Nobel Prize laureate Françoise Barré-Sinoussi is furious

Bacterial Immune Evasion: A lesson in redundancy

Breaking the malaria cycle

Immuno Valley: Broaden your scope at the One Health Congress

Theme
Infectious Diseases

Peter Reiss
HIV co-morbidity and the immune system

Dick van Bekkum
On immunology and NVVI

Dutch Society for Immunology
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Joining forces

Dr. Ellen Wehrens of Utrecht University / Wilhelmina Children’s Hospital, from the group of Berten Prakken, has received an NWO Rubicon grant for a two year stay at the University of California, San Diego, Division of Biological Sciences. Recently a CD4 T cell was discovered with a deadly function. The researchers at University of California, including Wehrens, will investigate whether these cells are capable of killing cells that are infected by viruses – and hence whether they could be used for treatment of infectious diseases.

Wehrens got her Ph.D. in 2013 for the thesis ‘Vive La Résistance!? – How CD4 T cells escape regulation in autoimmune inflammation’. FOXP3+ regulatory T cells can suppress the activation and effector functions of a wide range of immune cells. They are critically involved in maintaining immune homeostasis. Studies in both mice and humans show that a shortage of regulatory T cells can lead to autoimmune diseases. Therefore, regulatory T cells are considered important targets for the treatment of autoimmune disease. Several strategies to enhance regulatory T cells in patients with autoimmune disease are being explored. In her thesis Wehrens investigated regulatory T cell numbers and function in patients with juvenile idiopathic arthritis (JIA). She established that regulatory T cells are not deficient in JIA patients and these cells display efficient suppressive capacity. Instead, the effector cells driving joint inflammation are so highly activated that they are no longer responsive to suppression. This unresponsiveness of effector cells to suppression should therefore be targeted to treat autoimmune inflammation in patients with JIA.

How memory cells protect the skin against viruses

Researchers from the Netherlands Cancer Institute have discovered how cells of the immune system that are present in the skin offer protection against renewed infections. Their study was published in Science.

The study was supervised by prof. dr. Ton Schumacher. As an immunologist, he studies how different parts of the immune system work. Memory cells are cells from the immune system that are able to remember what harmful bacteria and viruses look like. This way, they can quickly come into action when they sense the presence of a previously encountered intruder. However, a lot of questions about the exact function of these cells remain unanswered.

Schumacher studied memory cells called CD8+ T cells. Schumacher: “We have known for some time that these cells remain in the skin after an infection and offer protection against renewed infections. But their numbers are small. So how is it possible they can offer protection to a large area of tissue?”

Alarm signal

Schumacher’s team has now discovered that these memory cells protect the skin by sending out an ‘alarm signal’ when they again encounter a known intruder. This alarm system, consisting of so-called cytokines, tells large numbers of skin cells within the surrounding tissue to switch on a broad variety of anti-bacterial and anti-viral genes. The genes that become active when this alarm signal is received are, for instance, genes that can help prevent viruses from entering cells and thus prevent them from multiplying.

“Of the surprising things we found, is that the genes that are switched on offer protection to a broad range of bacteria and viruses”, Schumacher says. So if, for instance, the memory cells recognize a herpes virus, they will switch on genes in the surrounding tissue that not only target the herpes virus but also other, unrelated types of intruders. Thus, this immune response offers a broad first line of defense against infections.

Immunotherapy

New insights like these are important for the prevention and treatment of a number of diseases. Schumacher himself works on the development of cancer immunotherapy, a new and promising type of cancer treatment in which the body’s own immune system is stimulated to fight cancer cells. In the same issue of Science, a study by the research group of dr. David Masopust from the University of Minnesota appears. Using a slightly different approach, their work also demonstrates how memory T cells provide protection by sending out alarm signals. This group aims to use these new insights for the prevention of general diseases such as infections with herpes virus or HIV.

38 million euros for 152 talented Veni researchers

152 highly promising researchers can realise their research plan over the next three years thanks to a Veni grant from the Netherlands Organisation for Scientific Research (NWO). A Veni grant is worth a maximum of 250,000 euros, made available by the Ministry of Education, Culture and Science and is one of the individual grants from NWO to promote scientific talent. Among them the following researchers:

- Dr. R.J. (Richard) Hickman (m), Utrecht University – Phytopathology: Elucidating the immune signalling regulatory network in Arabidopsis thaliana with digital genomic footprinting
- Dr. J. (Jong) van Loostregt (m), University Medical Center Utrecht – Paediatric Immunology: How a hungry immune system can be influenced
- Dr. M. (Meta) Roestenberg (f), Leiden University Medical Center – Parasitology: In the skin of malaria parasites
- Dr. M. (Mitchell) van der Vlist (m), University Medical Center Utrecht – Immunology: Novel means to inhibit immune responses: CD200r interferes with TLR trafficking
- Dr. P.R. (Robert) de Vries (m), Utrecht University – Faculty of Natural Sciences: Inhibiting the highly diverse receptor binding pocket of Influenza A Virus using its conserved ligand.

The Dutch Society for Immunology acts as a facilitator of interaction between stakeholders. The debate will take place in Amsterdam. All stakeholders are invited and very welcome to express their views. Save the date! We do not leave it at that. On Thursday November 20th, organizing meetings and by publishing Immuun. But透过相互之间的交流和协作，我们能够更好地理解免疫系统的运作及其对各种感染的反应。通过这些合作，我们能够开发出更有效的治疗方法，从而为战胜重大的疾病提供可能性。
**KIELM subsidy for diagnosis of rheumatoid arthritis**

Professor Ger Pruijn (RU) and NovioSmart receive a KIELM subsidy to develop a simple blood test for the diagnosis of rheumatoid arthritis. The test should detect auto-antibodies that present themselves specifically in the blood of RA patients. The test is based on the agglutination of red blood cells and requires only a drop of blood and a modified molecule.

KIELM projects, funded by Fonds Nieuwe Chemische Innovaties at NWO, aim at bringing together a SME and a knowledge institute. NWO quadruples the initial of the SME (SMI 3.700 euros / NWO 15.000 euros). So far, 18 KIELM projects have been granted.

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**Anders Harfstrand**

Leiden based biotech company to-BBB technologies, developing medicines for the treatment of brain diseases, appointed Dr. Anders Harfstrand as its new CEO.

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**NEWS**

**IMMUUN**

October 2014

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**IMMUUN**

**Nina van Sorge, PhD. D. at UMC Utrecht, an Immuno Valley consortium partner, will be one of the scientists pitching at the Immuno Valley Annual Conference 2014.**

Van Sorge is appointed as the new CEO of biotech company to-BBB technologies, developing medicines for the treatment of brain diseases. Her appointment is aimed at strengthening the company’s focus on developing brain-targeted drugs.

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**“Saccharides key to a Group A Streptococcal Vaccine”**

Nina van Sorge studies infectious diseases caused by Gram-positive pathogens. "My focus is on streptococcal species that influence human and animal health. Whereas Streptococcus pyogenes, also known as Group A Streptococcus (GAS), affects human health, Streptococcus equi species impact animal health. What do they have in common? They share 80% of their genes, so it stands to reason that findings in GAS also tell us a lot about S. equi species, and vice-versa." Last year, Van Sorge received a NVA-VDI grant to further investigate the virulence factors these pathogens produce and to unravel their role in pathogenesis at the molecular level. "I am especially interested in the biosynthesis of streptococcal cell wall polysaccharides", she says. The role of saccharides in the immune system is underexposed, probably due to their diversity and highly complex structure.

Van Sorge will combine glycoscience, microbiology, and immunological expertise to conduct her research.

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**Patent**

Van Sorge’s research was initiated during her post-doc at the University of California San Diego (UCSD), United States, where she demonstrated that the characteristic cell wall polysaccharide of GAS contributes to pathogenesis and presents a promising vaccine antigen. In addition, these cell wall polysaccharides seem essential to many streptococcal species, making them attractive targets for antimicrobial therapy. Van Sorge and Victor Nizet patented the finding.

At the Immuno Valley Conference Van Sorge would like to find a partner for the development of a vaccine. “A Group A Streptococcus is responsible for no less than 700 million infections in humans per year”, she says. “Each year, half a million humans die from them, which ranks GAS among the ten most deadly pathogens. Also, GAS may induce acute rheumatic disease. Nizet and I demonstrated in animal models that our cell wall polysaccharide has a protective effect against GAS.”

Alinda Wolthuis
Bacterial Immune Evasion: A lesson in redundancy

The strategy applied by Staphylococcus aureus to block receptors used by the immune system proves to be far more refined than could be imagined during the discovery of its first inhibitory protein some fifteen years ago. This could explain why it is so hard to develop a vaccine against MRSA. But ‘hard’ is by no means ‘hopeless’. Furthermore, valuable insights as well as targets against inflammatory diseases are picked up along the way, explains professor Jos van Strijp Ph.D. of the Department of Medical Microbiology at the University Medical Center Utrecht.

In total, there are about ten million different bacteria species. During evolution, only a select group of about a hundred species has managed to trick the deadly efficient human immune system enough to be able to survive, inside the human body— the intestinal tract excluded. In order to survive this bacterial elite uses several strategies to evade the immune system. One strategy is to hide under a thick capsule of neutral sugars, so that the bacterium underneath remains undetected by the immune system. Pneumococci are the real masters in this respect, with a capsule almost as thick as the bacterium itself. This is, however, an energy-costly strategy. Furthermore, the bacterium will have to release its capsule every now and then in order to attach itself to body cells and structures to perform its pathogenic tasks, thus exposing itself.

"Bacteria have learned to apply multiple approaches to evade the immune system; we have to learn from their evasion strategies".

A second evasion strategy is to invade human cells and persist intracellularly. A well-known example is Mycobacterium tuberculosis, which chooses macrophages as its host. Luckily for us, this strategy isn’t flawless either. By entering a human cell, the bacterium evades the immune system outside the cell, but still has to cope with the immune system inside the cell (inflammascence, NOD-like receptors et cetera). Finally, a third strategy is to produce a portfolio of proteins that is able to block every receptor of importance used by the immune system. Staphylococcus aureus is the bacterium that has taken this strategy to perfection. It was about fifteen years ago that the first of such proteins, named CHIPS, was discovered by Van Strijp.

Counter attack

‘At first we thought: this is it; CHIPS is the reason why the immune system cannot attack the (MR)SA’, Van Strijp recalls. ‘This seemed to good to be true—and it was. MRSA has 2,200 genes. About two thirds of these are important for growth, division and metabolism. One third of the genome is variable and related to virulence. It would be peculiar if only one gene would be essential for blocking the immune system—and thus for virulence. Indeed, not much later, it proved to be not only one gene and we discovered another protein with an immune blocking function, and another, and yet another’. Neutrophils are main players in the defense against, and killing of, bacteria. The more proteins produced by the bacterium to block receptors on neutrophils were discovered, the more it became clear to Van Strijp that this protein production capability was the third bacterial strategy to evade the human immune system.

Van Strijp: ‘The innate immune system is laid out redundantly. Redundancy is a biological fact. Therefore it is not that astonishing that the bacterium has developed a counter attack system that is equally redundant’. By now, the counter points at 35 different proteins produced by MRSA, all equipped with the same task to evade the immune system. The sole identification of novel proteins is the easy part of the research in Van Strijp’s group. Figuring out the exact molecular mechanism of action is the most labor-intensive and challenging part of the process. Many of these proteins are directed against some part of the complement system or at neutrophil receptors.

Refined system

The 35 discovered genes and proteins make the MRSA the world record holder in protein-based bacterial immune evasion. In all staphylococci, all these 35 genes encoded for proteins that can block receptors leading to inhibition of the immune system are present. ‘It is overwhelming to realize that these proteins attach to any receptor at the immune system’s disposal’, Van Strijp remarks.

The 35 proteins which are discovered thus far are not the end. Van Strijp: ‘Each year, new genes are being discovered. In total, around two hundred to three hundred genes in the SA are potentially related to immune evasive protein production; but until now their function is as yet simply unknown. We only start to get a glimpse of the functioning of the system as a whole, with also a minor role dedicated to the adaptive immune system. It seems to be a sophisticated system in which at least fifty genes are involved.’ Since in other bacteria a maximum of five of such proteins are discovered, the question is whether (MR)SA is unique in this respect? ‘An explanation could be that MRSA is by far the most popular research object, leading to more discovered proteins. It can be expected that there are species around with a similarly refined system in place’, Van Strijp assumes.

Structure chemistry

‘As to our methodology, because we are looking for unknown proteins, predictions from gene sequencing are of no direct use’, says Van Strijp. ‘In our search for unknown proteins, the functional assays in fresh human blood are essential and central. But with 35 molecules now known to be in the data, research comes within reach. We do collaborate with the structural chemists of Pet Gross’s group in order to make predictions on the basis of molecule structure comparisons. The lack of good in vivo models is a limitation in our MRSA research. The use of humanized mice and zebra fish in the near future enables the fascinating new possibilities of in vivo imaging. You will actually be able to see happening what is described in the textbook’.

MRSA is by far the most popular research object, leading to more discovered proteins. It can be expected that there are species around with a similarly refined system in place’, Van Strijp assumes.

Practical application

Unraveling the mechanism is splendid fundamental science. Are there also practical applications of this knowledge? Van Strijp: ‘Firstly, it provides insight into the pathogenesis of infections. It was long thought that the immune system regarded bacteria as ’innocent bystanders’, but it is now clearly shown that this is not the case. In fact, pathogens provide the worst examples to study the efficacy of the immune system in rounding up bacteria. It is ironic that the bacterium which elude the immune system, provide the insight how difficult it actually is to evade the immune system.’

‘The knowledge on the third bacterial evasion strategy holds

Medical Microbiology at UMCU

Molecular Microbiology at UMCU values its complementary mix of cell biologists and immunologists. It is difficult to separate the actions of bacterial pathogens from the immune response of the innate immune system. Professor Jos van Strijp PhD leads the research group of about thirty persons targeting Bacterial Immune Evasion and is specialist on the virulence of Staphylococcus aureus. Van Strijp is also director of the research school Infection and Immunity with 180 members. Van Strijp Ph.D leads the research group of about thirty persons targeting Bacterial Immune Evasion and is specialist on the virulence of Staphylococcus aureus. Van Strijp is also director of the research school Infection and Immunity with 180 members.

Assistant professor Suzanne Rozijn and PhD recipient of a VIDI grant in 2010, specializes in the complement system,ej. assistant professors van Kessel is a specialist in the fields of functional assays and pharmacology and assistant professor Nina van Sorge won a VIDI grant in 2013 for setting up research on Streptococcus. Apart from Bacterial Immune Evasion, the Medical Microbiology Department also has research groups on Antibiotic Resistance under professor Marc Bonten, MD, PhD and on Virology under professor Emmanuel Wiertz, Ph.D.

The knowledge on the third bacterial evasion strategy holds...
promises for infectious as well as inflammatory diseases. “As to infectious diseases: after thirty years of development, there is still no vaccine against MRSA staphylococci. My hypothesis is that these receptor blocking proteins come a long way to explain the difficulties in generating an efficient vaccine. Yes, for decades we are able to generate antibodies against MRSA and we can get these antibodies to attach to MRSA. But if neutrophils and the complement system are not able to clear these opsonized bacteria, then the bacterium survives, with the antibody attached to it.”

Vaccine development
Van Strijp’s group has received several grants to study the potential application of molecules derived from the blocking proteins for vaccine development. “The entire pharmaceutical industry is searching for a vaccine against MRSA, but we have to admit it will still be a long way before we get there. Costwise, it is impossible to include dozens of molecules in a vaccine, therefore the industry indicates that five is the maximum. Five essential molecules could be enough to crack the bacterium’s defenses. It is, however, unclear which those molecules are. Which ones are vital, that’s what we are going to find out. Thanks to the work of protein chemists who succeeded in combining several proteins at a molecular level, it is reasonable that only five proteins could indeed be sufficient. Their work could give us five proteins with the functionality of maybe ten proteins we are looking for.” It is not an easy task to accomplish. Van Strijp explains: “The molecules of interest are not functional in mice because many of the virulence factors are 100% human-specific. One would need 500,000,000 of these bacteria to be able to induce a MRSA infection in a mouse. Luckily, only one hundred staphylococci are enough to infect a cow. Therefore the cow provides a magnificent model to study MRSA-vaccination strategies. Even more so because the same research, brought together in the ALTANT project together with the Faculty of Veterinary Medicine, could help rid the cow from her economically very damaging mastitis. This makes it ethically far more acceptable to use the cow as a model. The cow model comes with drawbacks: because it is both expensive and very time consuming.”

“Given the redundancy in the immune system, IT IS NO USE TRYING TO SOLVE INFLAMMATIONS WITH ONLY ONE COMPOUND”

Therefore, the cow model is combined with an ex vivo human model and a humanized zebrafish model. “We believe that the combination of these three models provides the most cost effective way to finally bring us closer towards a vaccine against MRSA.”

Monoclonal antibodies
Monoclonal antibody therapy could be developed earlier than a vaccine. Van Strijp: “Initially monoclonal antibody therapy was considered to be much too expensive, with one shot of antibodies costing the same as 1,500 antibiotics treatments. But when antibodies just don’t work, you have to do something. Trials with monoclonal antibodies against bacterial pathogens are already ongoing in humans and we are glad to be involved in these studies. The patient material from these trials gives us the opportunity to perform functional assays in fresh human blood, from which we learn a lot about the virulence of Staphylococcus aureus.”

Inflammatory diseases
According to Van Strijp, from the third bacterial evasion strategy we can learn a general lesson regarding inflammatory diseases: “Given the redundancy in the system, it will be unfeasible to try to treat inflammation with only one compound. Bacteria have learned to apply multiple approaches to evade the immune system; we have to learn from their evasion strategies.” The 35 proteins produced by MRSA which enable the bacterium to evade the innate immune system, provide a set of potent anti-inflammatory molecules that have the potential to be used in the treatment of inflammatory diseases. Van Strijp: “They can inhibit the immune system. We cannot use these bacterial proteins unaltered, since humans generate inhibiting antibodies against all of them. But they can be used as a starting point to make peptide mimics. These have the same functionality as the whole protein, but without the reactivity to antibodies.”

For decades already there has been a search for a malaria vaccine. “We need a vaccine, because we won’t be able to fully control or eliminate malaria with the existing means”, Teun Bousema emphasizes. “The parasite manages to spread extremely efficiently.” Robert Sauerwein: “Even if nothing would change in the relation between mosquito, parasite and drugs, new means will be necessary. In reality the urgency is even higher, as there is no such status quo.” The Nijmegen vaccine project has led to such new means; clinical trials with a vaccine are about to start.

Malaria is one of the most serious infectious diseases. Until 1955 it was endemic in The Netherlands. Nowadays, still some 750,000 patients die from it annually, mostly children under five years old in Africa. In many malaria regions, older individuals will have acquired a certain level of immunity that prevents mortality and severe morbidity. Even so, the number of clinical malaria episodes is staggering - 200 million new cases every year. Fortunately, the global malaria trend is downward. More than a decade ago the mortality rate was two million people annually. Countries like Kenya and Gambia have experienced a reduction in malaria burden of approximately 50% in recent years. Twenty countries actively strive for malaria elimination that was recently achieved in Morocco and Sri Lanka and on the island of Zanzibar. For instance, malaria incidence is now only ten per cent of what it used to be fifteen years ago. This favourable trend is a result of higher malaria control budgets, enabling deployment of existing means such as rapid, efficacious malaria treatment and impregnated bed nets. At the same time the R&D budget doubled since malaria became a priority of the Bill and Melinda Gates Foundation.

Risk of malaria resurgence
Good news, but during the last three years the fight against malaria suffers from its own success. As the urgency drops, the will to strike the final blow dwindles. Budgets don’t rise anymore. Professor Robert Sauerwein PH.D, head of the Medical Microbiology Department at the Radboud University Medical Center and leader of the Nijmegen malaria vaccine research project: “That is a pity, because worldwide we are still not even at half the budget necessary to eradicate malaria.” A vaccine will be necessary for eradication. Sauerwein: “Treatment and mosquito control can be effective if properly
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Teun Bousema (Photo Bureau Lorient Communicatie)

Robert Sauerwein: “It doesn’t matter in which stage you break the cycle, only that you break the cycle.”

“Prevention is the best weapon to contain Malaria.”

THEME: INFECTIOUS DISEASES

Versatile pathogen

The extremely versatile parasite forms an enormous challenge for vaccine developers. It is able to survive seemingly effortlessly in the totally different circumstances of the human liver, the human blood and the mosquito. The transmission biology and development and test transmission-studies in several African countries to understand malaria transmission are incredibly diverse. Bousema says: “For malaria elimination, prevention of parasite transmission should be a key ingredient. That is where the largest gain is to be made. In order to establish whether malaria-infected individuals can infect mosquitoes, we take blood, feed this to fresh mosquitoes and determine whether these become infected. During my Ph.D. research on malaria transmission in Kenya and Tanzania, I noticed a transmission-blocking immune reaction in five to ten percent of the population. In these cases transmission-blocking antibodies completely prevent the mosquito from becoming infected. If this naturally acquired immunity could be stimulated in others through vaccination, this could lead to a drastically diminished transmission of malaria and thereby reduce malaria risk for the entire community.”

Links in the chain

In Nijmegen two vaccination strategies are explored that focus on preventing the transmission of malaria between man and mosquito. The first aims to prevent infected mosquitoes from successfully infecting humans. A vaccine could play an important role in securing the gains of malaria control and shifting the balance permanently towards elimination.

Dutch ‘malaria capital’ Nijmegen

Towards the end of the seventies, Nijmegen was one of the first centres in the world to recreate the complete malaria cycle under lab conditions. It is now Europe’s largest production site of parasites and mosquitoes – 10,000 per week. In 2002 the mother of all laboratory strains, Nijmegen-Fal Pol (NF54), was sequenced here. The source of this parasite was a case of airport malaria found in a girl in Haarlemmermeer. Nijmegen research focuses on transmission: how the immune system interacts with the parasite through recognition, regulation and effector mechanisms. This knowledge is meant to be translated into a vaccine, preferably including transmission blocking capabilities. The specialisation in drugs and transmission research is brought to the market through the spin-off company TransQ Health Sciences.

Prevent mosquito infection

Of the various options to fight the parasite, Bousema concentrates on mosquito infection, the parasite stage that infects mosquitoes. He is involved in epidemiological and clinical studies in several African countries to understand malaria transmission biology and develop and test transmission-blocking tools. One of the long term goals of both Sauerwein and Bousema is to utilise the human immune responses to intervene with parasite development at the moments of transition between mosquito and human. Sauerwein: “A vaccine that could block the way from human to mosquito would be a great addition to a vaccine that prevents infection from mosquito to human. Especially the risk of escape mutants could be countered effectively. It doesn’t matter in which stage you break the cycle, only that you break the cycle.”

Bousema: “For malaria elimination, prevention of parasite spread should be a key ingredient. That is where the largest gain is to be made. In order to establish whether malaria-infected individuals can infect mosquitoes, we take blood, feed this to fresh mosquitoes and determine whether these become infected. During my Ph.D. research on malaria transmission in Kenya and Tanzania, I noticed a transmission-blocking immune reaction in five to ten percent of the population. In these cases transmission-blocking antibodies completely prevent the mosquito from becoming infected. If this naturally acquired immunity could be stimulated in others through vaccination, this could lead to a drastically diminished transmission of malaria and thereby reduce malaria risk for the entire community.”

Big data

Although a vaccine is within reach, this doesn’t mean the interactions taking place between pathogen and the immune system are fully understood. Sauerwein: “The pathogen causes a storm of immune reactions which is so complex, that it is impossible to predict which individual (without vaccination) will become ill and which individual will become asymptotically infected. There are no proper bio-markers to chart this unknown territory. We are specifically interested in what the ‘nine thousand known volunteers with transmission blocking capabilities’ react to. We put Big Data research in place to get to the secret of the immune signature of protection. We’re just at the beginning with this. So far, we have no more than a telephone book without the addresses. There is still a world to be won.”

A candidate vaccine

“There are several vaccination approaches,” Sauerwein explains, “from an approach where you use the complete organism in a weakened form to strategies that carefully choose single proteins or combinations of proteins. For the latter approach, the most important question is which proteins produced by the parasite are essential, eliciting strong immune responses and have little variation between naturally circulating parasite clones. To prevent malaria transmission from man to mosquito, our current prime target is the Pf48/45 protein. We collaborate with an Indian firm to produce our Pf48/45 vaccine candidate in large quantities and according to international manufacturing standards.”

5,000 genes of the malaria parasite are essential, eliciting strong immune responses and have little variation between naturally circulating parasite clones. To prevent malaria transmission from man to mosquito, our current prime target is the Pf48/45 protein. We collaborate with an Indian firm to produce our Pf48/45 vaccine candidate in large quantities and according to international manufacturing standards.”

“Our aim is to control both gates: the entrance as well as the exit of malaria parasites.”

Bousema is supporting the development of the Pf48/45 vaccine in the field and at the same time works on the portfolio of the next generation of vaccine candidates. “My team aims to profile the immune responses of people who prevent transmission. For this we will use a chip with several hundreds of parasite proteins that may play a role in malaria transmission. We will screen endemic populations to determine how important Pf48/45 antibody responses really are for naturally occurring transmission and try to identify other promising proteins as possible additional vaccine targets.”

It is very valuable to have integrated lab and field research, says Sauerwein. “Thanks to the fieldwork, we now know that some people have hundred percent effective immune response for the transmission of man to mosquito. This inspired us to a vaccine strategy. And thanks to the controlled infection in our lab, we now know that hundred percent asexual protection from a mosquito to man is possible. So now we control both gates, the entrance as well as the exit, where the parasite is at its weakest in numbers and genetic variance.”

Lemert van der Ent
Ultra High throughput screening: “We can analyze anything, as long as it fits in a microtiter plate”

The Pivot Park Screening Centre (PPSC) located at the Life Sciences Park Oss, is ensured of work on behalf of the European Lead Factory until 2018. Other collaborations with companies and knowledge institutes have been started for the testing of substances in the ultra-High Throughput Screening (u-HTS) lab.

Robot arms, swiftly moving 1536-wells microtiter plates from one to the next processing station, are the eye-catchers at PPSC. The company could make a headstart in 2012, because all the necessary equipment, infrastructure and expertise was already put in place by MSD. A winning bid for a EU-project, called European Lead Factory, entailing the development of 120 screening assays for 500,000 substances in five years, now secures a consistent workload for the PPSC.

The u-HTS lab contains three ‘pods’, platforms with a central robotic arm, each surrounded by ten to twenty work stations on mobile carts. The pods for filling of wells in microtiter plates, adding reagents & incubation and results output respectively, are connected by a conveyor line. Together this set-up forms a circuit for screening of up to 2.5 million substances.

Invisible

Less conspicuous but far more laborious are the process steps before and after the robot. “The robots need two to three days to screen over 500,000 compounds, whereas a typical project spans nine months to a year”, says Helma Rutjes, head of the assay development department. “The client offers (an idea for) an assay, developed for execution on the bench. We start by checking its functionality. Then we assess whether the assay is suited for miniaturisation in smaller wells and for process automation.”

Miniaturisation automatically implies reassessment of the kinetics and reagent ratios. Especially when working with more complex systems, like (primary) cells, organisms or even complete organisms, volume downscaling needs to be performed accurately. The trend is to use high content analysis in an early stage of drug discovery. “Within PPSC we have the Operetta technology to fulfil this need. General workflow is to start screening using ultrahigh throughput approach, confirm the active, check selectivity and potency, followed by more complex high content analysis.”

Bridging the gap

The PPSC is also fit for smaller projects, says Business developer Steven van Helden: “We have our own database of 200,000 substances for customers to select on the basis of all sorts of characteristics. Brining in a customer’s set of compounds is also possible. Finding targets has become the domain of universities and biotechnology start-ups. We offer the next step to that. In this way, we bridge the gap that originated from the pharmaceutical industry’s retreat from early drug discovery. “Within PPSC we have the Operetta technology to (ful)fill this need. General workflow is to start screening using ultrahigh throughput approach, confirm the active, check selectivity and potency, followed by more complex high content analysis.”

Artificial virus for therapy

Researchers in Leiden, Eindhoven and Nijmegen, led by Wageningen University, have succeeded in developing an artificial virus. The virus can for instance be used in biomedical and biotechnological applications, such as targeted delivery of nucleic acids for gene therapy. The discovery was published online in Nature Nanotechnology.

Viruses are among the simplest biological systems and are highly effective vehicles for the delivery of genetic material into susceptible host cells. Artificial viruses can be used as model systems for providing insights into natural viruses and can be considered a testing ground for developing artificial life. Moreover, they are used in biomedical and biotechnological applications, such as targeted delivery of nucleic acids for gene therapy and as scaffolds in material science. In a natural setting, survival of viruses requires that a significant fraction of the replicated genomes be completely protected by coat proteins. Complete protection of the genome is ensured by a highly cooperative supramolecular process between the coat proteins and the nucleic acids, which is based on reversible, weak and allosteric interactions only. However, incorporating this type of supramolecular cooperativity into artificial viruses remains challenging. The researchers report a new principle for the assembly of a minimal viral coat protein based on simple polypeptide domains. Their coat protein features precise control over the cooperativity of its self-assembly with single DNA molecules to finally form rod-shaped virus-like particles. The researchers confirm the validity of their design principle by showing that the kinetics of self-assembly of their virus-like particles follows a previous model developed for tobacco mosaic virus. They show that their virus-like particles protect against enzymatic degradation and transfect cells with considerable efficiency, making them promising delivery vehicles.


Dr. Ina Niess (Eindhoven University) developed together with Dr. Veronique Egger (Eindhoven University) and Dr. Paul van der Schot (Eindhoven University of Technology) a theoretical physical model for the assembly of a natural virus.

This expertise we are now developing a screening method for the entire organism. The first results are encouraging. If this succeeds, we will be able to assess the chance of success of leads already in the earliest development phase, for instance through excluding toxic effects. This might add speed as well as efficacy to the development process.”

The Pivot Park Screening Centre (www.pivotparkscreeningcentre.com) uses approximately five hundred 1536-wells microtiter plates per screening project for the European Lead Factory. Strength and dimensional accuracy, also between batches, is very important, as is a broad supply of variants. The PPSC preferably uses 384- and 1536-wells plates, such as those of Greiner Bio-One. This article was made possible by the kind support of Greiner Bio-One. www.gbo.com
The intriguing link between HIV co-morbidity and the immune system

In The Netherlands, around 18,000 patients are known to be in care with HIV infection. Prof. Dr. Peter Reiss is Director of Stichting HIV Monitoring (SHM) and Professor of Medicine at the Academic Medical Center in Amsterdam. “The median age of patients in care continues to rise”, he says. “These patients seemingly have to deal with age-related co-morbidities sooner than others, and more often suffer from a combination of problems.” These findings give rise to research. “Maybe the chronic activation and deficiency of the immune system makes patients amenable to these co-morbidities.”

Since February 1, 2013, Peter Reiss has been director of SHM, the foundation that monitors HIV-infected persons in Dutch treatment centers. “We aim to further the knowledge and understanding of the epidemiology and the course of the treated and untreated HIV infection. We collect and maintain data from HIV-infected patients, process these data and make them available to HIV-infected individuals and their physicians. We monitor the Dutch HIV care and we also provide anonymous data for the benefit of scientific research or policy makers”, he says.

DOES THE CHRONIC ACTIVATION AND DEFICIENCY OF THE IMMUNE SYSTEM MAKE PATIENTS AMENABLE TO CO-MORBIDITIES?

One of his ambitions for SHM is to increase the involvement of clinical colleagues in SHM’s work and to develop bidirectional collaborations. In this way, Reiss hopes to secure SHM’s scientific productivity, while further strengthening its scientific output on its own. “If you need large national or international observational datasets, SHM is the organisation to turn to”, he says. Before becoming SHM’s Director, Reiss himself acted as a principle investigator and steering committee member for SHM in a number of collaboration studies. Today, in addition to his job at SHM, he still conducts research and clinical care at the AMC and the Amsterdam Institute for Global Health and Development one day a week.

Age-related co-morbidities

Reiss gives an overview of the current situation regarding HIV-“Currently in The Netherlands over 18,000 persons have been linked to care for HIV infection. 12,000 of them currently remain in HIV care, of whom 14,795 receive combined anti-retroviral therapy and 13,955 patients have suppressed HIV infection”, he says. Unfortunately, an estimated 7,000 to 8,000 HIV-infected persons are not aware of their condition. They therefore do not receive proper care and are liable to spread the infection. This partly explains the 1,000 new infections per year. The annual number of newly diagnosed patients remains stable, but shows no decline. Two thirds of these newly diagnosed individuals are ‘men who have sex with men’. Thanks to cART the median age of patients in care is now 42 years. ‘In 1996 only 9% of the patients were 50 years or older, whereas 3% of the patients had reached that age in 2013’, Reiss says. “With the rising age, age-related co-morbidities present themselves. In fact, these co-morbidities seem to present themselves more frequently and possibly sooner in HIV-infected patients than in non-HIV-patients. Also, these patients are more likely to suffer from a combination of problems.”

Growing old sooner?

It has become the object of Reiss’ own research line. “The question is, whether HIV-patients grow old sooner than non-HIV-patients and, if so, what can the explanation be. Does the chronic activation and deficiency of the immune system make patients amenable to co-morbidities? And what is the influence of cART on the aging process?”

The AMC and the communal health service (GGD) Amsterdam have included 6,000 HIV-patients of the AMC and 6,000 HIV-negative GGD-ent without any infections in a large scale cohort research project (the AGEnHIV Cohort Study). The research started in 2010. Reiss: “Results so far show that HIV patients suffer significantly more from age-related diseases, notably cardiovascular diseases, high blood pressure and chronic kidney failure. Also, but less significantly, diabetes, lung problems, osteoporosis, non-traumatic fractures and non-HIV-associated tumors occur more often in HIV patients, reducing quality of life and participation in society. We have found evidence that the virus itself, the immune deficiency and the long-term use of cART contribute to the risk of having one or more of these conditions, but we are still researching the individual effects of these factors.”

Biomarkers

The outcomes of the study will have impact on HIV care. “We must pay more attention to finding and treating the risk factors for co-morbidities. I also hope that immunological research will identify biomarkers predicting specific pathologies in patients.” Furthermore, the field must develop a protocol for systematic screening and patients must be advised on lifestyle issues: stop smoking, eat healthy and exercise. “Multidisciplinary expertise is necessary.” Research continues to examine whether it is beneficial to start treatment earlier, before immune deficiency presents itself. Also, the effect of the use of cART on co-morbidity is still being researched.

Reiss also hopes to learn more about the aging process. “Besides the consequences for HIV-treatment, the results may give insight into aging in general and into similar processes in other chronic infectious diseases such as rheumatoid arthritis, psoriasis or Crohn’s Disease.”

Leading scientists

Reiss’ research receives a lot of international attention. Until recently he was the regional representative for Europe, Central Asia on the Governing Council and Executive Committee of the International AIDS Society. As such, he is well positioned to appreciate Dutch research in an international context. “As a small country with limited research resources, we do a lot of internationally acclaimed research. The Netherlands in general are a prominent party in HIV/AIDS science”, he concludes. “From the early days of the epidemic up to the present we have been conducting research. This research spans the range of clinical, epidemiological, basic, translational, prevention, social and behavioral as well as implementation science. It is often ahead of the game and has contributed much to understanding the disease, from immunology to vaccine research.”

Alinda Wolthuis

Peter Reiss: “In monitoring HIV patients, hospitals mainly check the CD4 cell levels. This, however, is not an optimal reflection of the immune system. Unfortunately, we do not have another routine test that would give a better representation of the immune system. We would really welcome a better test.”

HIV monitoring test

Peter Reiss: “In monitoring HIV patients, hospitals mainly check the CD4 cell levels. This, however, is not an optimal reflection of the immune system. Unfortunately, we do not have another routine test that would give a better representation of the immune system. We would really welcome a better test.”
**NVVI co-founder Dick van Bekkum: A plea for the N=1 approach**

Prof. dr. Dick van Bekkum was one of the founders of the NVVI, back in 1964. To understand why the NVVI was established, Van Bekkum describes the scientific climate of that era. This offers a fine opportunity to make a comparison with the presence. Of course he sees a lot of progress and growth, but according to him not all developments are favourable. He notices for instance the pitfalls of super-specialisation, bureaucracy and risk avoidance and has some important messages regarding magistral preparation, publication pressure and laboratory animal use. “Immunologists, if you want something, just take your fate in your own hands and do it yourself.”

“Nuclear Power evoked attention to the Immune System”

Quite a difference with the early days of ICT, Van Bekkum recalls, when he set up the Radiobiology Institute in Rijswijk as part of the Health Organisation TNO in the early nineteen-sixties, focusing on radiation protection and the medical applications of ionizing radiation and radioactive isotopes. “It was part of an informal international group of scientists sharing knowledge. This bunch of about thirty sent each other stencilled leaflets by physical mail. Those were also the days of data cards. We needed to keep a laboratory animal administration that could hardly be done by hand, so we were among the early ICT-adopters. We produced four generations of mice a year, 10,000, and 30,000 rats, all neatly divided into inbred strains. The pedigree and immunological features of all of these had to be carefully recorded. IBM was one of our ‘neighbours’ in Rijswijk, so we made a deal and someone went there every week with a bag of punch cards to be processed by them. We have profited from the rapid developments in ICT ever since.”

Science as a hobby

“Then I received a broad training and was expected to follow more or less the entire medical field. Disciplines weren’t that far apart and shared knowledge. That is the rationale behind the establishment of Federa as the Federation of Medical Scientific Associations in 1953 by David de Wied and me. Specialisation came later in one’s career. I wanted to get familiar with the emerging biochemistry – amino acids, enzymes and vitamins – which was revolutionizing medicine at the time, so I went to Oxford to study it.”

After the war it had become clear that scientific discoveries had had a huge impact on events, an insight that prevailed throughout the cold war: “An Immunology Renaissance” occurred, partly as a consequence of the invention of the atom bomb, isotopes and nuclear reactors. “Prior to Hiroshima and Nagasaki there was no knowledge on the consequences of radiation. Most casualties didn’t die from the blast of bombs, but from radiation disease. After exposure, blood cells are no longer produced and the immune system stops functioning. People died from bleedings and infections. In this way it was nuclear power that evoked attention to the immune system. For me this was in a nutshell what put me on the track of bone marrow transplantation.”

Impact

The funny thing was, that this renaissance occurred before immunology existed as such. Immunology gradually emerged from separated fields such as chemistry of antibodies moving towards biology, Van Loghem’s field of ‘blood transfusion towards infectious diseases. At that time, cellular immunity and autoimmunity were just emerging. Van Bekkum was among the first medical doctors to get involved in bone marrow and organ transplantation. He recalls: “Establishment of the NVVI in 1964 emphasized that immunology was becoming an important separate discipline. By that time, there were maybe a hundred people active in some kind of immunological research in the Netherlands.”

The NVVI was set up to unite these scattered researchers and to promote their communication. It also served a very practical purpose, says Van Bekkum, namely to establish formal contacts with the immunological societies of America (1913) and Great Britain (1958). “We actually founded the third national society for immunology and were ahead of France (1956) and Germany (1960). The impact of NVVI was immense. Internationally, Dutch immunology became firmly established. On the national level it brought cohesion between the scattered activities in the field. It also helped shape the discipline, by organizing trainings for medical doctors and biologists to become certified clinical immunologists or laboratory immunologists.”

From specialisation to super-specialisation

During the period of pioneering, congresses were still rare, let alone international traffic. “I made my first trip to the USA – to visit nuclear installations - in a military airplane”, Van Bekkum recalls. “Communication was cumbersome. When scientists from various countries finally got together, they took several months, sometimes a week to exchange findings. And, most importantly, they attempted to connect these with progress outside their own field of interest. I was privileged to have landed in radiation biology, because this completely new subject was shaped into one of the most interactive areas of research, thanks to the vision of the U.S. Atomic Energy Commission. Their large nuclear research installations included Biological and Medical Divisions, staffed by a diversity of biologists, physicians, physicists and chemists. I remember a symposium in 1956 on the recently discovered phenomenon of Genetic Recombination and another one in 1959 on Structure and Function of Genetic Elements. These were no commercial or publication imposed restrictions to our exchanges, surprisingly not even in the military domain. Everybody spoke about his data and ideas freely and you could look everywhere you wished in the lab. Needless to say, this all has changed completely due to the expansion of scientific research with its super-specialization, the advance of internet and the utilitarian pressures on scientists to commercialize their inventions.”

Surely, these developments have brought enormous gains of knowledge. Van Bekkum admits: “But we shouldn’t forget that we also lost something. In a smaller scientific world it was easier to follow what went on in neighbouring fields. Now one needs a couple of days to fully understand the contents of a paper.”

“The N=1 approach will not bring you scientific recognition nor publication, but it can save lives.” (Photo Bureau Lorient Communicatie)
Progress in the Fight Against Tuberculosis

Leading immunologists expect to see some clear advances in the fight against tuberculosis. Professor Stefan Kaufmann, Director at the Max Planck Institute for Infection Biology in Berlin, echoed these sentiments at the 64th Lindau Nobel Laureate Meeting in July. “In the past ten years, numerous attempts have been made to develop an improved vaccine. We are now justified in hoping that our vaccine will be effective”, explained Professor Kaufmann. The vaccine developed by Kaufmann’s research group is already undergoing Phase I/IIa clinical trials, during which its effectiveness and tolerability will be tested by trial participants.

Systems biology

Kaufmann attributed advances such as this in the fight against infectious diseases to the greater depth of knowledge acquired in recent decades about the body’s own immune system defences. Kaufmann, who is also Professor of Microbiology and Immunology at the Charité in Berlin, has a clear perspective on the direction in which the research area will continue to develop: “Over the next few years we must come to understand the immune system in the context of systems biology.” One of the keys to this understanding lies in identifying the molecular and functional diversity of immunocompetent cells. Another lies in investigating the complex interactions with the body’s own, as well as foreign cells and substances.

Activate killer cells

The complexity of the biological and biochemical foundations that underlie the human immune system is one reason why the pathogen Mycobacterium tuberculosis, which has existed for thousands of years, is still being combated with a vaccine that is itself almost a hundred years old, and has proven to be of little effect. The pathogen Mycobacterium tuberculosis skilfully evades the weapons available to the body, as well as to medicine. “The pathogen establishes itself in macrophages and obstructs an efficient immune response”, Stefan Kaufmann explained. Inside these phagocytes the bacteria can remain inactive and survive for long periods of time, and to escape the majority of antibiotics. The thick, impermeable fat layer in the cell wall also provides protection for the pathogen.

“The old BCG vaccine against tuberculosis primarily activates only helper cells. The trick with our new vaccine is to additionally activate the killer cells, which in turn can trigger an improved immune system response.”

Photo Christian Schumacher

Leendert van der Ent

“Admittedly, this IW approach will not bring you immediate publications nor registration of the new drug, but it can provide proof of principle and thereby speed up its introduction. This seems to have become forgotten. Rules and regulations shouldn’t make researchers stop thinking independently. It simply comes down to this: every medical doctor in the Netherlands can prescribe what he thinks is in the patient’s best interest and every pharmacist is allowed to provide it as a magisterial preparation.”

“Few report significant data before they have been solicited for publication and/or patented. Therefore criticism has become water under the bridge.”

Magistral preparation

From a small specialist, Immunology has become a major scientific and clinical field, bordering to almost all other medical specialisms and influencing them. Relevance to the pharmaceutical industry is also high. “Why is it then”, Van Bekkum wonders, “that immunologists still feel the need to be recognised”? The answer lies, according to him, partly in unnecessary dependance on others. “Immunologists wish to deliver their knowledge to the industry because they think it’s the only way to get new immunological therapies to the patient. But why depend on others for the practical application of your discoveries? Why not do it quicker, better and cheaper by yourself?” Real innovations rarely come from industry, as the nature of industry is risk aversion. Its stimulus is money making, which isn’t the best one for renewal. At some point in our research, in 1993, my collaborator Dinko Valerio and I decided we’d better establish our own company. That was the start of Crucell’s predecessor Introgene and also the beginning of the end of our endeavours in gene therapy.

If your drive is to save patient’s lives in an academic setting, there is nothing to hold you back from one patient-stepwise testing of your new treatment, Van Bekkum underlines.

Moreover, the sequence and way of information dissipation have changed. “Van Bekkum: ‘Back then, the presentation came first and only then the publication followed, so criticism could be addressed beforehand – peer review instead of peer review. Now it’s the other way round. Few report significant data before they have been submitted for publication and/or patenting. Therefore criticism has become water under the bridge. Also, through collaboration with industry it is not allowed to disclose all information.’

Publication pressure has become suffocating, to the extent of keeping scientists from their core activity, says Van Bekkum: “With grants it is the same. When a student has found something unexpected and suggests to pursue it, the first questions from his mentors will be: can it be published and does it fit in our grant? If not, a promising idea is doomed to go to waste. Only the expected fits into a successful grant application. How can scientists be creative if only allowed to investigate what is foreseen? It’s about time to convince universities and granting agencies to stop this nonsense. From the United States I hear about emerging change; some faculty deans are hesitant to hire people with too many publications to their name.’”

“Of course you need the approval of the medical ethical committee, as is necessary for all clinical experiments and for publications nor registration of the new drug, but it can provide proof of principle and thereby speed up its introduction. This seems to have become forgotten. Rules and regulations shouldn’t make researchers stop thinking independently. It simply comes down to this: every medical doctor in the Netherlands can prescribe what he thinks is in the patient’s best interest and every pharmacist is allowed to provide it as a magisterial preparation.”

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**Mucosal immunology: The benefit of crossing borders**

From a historical perspective, human mucosal surfaces and their luminal content have been considered unesthetic and a principal cause of many human diseases for thousands of years. Elie Metchnikoff stated in 1903 that “The large intestine is a vestige of mammalian evolution, does not serve any meaningful purpose and is harmful to human health and life”. That point of view has changed dramatically. The field of mucosal immunology has exploded during the last decades, thanks to breakthroughs in the understanding of the biology of the border between the microbial community and the host immune system. Lactational products of mammalian species have long been associated with unique healing powers. This inspired clinicians and scientists to revisit the biology of mucosal surfaces.

Nowadays, mucosal borders are appreciated as the key sites of crosstalk between microbes and the immune system. This crosstalk determines the delicate balance between tolerance and immunity. Fiona Powrie of the University of Oxford makes clear that the mucosal surface is not the only border to be crossed during the meeting in Lunteren (see box). The traditional division in innate and adaptive immunity has been challenged by the recent astonishing discovery of various novel types of the family of so-called innate lymphoid cells (ILC). ILC comprise a group of cells with lymphoid morphology, which lack the expression of known cell lineage markers and antigen-specific receptors, but have the distinct capacity to produce large amounts of cytokines. ILC are particularly prevalent at mucosal surfaces, where they emerge as key regulators in immune surveillance and the initiation of immune responses. Fiona Powrie now points at the multiple pathways through which the cytokine IL-25 promotes intestinal inflammation. IL-25 acts directly on Th cells by binding IL-13Rα1 which heterodimerizes to promote T helper (Th) 2 responses and at the same time to block regulatory T cells. Moreover, IL-25 drives the novel population of ILC2 that are potent producers of IL-17, IL-22 and IFN-γ. These ILC2, together with pathological Th1 responses, induce intestinal inflammation, autoimmunity and colitis. Thus, IL-25 plays a pivotal role in orchestrating mucosal inflammation, and several genes in the IL-25/Th17 pathway confer the risk of inflammatory bowel disease.

**RORγt: a master regulator**

Both Th17 cells and ILC2 express the key transcription factor RORγt. RORγt-expressing ILC2 play a critical role in intestinal homeostasis and host defense. They are programmed to develop in the fetus and after birth independently of microbiota. However, their reactivity is tightly regulated by mucosal microbiota. In contrast, RORγt-expressing Th17 cells are induced by microbiota, in particular by segmented filamentous bacteria. Gerard Eberl of the Institut Pasteur in Paris shows that RORγt-expressing regulatory Th17 cells are also induced by the microbiota and surprisingly control type II immunity and IgE levels. In RORγt-deficient mice type II immunity is increased, with enhanced activity of both classical Th2 cells and ILC2, which have the capacity to produce large amounts of IL-5 and IL-13.

**ILC2 and lung inflammation**

ILC2 are also discussed in detail by Tim Halim of the MRC Laboratory of Molecular Biology in Cambridge. ILC2 accumulate in the lungs shortly after allergen exposure and share many features with Th2 cells. These have always been regarded as the key orchestrators of allergic airway inflammation. IL-5 and IL-13 are the main cytokines responsible for the eosinophilic inflammation and bronchial hyper-reactivity, which characterize allergic asthma. The precise contribution of ILC2 to asthma pathogenesis is still largely unclear. Moreover, the central question how ILC2 interact with cells of the adaptive immune system remained unexplored. In this context, Halim shows that in a murine model ILC2 induce efficient Th1-mediated allergic lung inflammation: ILC2-derived IL-13 is critical for the adaptive Th1 immune response to inhaled papain allergen. Interestingly, ILC2-derived IL-13 promotes the migration of activatedCCR6+ lung DC into draining lymph nodes, where they prime differentiation of naive T cells into Th2 cells.

**Microbiota and mucosal B cells**

In the intestine, the adaptive immune system is directly shaped by the complex microbial community as evidenced by the poor developed Peyer’s patches, mesenteric lymph nodes and isolated lymphoid follicles in germ-free mice. Mucosal B cell responses are dominated by production of IgA. That not only helps to prevent mucosal bacterial overgrowth via direct neutralization, but also helps to improve digestive function. Andrew Macpherson of the University Hospital of Bern points out.

**Shifting the gut microbiome might be an effective therapy to treat immunological diseases**

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Besides antibody producers, B cells are also potent cytokine producers. Claudia Mauri of the University College in London emphasizes the importance of regulatory B cells which inhibit immune responses by production of IL-10. There is currently no consensus whether regulatory B cells represent a unique lineage or whether all B cell subsets can adopt a regulatory phenotype dependent on the inflammatory environment as the new view on the plasticity of lymphocytes suggests. For example, pro-inflammatory cytokines (IL-6, IL-18) produced in response to the gut microbiota induce regulatory B cell differentiation in peripheral lymphoid tissue. Moreover, the composition of the mucosal microbiome directly influences the function of regulatory B cells, as antibiotic treatment reduces IL-10 production. B-cell specific IL-10 deficiency leads to increased susceptibility to autoimmune disorders, a fact that underscores the importance of regulatory B cells in health and disease.

**Lunteren Symposium “Crossing Borders” Stimulating atmosphere**

This article is a report of the proceedings during the Lunteren Symposium of the Dutch Society for Immunology (NVVI) meeting ‘Mucosal Immunology: crossing borders’ on April 3rd and 4th. The lectures gave rise to lively discussions that continued during the breaks. Traditional meet-the-speaker sessions added to the stimulating atmosphere of the meeting, which was attended by 450 researchers.
**Novel functions of T cell subsets**

Troy Randall of the University of Alabama delineates the function of various T helper cell subsets in controlling B cell responses. Interestingly, depletion of regulatory T cells results in aberrant antibody production. This is due to increased IgG2 production by effector T cells. Thus, IgG2 impairs differentiation of T follicular helper cells, germinal center responses, and B cell responses in vivo.

The interplay between these three different CD4+ T cell subsets determines immunological outcome to maximize immunity to pathogens and to limit autoimmunity. Intra-epithelial T cells in the intestine are antigen-experienced T cells of which a large fraction consists of CD8αα effector memory T cells. The presence of Akkermansia muciniphila is inversely related to the severity of appendicitis, colitis and obesity.

Healthy gut flora can be classified into enterotypes, which are surprisingly independent from age, gender and host nationality. The microbial diversity within a given body habitat, defined as the number and abundance distribution of particular types of organisms, has been linked to several diseases. Low diversity in the gut is seen in obesity and inflammatory bowel disease. Therefore, metagenome-wide association studies can lead to the detection of diagnostic markers for host properties and disease. Mouse experiments already indicate that fecal transplants may be used to treat gut-related conditions, such as ulcerative colitis. So, rather than interfering with the immune system, shifting the gut microbiome might be an effective therapy to treat immunological diseases. Raes touches controversial territory and evokes lively discussions on the effects of diet on flora. Will bacterial enterotype classification really help to stratify patients? Is fecal transplantation really the way to go? In any case, it is clear that both our fundamental knowledge of the immune system and future treatment strategies for various immunological disorders will markedly benefit from scientific endeavors that cross the borders between immunology, bio-informatics and microbiology.

Rudi Hendriks (Erasmus MC) and Annette van Spriel (Radboud UMC)

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**“Use the NVVI’s considerable influence”**

Co-founder of the NVVI Prof. Dr. Dick van Bekkum has outspoken ideas about the course of the NVVI: “Is more support for immunological research by propagating and popularizing immunology or emphasizing its importance for society really necessary? In my opinion a number of other projects for boosting the impact and quality of academic research in immunology should be added to the successful activities in the area of training and education of immunologists.”

“My first plea regards more easily accessible and cost-friendly labs for magistral production of small amounts of clinical grade new monoclonal antibodies, vaccines, immunosuppressive drugs and therapeutic immune cells to enable first-in-patient use of new therapeutic agents in the university setting. This will help to reduce the time and ever increasing costs needed for commercial development of new therapies especially in view of the ongoing personalization of treatments.”

**Special fund**

“Second on my list and related to this, is lobbying with the University Medical Centers, NAKO, ZonMW, KWF and other granting agencies for the foundation of a special fund for small scale production of immunological agents for first-in-patient use. Furthermore, I would welcome a concerted effort to simplify and adapt where necessary the rules and regulations that govern the development of new drugs and other medical devices. These regulations are tailored for the commercial registration process and not for academic not-for-profit clinical investigations.”

** Publication pressure and patient representation**

“I also argue for the (argue) support by the NVVI of Transition in Science in combating the current publication for career pressure. A further point is, to promote the participation of patient representatives regarding decisions on funding of medical research projects in the field of immunology.”

**Animal models**

“Take a clear stand in the ongoing discussion on the value of preclinical research with laboratory animals. This position should be founded on knowledge of and experience with both animal models and in vitro systems, not on public sentiments against or high costs of animal experimentation. Considering that the immunological system interacts with all other body tissues, it is pivotal to identify the limitations of both in vivo and in vitro experiments. Where these are unsatisfactory for collecting the required preclinical information, the development of improved animal models and in vitro tests has to be stimulated.”

**Start cooking!**

“When it is membership of about 1,300 the NVVI has enough influence to provide a platform for bringing about the desired improvements in climate and facilities for immunological research on its own. It has to take leadership in accomplishing changes instead of merely insisting on more funding with the unavoidable consequence of independence loss. There is no such thing as a free lunch. When you are really hungry, don’t wait for a sponsor, start cooking!”

Take home message: Bioinformatics and microbiology enrich immunology

Rudi Hendriks and Annette van Spriel: “At the end of the meeting we felt that the main take home message turned out to be clear: both our fundamental knowledge of the immune system and future treatment strategies for various immunological disorders will markedly benefit from scientific endeavors which cross the borders between immunology, bio-informatics and microbiology.”

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**Who is Dirk Willem van Bekkum?**

Prof. dr. Dick van Bekkum (1925) studied medicine at Leiden during World War II – partly underground, after refusal to sign for loyalty to the German occupier. After the war his mentor professor Andries Querido advises him to study biochemistry at Oxford, where he investigates the effects of amino acid uptake on the healing of burns. He gets his Ph.D. in 1952 for his research on the enzyme D-amino acid oxidase. His military upbringing brings him to the Medical Biological Laboratory of the Defence Organization of TNO, where he studies radiation disease. This results in his first publication on stem cells and bone marrow transplantation in 1956. He becomes director of the newly founded Radio Biological Institute TNO in 1960, until retirement in 1990. He developed a cancer research program, which led to founding the EORTC (1963) and the first Comprehensive Cancer Center at Rotterdam (1977). The lack of organization in research inspires him to set up, with others, Federa in 1959, NVVI in 1964 and the Foundation Biosciences and Society in 1969. Towards the end of the eighties, Van Bekkum discovered that certain severe auto-immune diseases can be cured with autologous stem cells from the bone marrow, an unexpected finding that finds its way to the clinic. The refusal of Dutch granting agencies to support first clinical applications of newly developed gene therapies made van Bekkum and two co-founders start Introgene, later to become Crucell. In 2009, with radiation therapy he received the Trevor A. Parnell Award from the American Society for Radiation Oncology (ASRO) for non-profit development of targeted drugs and therapies. Crucell has launched its first products and has several others in the pipeline. Van Bekkum was Van Loghem Laureate in 1985 and received a great number of awards, among them in 2009 the Van Walsum prize (for his contributions to the popularization of medical research).
Françoise Barré-Sinoussi
“Hopeful that sustainable remission of HIV infection is achievable”

In June 1981, clinicians in the United States first reported a number of cases of Pneumocystis carinii in homosexual males. Subsequently, the first cases of what would later become known as AIDS were observed in France. In December 1982, clinicians provided Françoise Barré-Sinoussi, Luc Montagnier and Jean-Claude Chermann with a lymph node biopsy from an AIDS patient, with the aim of isolating the etiological agent causing the disease. The team discovered that a new human retrovirus was responsible for AIDS. The discovery was published in May 1983 in Science and was followed by an unprecedented effort in the science and medicine community to learn about the new disease entity, to develop tests and to provide treatment.

Responsibility

Ever since she co-discovered the virus, Françoise Barré-Sinoussi has been contributing to this effort. Winning the Nobel Prize in 2008 – together with Luc Montagnier – for discovering HIV did not slow her down, neither does age. “Formally, I should be retired by now, but I have been granted an extra three years at the Institut Pasteur”, she says. The President of the International AIDS Society manages her lab and travels the world to work with scientists and clinicians, patients and activists. Barré-Sinoussi cannot imagine retirement when there is so much work to do. “We scientists have a responsibility to develop tools for the benefit of people; we must be persistent and go on”, she says.

Progress in ART

After thirty years of intensive research there is still no cure for HIV. Barré-Sinoussi: “It makes me furious when people say ‘in 2020 a cure will be available’. Such claims may be good for fund raising, but they are almost a crime against patients.” Nonetheless, science has come very far since HIV was discovered. “Much progress has been made in the development of preventive tools, infection treatment and treatment access. Particularly the present wide array of anti-retroviral treatment (ART) has considerably transformed the face of the infection from a lethal disease to a chronic condition. Today, 34.2 million infected people have access to treatment, also in resource-limited countries. And so far, 4.2 million deaths could be avoided thanks to this.”

The life-long character of these therapies is a challenge to patients. They have to meticulously take drugs every day and they often have to deal with stigmatization and discrimination. Besides this, the cost of therapy is huge, which partly explains why 26 million people today still lack treatment. Barré-Sinoussi: “A curative therapeutic strategy, or at least one that induces sustainable remission in patients without the need to further take medication therefore remains an absolute necessity.”

Mistakes & prejudices

“When we started, we had extremely little information to work with. It was a terrible mistake to focus on homosexuals. If only because it incited discrimination”, Barré-Sinoussi says. She underlines the risks of generalisation: “It is often thought that HIV is predominantly an African problem, but in for instance Senegal there are less HIV cases than in Washington DC.”

We know much more of HIV reservoirs in cell subsets and tissues knowledge on molecular mechanisms of HIV and on its latency. We have learned much on HIV pathogenesis, we now have better assays to study and measure persistent infection; 4. Host and immune mechanisms that control HIV/SIV infections but allow viral persistence; 5. Assays to study and measure persistent infection; 6. Therapeutic agents and immunological strategies to safely eliminate latent infection in individuals on ART; 7. Strategies to enhance the capacity of the host response to control active viral replication.

The seven priority research areas of the International AIDS Society:

1. Molecular, cellular & viral mechanisms that maintain HIV persistence
2. Tissue & cellular sources of persistent SIV/HIV in animal models and in long-term ART-treated individuals
3. Origins of immune activation and dysfunction in the presence of ART and their consequences for HIV/SIV persistence
4. Host and immune mechanisms that control HIV/SIV infections but allow viral persistence
5. Assays to study and measure persistent infection;
6. Therapeutic agents and immunological strategies to safely eliminate latent infection in individuals on ART;
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In 1983 in Science and was followed by an unprecedented effort in the science and medicine community to learn about the new disease entity, to develop tests and to provide treatment.

Responsibility

Ever since she co-discovered the virus, Françoise Barré-Sinoussi has been contributing to this effort. Winning the Nobel Prize in 2008 – together with Luc Montagnier – for discovering HIV did not slow her down, neither does age. “Formally, I should be retired by now, but I have been granted an extra three years at the Institut Pasteur”, she says. The President of the International AIDS Society manages her lab and travels the world to work with scientists and clinicians, patients and activists. Barré-Sinoussi cannot imagine retirement when there is so much work to do. “We scientists have a responsibility to develop tools for the benefit of people; we must be persistent and go on”, she says.

Progress in ART

After thirty years of intensive research there is still no cure for HIV. Barré-Sinoussi: “It makes me furious when people say ‘in 2020 a cure will be available’. Such claims may be good for fund raising, but they are almost a crime against patients.” Nonetheless, science has come very far since HIV was discovered. “Much progress has been made in the development of preventive tools, infection treatment and treatment access. Particularly the present wide array of anti-retroviral treatment (ART) has considerably transformed the face of the infection from a lethal disease to a chronic condition. Today, 34.2 million infected people have access to treatment, also in resource-limited countries. And so far, 4.2 million deaths could be avoided thanks to this.”

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Eradication may not be possible, but Barré-Sinoussi hopes (Mississippi baby). “Also we transplantations (Berlin patient, two Boston patients). “Also we Non Human Primates and at progress in bone marrow rise to great optimism”, she says.

“Besides, we have reports of proof of concept studies which give research areas (see box).

Aids Society published a scientific road map with seven priority scientific community and accelerate research. “ The International AIDS Society aims for. “We need to mobilize the curing HIV, exactly what the ‘Towards an HIV Cure’ initiative of She therefore thinks now is the time to accelerate research into and have better knowledge on the persistence of latent infected cells. Also, we know more about drivers of chronic activation. “The virus has already taught us much on the innate and reactivation drugs and about allogenic stem cell transplants. “Gene modification of T cells is very interesting, but it may not be feasible or affordable for the whole world. Bear in mind that we are looking for a strategy that is internationally feasible, affordable and scalable.

Even if there would emerge a cure, HIV research will never be finished. "HIV is a wonderful tool to understand other diseases. It is important in high IgG subclass concentration diagnostics to design the test strategy in such a way, that the high dose hook effect’ is prevented, the situation where ample antigen inhibits the agglutination with antibodies. This article was made possible by Sanquin Reagents

**Who is Françoise Barré-Sinoussi?**

Françoise Barré-Sinoussi (1947) is a French virologist and director of the Unit of Regulation of Retroviral Infections at the Institut Pasteur in Paris, France. She carried out fundamental work in the identification of the Human Immunodeficiency Virus as the cause of AIDS. In 2008, she was awarded the Nobel Prize, together with her former mentor Luc Montagnier for their discovery of HIV in 1983. Among Barré-Sinoussi’s research contributions, are studies of various aspects of the adaptive immune response to viral infection, the role of innate immune defenses of the host in controlling HIV/AIDS, factors involved in mother-to-child transmission of HIV and characteristics which allow a small percentage of HIV-positive individuals to limit HIV replication without antiretroviral drug. Barré-Sinoussi actively contributes to many scientific societies and committees on HIV/AIDS. She initiated several collaborations with developing countries. She constantly works on establishing links between basic research and clinical research. Since July 2012, Barré-Sinoussi is President of the International AIDS Society.

Immunoglobulin G (IgG) makes out 75% of the total immunoglobulin content in plasma. Antibodies of the IgG class play an important role in the secondary immune reaction.

In comparison to IgM class antibodies, the IgG class stands out for relatively high affinity. They also remain longer in circulation. Four clearly defined IgG subclasses are distinguished: IgG1 to IgG4. Deficiencies of IgG subclasses are an indication for immune system distortion and related illnesses.

**Immunoglobulin G subclasses:**

**Important proteins in the humoral immune response**

Plasma contains more IgG1 than IgG2 and the IgG2 amount is larger than the equally small amounts of IgG3 and IgG4. IgG subclasses are characterized by the length and flexibility of their ‘hinge region’ between the Fragment antigen binding (Fab) arms and both heavy chains. The hinge region of IgG1 contains amino acids 216 – 231 and the Fab-fragments are able to turn around their symmetric axis. IgG1 has a shorter hinge than IgG2, with 12 amino acids and 3 disulphide bridges. This limits its IgG2’s flexibility. IgG1 stands out thanks to a prolonged ‘hinge region’, its 6 amino acids make it four times as long as the IgG1 ‘hinge’. This results in a higher molecular weight for IgG3 in comparison with the other subclasses. IgG3 on the other hand is characterized by an even shorter hinge than IgG1 and a flexibility between that of IgG1 and IgG2 (see figure 1).

**IgG deficiency and disease**

Since a decreased level of one IgG subclass may be accompanied by increased levels of one or more of the other subclasses, the total IgG level may well be normal. Therefore it is important to always define the concentrations of the subclasses in case of suspected disturbed immunity.

Deficiencies of the various subclasses manifest themselves in different ways. IgG1 deficiency leads to a lowered total IgG and common variable immunodeficiency. This often coincides with IgG2 deficiency and leads to recurrent (respiratory tract) infections.

IgG3 deficiency is often associated with recurrent otitis and/or sinusomal inflammations with diminished immune reaction to polysaccharide antigens.

IgG4 deficiency, often combined with lowered IgG1 level, is associated with infections of the lower respiratory tract. Lowered IgG4 is associated with recurrent respiratory tract infections and is often combined with IgG2 deficiency.

Measuring IgG subclasses has until now only been related to deficiencies. A recent article in Orphanet Journal of Rare Diseases underlines the importance of measuring high IgG concentrations, especially IgG4 in relation to IgG4 related diseases (IgG4-RD). The most common in IgG4-RD is autoimmune pancreatitis.

It is important in high IgG subclass concentration diagnostics to design the test strategy in such a way, that the high dose hook effect is prevented, the situation where ample antigen inhibits the agglutination with antibodies.

This article was made possible by Sanquin Reagents

**Passionate**

Françoise Barré-Sinoussi is passionate about research. She married on a Saturday, usually a holiday, and couldn’t resist to go and check things. “I completely forgot the time, until my future husband asked me whether I would make it in time for the ceremony which would start in half an hour.” Luckily, she managed it to the Hôtel de Ville in time.
Primary immunodeficiency (PID) is caused by a minor mistake in the genome. It illustrates what happens if only a part of the immune system is disabled. In this case, it makes patients extremely sensitive to infections. Formerly, there was no option for severe PID patients than to live inside a sterile plastic bubble to protect them from harmful pathogens. One of the PID variants is CVID. Patients would benefit from early diagnosis.

PID was made familiar to the general public by the 1976 movie “The boy in the plastic bubble”, starring a young John Travolta. PID is in fact a heterogeneous group of inherited disorders, presenting diverse clinical features. Nowadays, plastic bubbles belong in the past. Instead, we expose patients to the open and we aid their immune system to withstand attacking pathogens. However, every patient is different and brings its unique challenges in fighting off pathogens.

CVID diagnosis difficult

The most common symptomatic PID, with an estimated prevalence of one in twenty-five to fifty thousand adult Caucasians, is Common Variable Immunodeficiency (CVID). CVID patients are unable to produce sufficient amounts of highly specific antibodies (Abs) against pathogens. Hence, CVID is characterized by recurrent infections, especially of the respiratory tract. For treatment, CVID patients are routinely supplemented with Abs derived from healthy volunteers. Still, each patient faces unique challenges leading to occasional breakthrough infections and progression of disease symptoms, despite treatment. Improvement can be achieved here by implementation of personalized therapeutic options. This, however, requires clarification of underlying causes of specific CVID cases. Moreover, CVID patients may also have other related complications, including for instance enteropathy and malignancies. It illustrates the heterogeneous nature of CVID disease and the complexity of diagnosing CVID. Rapid diagnosis would allow earlier initiation of effective treatment, thereby improving patient’s health. But only ten percent of the CVID patients can be genotypically diagnosed following initial symptomatic onset.

Understanding of underlying causes

Production of highly specific Abs requires help, predominantly delivered by T cells. T cell help depends on B cells presenting pathogen-derived products. It is shown that expression of mutated proteins decreases T cell help by degrading the pathogen-derived products, putatively before it can be presented by B cells to T cells. In conclusion, the identified mutation underlies CVID disease by disabling protein function, which causes diminished highly-specific Ab production by interfering in essential B cell proliferation and recruitment of T cell help. This discovery will potentially aid future CVID diagnosis. Moreover, it enhances understanding of underlying causes in specific CVID cases. On a general level, studying CVID disease with the latest techniques can teach valuable lessons about human immunology.

Unique mutation

To facilitate CVID diagnosis and to enable research into CVID’s underlying mechanisms, at the Boes laboratory of UMC Utrecht a Next Generation Sequencing (NGS)-based diagnostic tool has been developed. This novel tool identifies differences between CVID-related genes of patients and healthy individuals in a robust, time- and cost effective manner.
One Health Congress 2015

“A vital context for choices in immunology research”

Why should immunologists attend the One Health Congress 2015 in Amsterdam? Professor Roel Coutinho MD Ph.D.: “In modern science everyone has become a super-specialist in his own field. In that situation it is more useful than ever to get an overview once in a while, for instance to define future research opportunities. The One Health Congress 2015 offers golden opportunities for that.”

The concept of ‘One Health’ stands for the notion that veterinary and human health are closely interrelated and that better cooperation between veterinary and human medicine will contribute to the solution of serious global health problems. “Neither the term nor this notion are new, but attention and interest are growing”, says Roel Coutinho, professor of Epidemiology and control of infectious diseases at the University of Utrecht and member of the organising committee of the One Health Congress 2015 in Amsterdam. “In The Netherlands we have our own share of problems related to animals transmitting micro-organisms to humans; think of Q fever and the livestock associated MRSA. There is a general impression that this kind of transmission occurs more and more frequently worldwide. This growth is mainly attributed to societal and ecological changes: more densely populated areas emerge, more hospitals are built – which ironically function as potential infection hotspots – and more people are traveling the world. Moreover, changing culinary trends and agricultural changes are also seen as influential factors.”

Multidisciplinary field

The most dramatic example of a current One Health related problem is ebola. It is already known since 1976 in Central Africa, but now all of a sudden it has emerged in West Africa. Coutinho: “It is highly probable that the illness is transmitted through bats. It is highly probable that the illness is transmitted through bats. For me as a medical doctor the widespread use of antibiotics has almost disappeared from the public radar. MERS is transmitted through dromedaries in an unknown way and this disease still makes casualties.”

This situation sketch allows for a number of conclusions, according to Coutinho. “Because of the high number of variables involved, every zoonotic outbreak will be different. There is no universal concept nor general approach imaginable to solve it. Moreover, the fight for prevention and against outbreak asks for a coherent, multidisciplinary approach, which not only involves veterinarians, doctors and microbiologists, but also public health policymakers, social scientists, epidemiologists, virologists, parasitologists and immunologists.”

The first One Health Congress in Australia in 2011 concentrated in agriculture has been an eye-opener. “To stick into preventive measures. Multidisciplinary collaboration leads to eye-openers and knowledge from other fields can help to define one’s position in one’s own field. There is an ongoing tendency towards more and more specialisation in science. This in understandable, but the more this specialisation proceeds, the more urgent it becomes to zoom out to the larger picture.”

Contextual awareness

In agriculture has been an eye-opener. I can imagine that for veterinarians the interrelation between agricultural antibiotics use and human health was likewise surprising. It is only a small example that proves how useful it is to make use of each other’s knowledge.”

Abstracts welcome!

Coutinho not only calls on immunologists to attend and get knowledge, but also to bring in useful knowledge – read abstracts – for scientists in neighbouring fields. “We are highly interested in topics like vaccine development, treatment, antibiotics resistance or newly emerging zoonosis.

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The first One Health Congress in Australia in 2011 concentrated on science. The second edition in Thailand had its main focus on policy. In 2015 in Amsterdam the emphasis will be back to science. The emphasis on science doesn’t mean there will be no interaction with policymakers. There will be a special ‘spi track’ to stimulate interaction between science, government and policymakers. In agriculture has been an eye-opener. I can imagine that for veterinarians the interrelation between agricultural antibiotics use and human health was likewise surprising. It is only a small example that proves how useful it is to make use of each other’s knowledge.”

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Mutually beneficial

In the Netherlands the Q fever outbreak has stimulated the collaboration between veterinarians and medical doctors, which was limited until then. Coutinho: “Before the outbreak the veterinary science and the medical science worlds were hardly interconnected. Lessons were learned and this situation has already improved by now. Q fever has brought both worlds together.”

Consequence that the yet unsolved threat of MERS has almost disappeared from the public radar. MERS is transmitted through dromedaries in an unknown way and this disease still makes casualties.”

“We are highly interested in topics like vaccine development, treatment, antibiotics resistance or newly emerging zoonosis.”

“Collaboration is mutually beneficial, that is the basis of One Health thinking.”

It will for instance make clear what scientists from other fields would like to see solved by immunologists. “To stick with the example of ebola”, says Coutinho, “until recently, the risk seemed limited and there was hardly an urge for vaccine development. That situation has changed drastically almost overnight. A vaccine would contribute greatly to a solution of this problem and as a consequence funds become available to solve related immunologic questions: how does the defense against ebola work? What can we learn from the fact that infected bats do not become ill? For treatment it is equally vital to understand the immune reactions taking place.”

“The more specialisation proceeds, the more urgent it becomes to zoom out to the larger picture.”

Lemondt van der Ent

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It has put antibiotics resistance high on the agenda. Coutinho: “For me as a medical doctor the widespread use of antibiotics in agriculture has been an eye-opener. I can imagine that for veterinarians the interrelation between agricultural antibiotics use and human health was likewise surprising. It is only a small example that proves how useful it is to make use of each other’s knowledge.”

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Scientists working in interdisciplinary research groups know how stimulating it can be to apply knowledge from other fields to complete the picture.”

Immunologists shouldn’t attend the One Health Congress to improve their knowledge on immunology. “It will not go into what a T-cell does, but it will provide a context regarding underlying mechanisms of major issues”, says Coutinho. “In my opinion, it is of the utmost importance for scientists to be aware of the context they are working in, in order to be able to make well-considered choices for the direction of their own research. The One Health Congress 2015 will offer golden opportunities to get an overview of the challenges we are facing in public health.”

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Lemondt van der Ent
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NIW Congress, Efteling, Kaatsheuvel
December 17 & 18, 2014

Peter Peters, first university professor in Maastricht: Studying the immune system on the nano scale

Peter Peters recently became Maastricht University’s first university professor. The professor of Nanobiology is a leading expert in nanomolecular research on the immune system. He is setting up the Institute of Nanoscopy.

At the age of 16, Peters had an experience that would change his life. The Limburg farmer’s son saw a bull mount an artificial cow and was allowed afterwards to look at the sperm cells through a microscope. He became hooked instantly: “I was fascinated by the lab environment and the image of those living, moving sperm cells.” Peters studied Medical Biology at Utrecht University, where a gaze through an electron microscope made a similar impression.

After his PhD in Utrecht, he spent three years doing research in the USA and fifteen years at the Netherlands Cancer Institute/ Antoni van Leeuwenhoek Hospital in Amsterdam before coming to Maastricht University. He studies the role of white blood cells in infection and the development of cancer: “Tumour cells are actually degenerate cells that have learned to escape the immune system. Our task is to discover how they do that and how you can train the immune system to break them down.”

Minor changes – major dysfunctions

To understand what goes wrong, fundamental knowledge about the workings of cells is needed. At the nano scale, this is still largely uncharted territory. We can identify proteins, but how they come together in the form of a protein complex with a certain function remains a mystery. In the coming decade, Peters hopes to unravel the 3D structure and function of these protein complexes. Peters: “Proteins are the workhorses of the cell. We know that cancer is caused by an abnormality in our DNA code, which is then translated into a protein. But we don’t know what protein structures look like in 3D, nor what’s going wrong with them.”

Take for example cystic fibrosis, where a single abnormal line on the DNA causes a chloride pump in the intestines and lungs to have a slightly different 3D structure. Chloride emissions to the pancreas become blocked, the water balance is disturbed, resulting in cystic fibrosis and early death. Peters: “You want to know how that works and how we can reset that protein to its original form – because it is possible to influence protein structures.” In recent years, Peters has made important breakthroughs in the localisation of protein complexes in the cell, for instance regarding the tuberculosis bacterium. Peters and others are still working on further fundamental research based on this finding, aiming to improve the vaccine currently used against tuberculosis.

A brighter way to use blue.

Maastricht University has the ambition to become a major player in scientific imaging. Brains Unlimited with its Tesla 7 and 9.4 scanners is one example, but Peter’s Institute Of Nanoscopy will be just as unique. It will be equipped with four highly advanced microscopes for making and analysing cell preparations. “My microscopes have to be extremely powerful and stable. It is like reading a newspaper on the moon from here.”

By Femke Kools (Maastricht University Webmagazine), edited and summarized by Leendert van der Ent.

A video portrait of Peter Peters can be found via http://bcove.me/ahm1avoe.

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Newspaper on the moon

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