythropoietin in our lab," Caval reports. Artificial recombinant erythropoietin is probably better known as the drug 'EPO.' It induces the production of red blood cells, thereby enhancing endurance. It serves as a medicine in e.g. anaemia after cancer therapy. Recombinant and natural EPO differ only in their glycosylation. Caval: "We have analysed about twenty different types of EPO from the pharmacy. By comparing the spectra we developed a methodology that discerns N-glycans."

Eye-opener

Dusoswa and Caval are about to start analysing the glycan structure of a glycoprotein known as CD63. It is an intracellular protein that carries large N-glycans and that can also be found on glioblastoma-derived extracellular vesicles, which are known to increase cancer malignancy. Dusoswa will isolate the glycoprotein; Caval will do the analysis. He expects the study to prove the power of the methodology: a first step towards wider introduction in R&D. Dusoswa aims to put glycans on the map in neuro-oncology. "I'm looking for an eye-opener. I want to hear neuro-oncologists say, 'We ought to pay more attention to these sugars.'" ■

Why vitamin A boosts the immune system

PhD project: Visualisation of vitamin A metabolism

Although vital for our health, little is known about vitamin A metabolism and how it boosts the immune system. Using self-designed self-made probes, PhD candidates Martje Erkelens and Sebastiaan Koenders identify the enzymes involved: an essential step towards a future in which diet advice strengthens one's health.

Biomedical scientist Martje Erkelens (VUmc, Amsterdam) blames the lipid character of vitamin A for the remarkable lack of knowledge on how it stimulates the immune system. Retinol and its active metabolite retinoic acid barely dissolve in water and stick annoyingly to the disposable plastics commonly used in the laboratory. Moreover, the molecules are too small to elicit antibodies. Erkelens: "Biology just lacks good tools to follow vitamin A in the body." But that is about to change. She has just spent a whole week in the lab together with her PhD partner, organic chemist Sebastiaan Koenders (Leiden University). Probably a successful week. "We need to do some further tests, but it looks good," Erkelens reports enthusiastically. And Koenders sounds just as optimistic: "The probe I synthesised seems to do what it was designed for."

Casting rod

The probe is a retinal-like molecule equipped with a reactive vinyl ketone group. It covalently binds enzymes that convert retinal to retinoic acid, which is known to stimulate the mucosal immune system. The vinyl ketone selectively reacts with the cysteine at the reactive site of retinal dehydrogenases. Erkelens and Koenders plan to use the probe as a 'casting rod,' collecting various retinal dehydrogenases from cell lines and identifying them using mass spectrometry. Probe variants, as yet to be designed and synthesised, may indicate the cells in which dehydrogenase are active and when. Furthermore, variants carrying a fluoregenic group may visualise retinal dehydrogenase activity *in vivo*. Koenders: "Now that the probe seems to work, I may start thinking about what the next most interesting probe would be and how to synthesise it. The freedom to figure that all out myself is probably the thing I like the most about science."
When Erkelens started the project two years ago, one main goal was to examine which foods or food metabolites stimulate the production of a particular dehydrogenase called ALDH1a1. However, her studies on an ALDH1a1-knock-out mouse revealed that ALDH1a1 is not the only enzyme capable of converting retinal to retinoic acid. Erkelens: "Nature often provides back-up systems for important metabolic routes." The scope was therefore broadened to identify all aldehyde dehydrogenases involved. And while waiting for Koenders to design and synthesise the first probe, Erkelens also worked on developing better *in vitro* models to study the intestine.

Antique recipes

In Koenders' experience vitamin A is not a hot topic in chemistry. "The most useful papers on the synthesis of retinol-like compounds date back to the beginning of the 20th century." The antique chemistry is robust Koenders discovered, but the historic product isolations are tedious. "Chemists seem to have spent their days distilling. Fortunately, there are now other options such as column chromatography."
Has studying the connection between vitamin A and the immune system changed their own diet? Erkelens: "Friends and acquaintances often ask me what I think about the newest food trends or ask for diet advice. However, it's such a complex relationship and much may depend on the composition of one's own intestinal flora. Therefore, the sole sound advice I dare to give, and follow myself, is to eat healthy." ■

"Vitamin A is not a hot topic in chemistry"

Sebastiaan Koenders, MSc
Leiden University, LIC/Molecular Physiology
Mario van der Stelt-group

Martje Erkelens, MSc
VUmc, Molecular Cell Biology and Immunology
Reina Mebius-group

FameLab 2018

Increasingly, researchers are asked to explain their research in a (very) short timeframe and to an audience of laymen. Quite a challenge to explain something you are unravelling for four years in just a few minutes! But mastering the skill of pitching is very useful for obtaining personal grants and, of course, to get attention on your next birthday party!

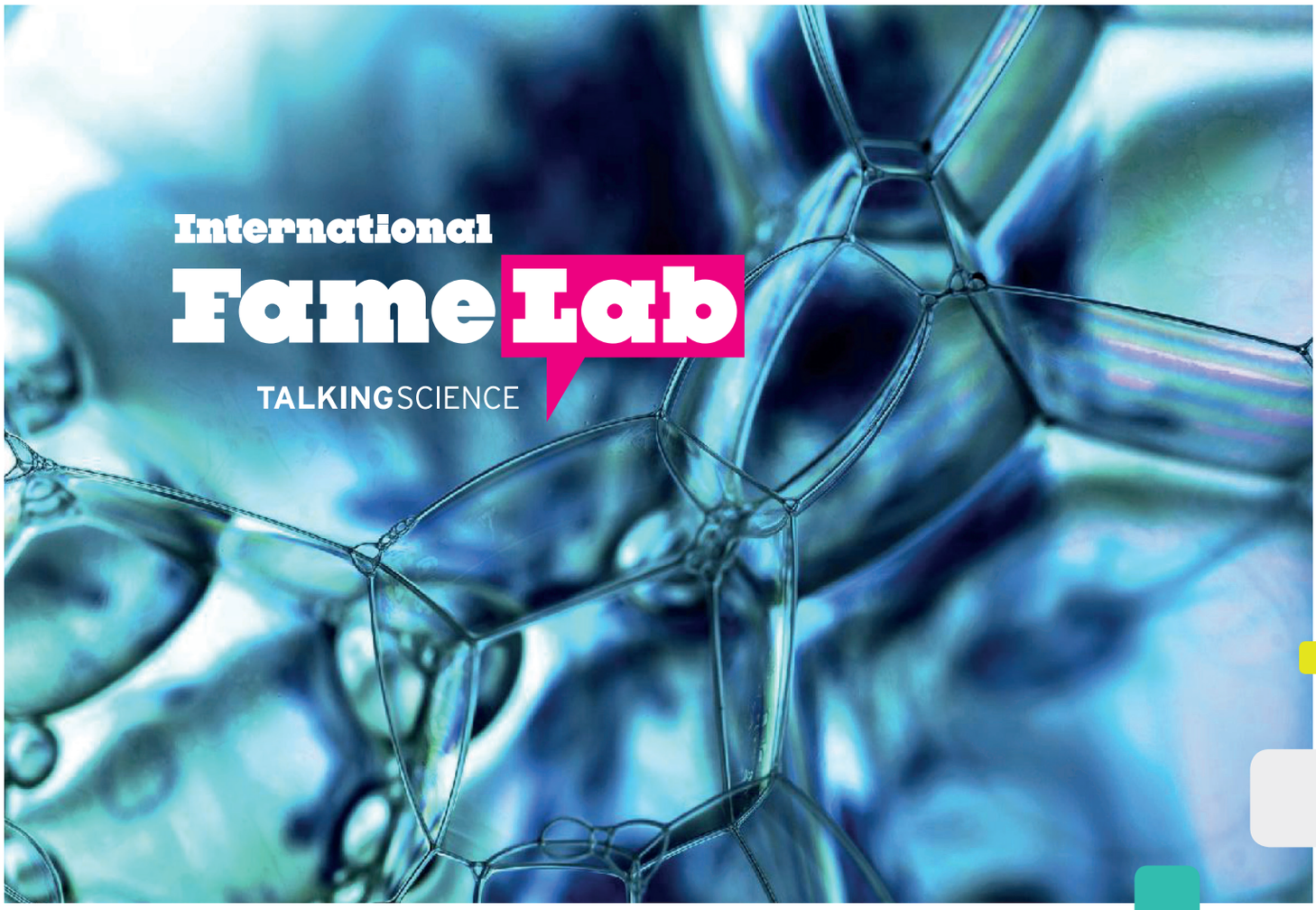
Science communication competition

Together with the Cheltenham Science Festival, the British Council organises a contest for researchers: FameLab. FameLab is one of the biggest international science communication competitions in the world, designed to engage and entertain by breaking down science, technology and engineering concepts into three minute presentations. Contestants from around the world take part armed only with their wits and a few props – the result is an unpredictable, enlightening and exciting way to encourage your curiosity and find out about the latest research. They will be judged by leading researchers, media personalities and science policy makers on the content, clarity and charisma of their presentation.

Local competition

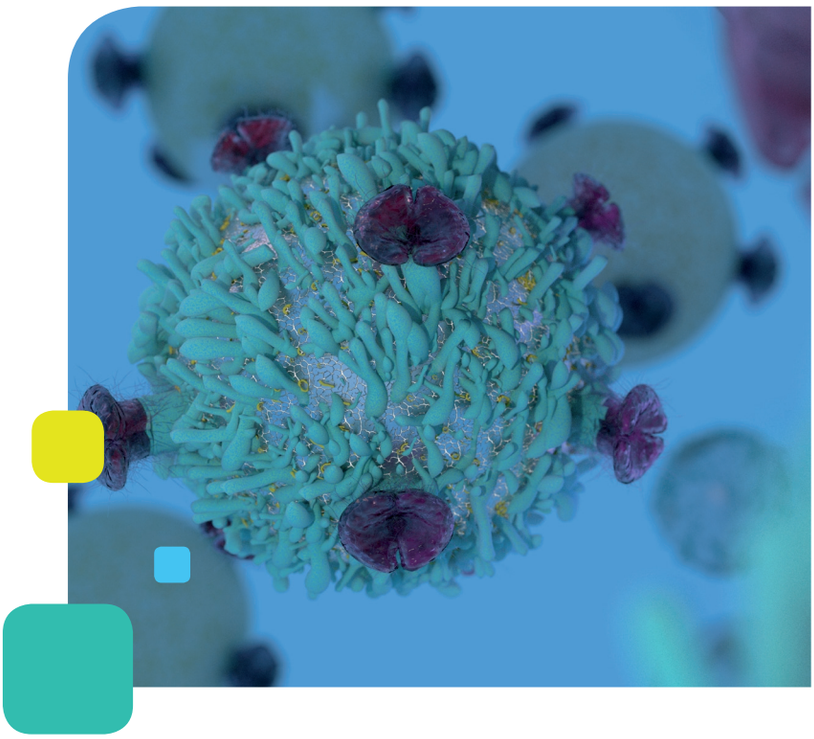
FameLab was started in 2005 in the UK by Cheltenham Science Festival and has quickly become established as a diamond model for successfully identifying, training and mentoring scientists and engineers to share their enthusiasm for their subjects with the public. Working in partnership with the British Council this global competition has already seen more than 5000 young scientists participating in over 25 different countries. Together Cheltenham Festivals and the British Council co-produce the FameLab International Grand Final. Each national winner goes on to compete against other contestants from around the world at The Times Cheltenham Science Festival in June. In the Netherlands several Universities take part in FameLab, amongst others Erasmus University Rotterdam, University of Amsterdam, Utrecht University and Leiden University.

FameLab is calling all scientist with a passion for public engagement to participate in FameLab 2018! If you would like to take part in the competition in the Netherlands, you can visit the British Council's website for more information or have a look at the website of your own University. ■



Unexpected regulator enhances PD-L1 stability

The protein PD-L1 is the target of multiple cancer immunotherapies, but its regulation was poorly understood. In August, a team comprising several ICI researchers published surprising new findings in Nature. An unexpected protein turns out to be a stabilising factor for PD-L1.



Immunotherapies against cancer can be roughly divided into two groups: those that aim to directly boost the patient's T-cell response or those that focus on removing the blockades employed by the tumour cells to inhibit a proper T-cell response. In this latter group, all eyes are on the PD-1/PD-L1 axis: the interaction between the protein PD-L1 which is expressed on tumour cells and PD-1 expressed on T-cells. "This is an important mechanism by which tumour cells control T-cell action. It is an inhibitory interaction that functions as a brake on the T-cell response," says Ton Schumacher, group leader Molecular Oncology & Immunology at the Netherlands Cancer Institute. "Being able to control T-cells makes perfect sense, because of their ability to kill other cells T-cells should be kept on a tight leash. However, tumour cells hack this control loop by expressing PD-L1 and taking over the protective mechanism to serve their own purpose."

New protein

Due to their central role in blocking the T-cell response, both PD-1 and PD-L1 have become the targets of choice for developers of immunotherapies. Schumacher: "A range of antibodies against PD-L1 has been developed and approved for about seven types of cancer." But what are the key regulators of PD-L1 expression? The interferon gamma pathway plays a role, but is not solely responsible. "Surprisingly little was known about PD-L1 regulation, even though this protein is the target of several currently applied therapies," says Schumacher. Nevertheless, when the idea came up to look for additional regulators using a screening technology developed by his colleague Thijn Brummelkamp, Schumacher was not immediately convinced. "Thijn has developed a beautiful technology using a haploid human cell line that is perfectly suited for genetic screening. Still, with so many people working on PD-L1, I didn't think we would find anything new. But because the technology was available, I decided we should give it a try and see." It was a good call. To everyone's surprise a completely new protein, CMTM6 – a protein that had never before been associated with PD-L1 – turned up in the screening results. The reason for that is probably due to the way CMTM6 controls PD-L1 levels. Schumacher: "CMTM6 regulates PD-L1 levels not by controlling gene expression, but at the protein level. Like PD-L1, CMTM6 is present on the tumour cell surface and directly binds to PD-L1, thereby protecting it from degradation. Mass spectrometry analysis by the Heck-group subsequently showed that the interaction between CMTM6 and PD-L1 has a high degree of specificity."

"To everyone's surprise a completely new protein turned up in the screening results"

Plenty of new avenues

The discovery of CMTM6 underlines the importance of technology development, says Schumacher. "Without Thijn's technology, we would never have seen this." With CMTM6 firmly on the map, Schumacher and co-workers have plenty of new avenues to explore, for example, the development of antibodies against CMTM6 which is now branded as a potential therapeutic target. "But we also want to understand the function of CMTM6; there has to be a reason for its stabilising activity. From studies in human material, we know that CMTM6 is localised in tissues associated with tolerance induction. That is of course an extremely interesting feature for a protein involved in immune responses." ■

Reference

Riccardo Mezzadra, Chong Sun, Lucas T. Jae, et al., Identification of CMTM6 and CMTM4 as PD-L1 protein regulators, Nature 2017, doi:10.1038/nature23669

Exhaled breath can identify bacterial infections

Physicists and cell biologists at Radboud UMC working in concert

Researchers at Radboud University have discovered a way to quickly detect bacterial infections using exhaled breath alone. According to the researchers, the presence of ethylene in the breath can be a biomarker of bacterial infection. The study was published last summer in Scientific Reports.[1]

Ethylene is mostly known as a plant hormone mediating developmental processes and stress responses to stimuli such as infection. "We can now show that systemic inflammation triggers ethylene production in humans, which is released in the breath," explains Laurent Paardekooper, first author of the research paper. "We succeeded in demonstrating that ethylene is a lipid peroxidation product formed by the respiratory burst."
Paardekooper is an ICI PhD student in Carl Figdor's Tumour Immunology Lab at Radboud UMC. His PhD study deals with unravelling the mechanisms behind systemic sclerosis (SSc), one of the most devastating rheumatic disorders. He focuses on the impact of oxidative stress. "We know that hypoxia, a lack of oxygen, plays a role on the cellular level. We also know that dendritic cells from SSc patients generate high levels of reactive oxygen species (ROS), creating hypoxic conditions that drive the development of SSc."
Although the present project is a little outside the area of his actual PhD research, cell biologist Paardekooper became involved due to his expertise with cellular oxidative stress processes. "It really broadened my understanding and insight," he asserts. "As a scientist, you have to be open to side tracks. You never know what will come your way."

Trace gases

The work was a collaborative effort between Paardekooper's supervisor Geert van den Bogaart and Simona Cristescu from the Life Science Trace Gas Facility at Radboud University. This facility operates a variety of unique state-of-the-art detectors that allow real-time measurements at or below ppbv level trace gases released by various biological samples in a seconds time scale. Physicist Cristescu focuses on trace gas analysis of the breath of patients during medical treatment or surgery. Breath analysis may provide insight into various processes occurring inside the human body as a consequence of the interventions.
"One such process is lipid peroxidation in which free radicals induce oxidative degradation of the polyunsaturated fatty acids, causing cell damage and cell death," Paardekooper explains. "In a normal situation, free radical formation and radical scavenging, for instance by vitamins E and C, are balanced, but under conditions like UV radiation, trauma or certain diseases this balance is disturbed, leading to pathological processes."
To gain more insight into this pathology it is important to find a way to quantify lipid peroxidation in the human body. Traces of volatile hydrocarbons such as methane, ethane, ethylene, propane and butane are known to be produced as a result of oxidative degradation of polyunsaturated fatty acids. Ethylene proves to be exhaled through breath and/or released through the skin. Cristescu succeeded in using laser photoacoustic spectroscopy for detecting very low concentrations of ethylene in patients' breath.
This approach provides a sensitive and non-invasive method for real-time monitoring ethylene in patient's breath in clinical and perioperative settings. The next step was investigating the role of ethylene production as a warning signal during infection and (systemic) inflammation. Cristescu therefore enjoyed working with Bogaart's group, which studies immune response and oxidative stress in health and diseases.

> *"Sharing knowledge pays off"*

Challenging research

One of the most fundamental mechanisms involving oxidative stress is the respiratory burst, occurring when neutrophils and monocytes encounter bacterial or fungal infections.

During this burst, large amounts of ROS are rapidly produced by NADPH oxidases. However, the effects of this response are indiscriminative, affecting both invading pathogens and host tissues. Paardekooper: "We hypothesised that ethylene is formed as part of endogenous lipid peroxidation caused by the respiratory burst and can be detected as a gaseous signature of systemic inflammation in exhaled breath."
To test this hypothesis, he first utilised an isolated lipid model to consolidate basic chemical mechanisms of ethylene release by lipid peroxidation. He then investigated ethylene release in isolated leukocytes activated by bacterial lipopolysaccharide (LPS) as a cellular model of infection. Finally, he evaluated ethylene release *in vivo* using the experimental human endotoxemia (LPS administration in healthy volunteers), a well-characterised model of systemic inflammation.
Experimental setups were challenging and laboratory skills were put to the test. Finally, however, the efforts created promising results. Paardekooper: "We clearly showed that ethylene release is an integral component of *in vivo* lipid peroxidation with clinical potency as an economical respiratory biomarker of bacterial infection."

The difference between life and death

The researchers compared exhaled ethylene with established biomarkers of endogenous lipid peroxidation and strove to clarify the temporal and mechanistic relationship between ethylene release and other biomarkers of the inflammatory stress response. "Ethylene proved to be a real-time respiratory marker for systemic inflammation," says Paardekooper in summarising the findings.
"Our results highlight that ethylene release is an early biomarker of bacterial infection. In humans, ethylene was detected at least half an hour earlier than the increase of blood levels of inflammatory cytokines and stress-related hormones. For patients in intensive care this could mean the difference between life and death," comments Simona Cristescu in the press release in response to the publication. "The first possible application I see is continuous monitoring of patients on artificial respiration. These people have an increased risk of dangerous infections, and because their breath is already going through a machine, it is easy to monitor it for ethylene," Paardekooper concludes. ■

Joint ICI PhD study

How low oxygen conditions sustain themselves

Laurent Paardekooper (Radboud UMC) and Andrea Ottria (UMC Utrecht) 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. 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 setup is that Laurent can see things that I cannot and vice versa. Together, we see more." Paardekooper agrees: "Collaboration is essential. With these kind of complex problems, you can't get anywhere on your own." ■

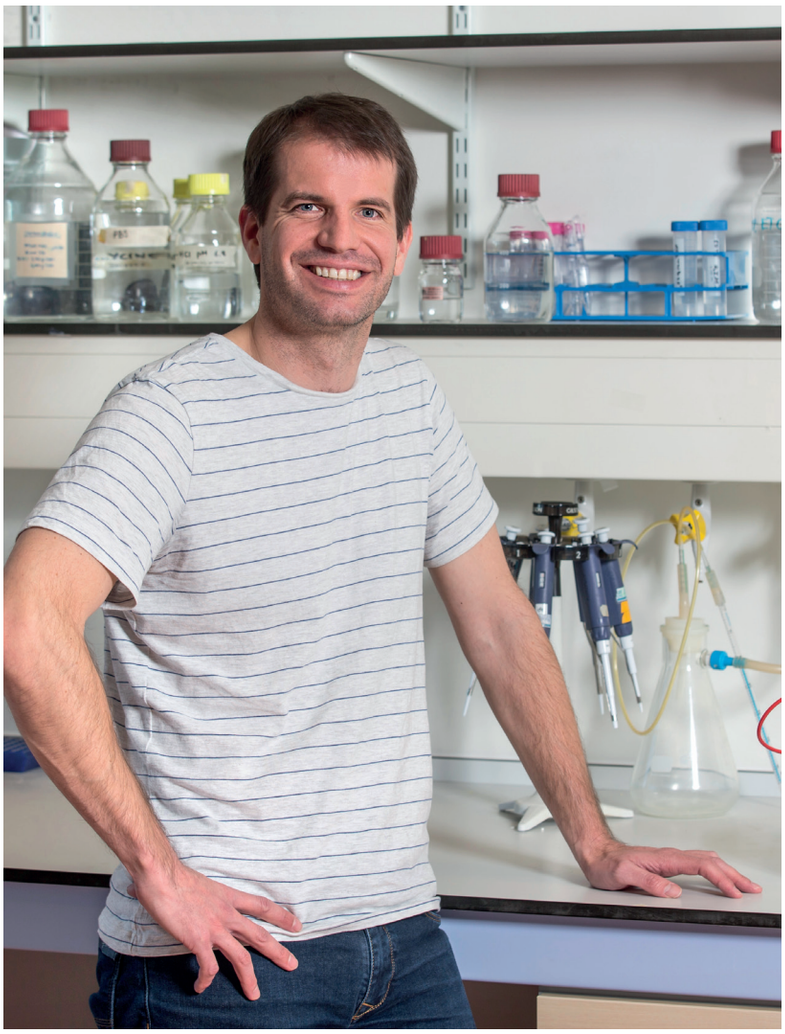
"As a scientist, you have to be open to side tracks. You never know what will come your way."

A crash-course in Chemical Immunology

"Chemical immunology is hot," says Martijn Verdoes, "the field is really attracting attention these days." The reason: a recent series of breakthroughs in anticancer immunotherapy. Verdoes: "Clinical successes appeal to people, of course." Being 'hot' helped in the selection of chemical immunology as the topic of the 2017 master class for students of the research master Molecular Mechanism Diseases (MMD) in Nijmegen.

It was a unique opportunity to interest them and others in chemical immunology, according to Verdoes, as the mini-symposia were open to everyone. Six scientists in chemical immunology presented their work: Sander van Kasteren (Leiden Institute of Chemistry); Geert-Jan Boons (Utrecht University / University of Georgia); Paul Parren (Leiden University); Patrick Beusker (Synthon Biopharmaceuticals); Mustafa Diken (Institute for Translational Oncology, Mainz); and Celia Berkers (Utrecht University). Verdoes: "It was a true showcase of what is happening in chemical immunology,

▼ *Martijn Verdoes, Assistant Professor at the Department of Tumor Immunology, Radboud UMC Nijmegen. One of the organisers of the mini-symposia in Nijmegen.*



and also a good opportunity for me and my co-workers to exchange views with the speakers and to discuss common problems and potential cooperation."

College Tour

For MMD honour students there was yet another event: all six scientists from the mini-symposium were guests on a live talk show inspired by the Dutch television show College Tour. The scientists answered questions of all types that the students had prepared. Verdoes: "Many concerned a career in science, since these students are in their last year." For example, Geert-Jan Boons was asked what his advice would be for a student their age. "Let your interests lead you," was his answer. Career planning is good and wise in the sense that you should be prepared for an opportunity, but you seldom know when and what opportunity will turn up. "The students were well prepared," says Verdoes. "They checked the backgrounds of the speakers thoroughly and even used social media. One of the questions to Geert-Jan was if he, being a full professor, still had time to walk his dog."

Exposing the elephant in the room

Sander van Kasteren presented the opening lecture. The first video he shows presents cytotoxic T-cells busy destroying cancer cells. "I was immediately and deeply impressed by their brutal efficiency," reports Van Kasteren. They were my inspiration for going into chemical immunology." He does not find it surprising that T-cells have become highly important in cancer research. "The recent success of checkpoint inhibitors, for example, proves that it was wise too." One of Van Kasteren's aims is to 'film' one of the most important steps in the activation of T-cells *in vivo*: the formation of the immunological synapse between an antigen presenting cell (APC) and a T-cell. "It's the elephant in the room. It happens, but no one has actually ever seen it *in vivo*." Many aspects of the process therefore remain a 'black box.'

The Van Kasteren-group develops chemical tools to study the process: a chemical marker or tag which allows tracking an antigen while it is picked up by an APC, fragmented, and presented to a T-cell. As first proof-of-concept, experiments are done with the widely used antigen epitope SIINFEKL, in which the lysine (K) is modified to an azido-lysine. This very small, two-atom transformation serves two purposes: it quickly 'betrays' the whereabouts at any moment through bioorthogonal labelling and state-of-the-art imaging techniques. Secondly, the azide on the 'masked' epitope can be chemically reduced to an amine, making it visible for specific T-cells at will. Although still in its infancy, the promise of this technology was further demonstrated using various masked and traceable epitopes to 'chemically' activate T-cells and by showing the ability to follow antigen routing in individual APCs. ■

News

Galenus Prize for van der Stelt

Mario van der Stelt (Leiden University) won the Galenus Research Prize 2017. The prize aims at promising young researchers in the field of fundamental or clinical drug research. According to the jury, Van der Stelt is a great research talent in Dutch pharmaceutical sciences, which will make an important contribution to pharmacochemical research in the coming years. He received the award for his work on the therapeutic applications of endocannabinoids, for which he uses the latest chemical-biological technology.

Two prestigious international awards for Piet Gros

Piet Gros has been awarded the Gregori Aminoff Prize in Crystallography 2018 by the Royal Swedish Academy of Sciences. He was presented with the award in recognition of his major contributions to our understanding of the complement system, a vital component of our immune system.

Neefjes and Ossendorp receive KWF Grant

KWF has awarded ICI researchers Professor Ferry Ossendorp and Professpr Sjaak Neefjes, both LUMC, with a grant. Ossendorp receives over 700,000 euros for the development of a cancer vaccine that can direct the immune system to tumors. The research proposal of Neefjes revolves around the relationship between food poisoning and colon cancer and is awarded a grant of more than 570,000 euros.

Recent publications

Dingjan I1, Paardekooper LM1, Verboogen DRJ1, von Mollard GF2, Ter Beest M1, van den Bogaart G3.
VAMP8-mediated NOX2 recruitment to endosomes is necessary for antigen release
Eur J Cell Biol. 2017 Oct;96(7):705-714. doi: 10.1016/j.ejcb.2017.06.007. Epub 2017 Jun 23.

Hammink R, Eggermont LJ, Zisis T, Tel J, Figdor CG, Rowan AE, Blank KG
Affinity-Based Purification of Polyisocyanopeptide Bioconjugates.
Bioconjug Chem. 2017 Oct 18;28(10):2560-2568. doi: 10.1021/acs.bioconjchem.7b00398.

Mezzadra R, Sun C, Jae LT, Gomez-Eerland R, de Vries E, Wu W, Logtenberg MEW, Slagter M, Rozeman EA, Hofland I, Broeks A, Horlings HM, Wessels LFA, Blank CU, Xiao Y, Heck AJR, Borst J, Brummelkamp TR, Schumacher TNM.
Identification of CMTM6 and CMTM4 as PD-L1 protein regulators.
Nature. 2017 Sep 7;549(7670):106-110. doi: 10.1038/nature23669. Epub 2017 Aug 16

Weiden J1, Tel J2, Figdor CG1.
Synthetic immune niches for cancer immunotherapy
Nat Rev Immunol. 2017 Aug 30. doi: 10.1038/nri.2017.89.

Qiu L1, Wimmers F, Weiden J, Heus HA, Tel J, Figdor CG.
A membrane-anchored aptamer sensor for probing IFNγ secretion by single cells
Chem Commun (Camb). 2017 Jul 13;53(57):8066-8069. doi: 10.1039/c7cc03576d.

Lagerweij T, Dusoswa SA, Negrean A, Hendrikx EML, de Vries HE, Kole J, Garcia-Vallejo JJ, Mansvelder HD, Vandertop WP, Noske D, Tannous BA, Musters RJP, van Kooyk Y, Wesseling P, Zhao XW, Wurdinger T.
Optical clearing and fluorescence deep-tissue imaging for 3D quantitative analysis of the brain tumor microenvironment.
Angiogenesis. 2017 Jul 11. doi: 10.1007/s10456-017-9565-6.

Paardekooper LM1, van den Bogaart G1, Kox M2,3, Dingjan I1, Neerincx AH4, Bendix MB4, Beest MT1, Harren FJM4, Risby T5, Pickkers P2,3, Marczin N6,7, Cristescu SM8.
Ethylene, an early marker of systemic inflammation in humans
Sci Rep. 2017 Jul 31;7(1):6889. doi: 10.1038/s41598-017-05930-9.

Goverse G1, Erkelens M1, Mebius R2.
Response to Comment on "Diet-Derived Short Chain Fatty Acids Stimulate Intestinal Epithelial Cells To Induce Mucosal Tolerogenic Dendrit ic Cells"
J Immunol. 2017 Jun 1;198(11):4188. doi: 10.4049/jimmunol.1700466.

ICI conference 2018

MARK YOUR CALENDAR AND MAKE SURE YOU WILL BE THERE!

Following the successful conferences in 2015, 2016 and 2017, ICI will host a conference in 2018 as well, that offers all participants the chance to learn something new. “Sharing your work with others and getting feedback from completely different angles is a great way to come up with new ideas”, says Sjaak Neefjes, ICI’s scientific director. Where most scientific meetings adopt a specific theme or focus on their program, ICI wants to celebrate the broad spectrum of research areas that are relevant to chemical immunology. Neefjes: “The strength of ICI is the wide range of scientific disciplines, methods and techniques. From synthetic chemistry to cell biology and from analytical chemistry to clinical expertise. And all these fields are closely linked: we have chemists who develop tools that are used by immunologists to tackle biological problems, which in turn generates new questions for the chemists to work on. By bringing all these researchers together, new ideas start flowing.”

Multidisciplinary design

The set-up of the conference in 2018 will be in line with previous ones. A PhD day for ICI PhD candidates, followed next day by the main conference intended for a wide audience. Neefjes explains: “We aim for a very broad and diverse attendance. Next to scientists, we will also invite clinicians, charity funds and other stakeholders. We really want to create a sense of urgency on the need for translational research.”

Keynote speakers are amongst others: Mustafa Diken (BioNTech) and Marc Vendrell (University of Edinburgh).

16 MARCH 2018
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Register now!

For more info about the program and to register, please visit our website **www.chemicalimmunology.nl**

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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