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IMMUUN

for every professional in the immunology chain

Exercise immunology

A world to discover

Longfonds:

"Focus on end result"

Paul Parren:

Mining for novel drugs

NVVI Winter School 2015
December 16 & 17
Noordwijkerhout

Theme

EXERCISE AND LUNGS

Youth?

It's in the blood!

Sjaak Neefjes

VAN LOGHEM LAUREATE

Contains **NVVI Winter School Programme**, p 30

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COLOPHON

Immuun is published by the NVVI and written and edited by Bureau Lorient Communicatie BV. In 2015, Immuun will have three issues. The target groups are NVVI members, relevant clinicians, suppliers and other partners of immunologists as well as policy makers.

PUBLISHER
NVVI
Contacts via Bureau Lorient Communicatie BV
Hoofdstraat 98 - 100
2235 CK Valkenburg ZH
T + 31 71 5890848
info@lorient.nl

LAY OUT & PRINT
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Jogger at Morro Beach (photo Mike Baird), Wikipedia, NKI

ADVERTIZING
Ellen van der Voort, LUMC
E.I.H.van_der_Voort@lumc.nl
T + 31715261865
Bureau Lorient Communicatie
info@lorient.nl
T + 31715890848

NVVI
DUTCH SOCIETY FOR IMMUNOLOGY

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The connecting factor

In recent years, our basic understanding of the roles, actions and countermeasures of various molecules and cell types which are at play in our immune system has improved a lot. This progress in systematic understanding enables us more and more to develop interventions for a wide range of diseases. A persuasive example is immunotherapy against cancer. And an excellent exponent of the ability to connect basic cell biology with clinical applications is this year's Van Loghem Laureate Sjaak Neefjes. How do bacteria manage to hide in a certain cell component? Detailed insight in this process allowed Neefjes to develop chemical inhibitors to block intracellulair growth of bacteria, exemplifying excellent research and fundamental understanding with the ability to transfer knowledge like this to the clinic. Our improved insight in what happens in our body at the cellular level also sheds light on the pivotal role of exercise to our health. And a fundamental cell biological insight in the field of exercise immunology in the Netherlands would allow a next step for the field of human movement sciences: sound research, understanding of human movement, insight in immunology ànd the ability to show the added value of such combined comprehension to others. And, more in general, as Dutch Society of Immunology, we recognize the importance of knowledge dissemination. We see it as our goal to inform the public in an accessible way about the immune system: to show how the immune system is a prime mover in many diseases as well as the gateway to effective treatment.

Reina Mebius, Dutch Society of Immunology

PhD for Niels van der Geest on immune system aging

Aging of the immune system may contribute to the development of aging-associated autoimmune diseases such as giant cell arteritis, polymyalgia rheumatica and rheumatoid arthritis. What are the aging-dependent changes of the adaptive immune system that promote autoimmunity in the elderly? Niels van der Geest built his thesis on answering this question. The research for this was carried out in the laboratory of professor Mieke Boots in the University Medical Center Groningen. On November 18th, Niels van der Geest got his PhD at Rijksuniversiteit Groningen. The first chapters of this thesis describe changes of the adaptive immune system occurring during healthy aging.

Furthermore, maintenance of particular T and B cell populations is linked to heritable risk factors for aging-associated autoimmune diseases and development of circulating autoantibodies. The final chapters of this thesis focus on changes of the adaptive immune system in patients with aging-associated autoimmune diseases, such as giant cell arteritis and polymyalgia rheumatica. Furthermore, the diagnostic potential of cellular and soluble immune parameters is explored in the latter two diseases.

Niels van der Geest (photo Bureau Lorient Communicatie)

AGENDA

12 januari 2016 (startdatum)
Immuunhematologie
Hogeschool van Arnhem en Nijmegen
16 bijeenkomsten op dinsdag 18.00-21.00 uur
Locatie: Amsterdam (Sanquin)
Kosten € 1.480,00
Informatie en aanmelding:
www.hanlifesciences.nl of
E: info.lifesciences@han.nl.

26 januari 2016 (startdatum)
Research Immunologie
Hogeschool van Arnhem en Nijmegen
6 bijeenkomsten op dinsdag 18.00-21.00 uur
Locatie: Amsterdam (Sanquin)
Kosten € 699,00
Informatie en aanmelding:
www.hanlifesciences.nl of
E: info.lifesciences@han.nl.

10 en 11 maart 2016
Workshop Genome Browsing
Inschrijven vóór 28 januari 2016
Cursusprijs: € 755,- (bij inschrijving vóór 24 december 2015 € 690,-)
Hogeschool Leiden, CBD,
website: cbd@hsleiden.nl

16 en 17 februari 2016
Masterclass Kwaliteitsanalyse van real-time PCR amplificatiemethoden
Inschrijven vóór 5 januari 2016
Cursusprijs: € 755,- (bij inschrijving vóór 9 december 2015 € 690,-)
Hogeschool Leiden, CBD,
website: cbd@hsleiden.nl

22 maart 2016
Alternatieven voor ELISA's: Luminex, MSD assay en AlphaLISA
Inschrijven vóór 9 februari 2016
Cursusprijs: € 490,- (bij inschrijving vóór 12 januari 2016 € 445,-)
Hogeschool Leiden, CBD,
website: cbd@hsleiden.nl

10 maart 2016
Immunologie voor microbiologisch analisten
Inschrijven vóór 29 januari 2016
Cursusprijs: € 440,- (bij inschrijving vóór 4 januari 2016 € 400,-)
Hogeschool Leiden, CBD,
website: cbd@hsleiden.nl

13 en 20 juni 2016
Statistiek voor analisten
Inschrijven vóór 2 mei 2016
Cursusprijs: € 755,- (bij inschrijving vóór 5 april 2016 € 690.-)
Hogeschool Leiden, CBD,
website: cbd@hsleiden.nl

6-9 December 2016
Joint BSI and NVVI Congress 2016
We are delighted to announce that the 2016 Congress will be a joint collaboration between the British Society for Immunology (BSI) and the Dutch Society for Immunology (NVVI). The Congress will take place at the ACC in Liverpool, UK, from December 6-9, 2016 and we hope to attract a large audience from both the UK and the Netherlands, as well as the rest of the world.

Introducing: Peter Katsikis, head of the Department of Immunology, Erasmus MC

Recently Peter Katsikis became the new head of the Immunology Department at the Erasmus MC. He sees an exciting new phase of discovery ahead.

Photo Erasmus MC

How did you get into contact with immunology?

"My initial contact with immunology was as a first year medical student at the University of Thessaloniki in Greece, as part of the Biology course. I took an elective that had as topic 'protein structure and function'. By serendipity, I chose the immunoglobulin structure as my project and I had to write up a small thesis and present a seminar to my fellow students. Digging through literature at the library, I came across a small book called "Essential Immunology" by Ivan Roitt (1st edition 1971).

What did it do to you?

"This little book with its clear graphics and photos made a huge impression on me. Immunology in my mind took the form of an exciting scientific discipline that involves distinct players and principles. This first exposure triggered a long-lasting interest in Immunology. This small personal story, I believe, highlights the impact we can have as immunology educators by stimulating and attracting talent to our scientific field. Years later, working as a PhD student and postdoc with autoimmunity and the patients it affects, I saw the potential for harm and suffering that the immune system's misfiring can cause from close up. I also witnessed first-hand how new therapeutics such as anti-TNFα therapies could be generated from basic research and dramatically change people's lives. My current research focuses on killer CD8+ T cells. It is aimed at trying to understand how they work and how we can improve them in diseases such as HIV and cancer, where on their own they often fail to control infection or tumors."

What do you expect for the upcoming years?

"I believe we are entering an exciting new phase of discovery as we are only now starting to understand why killer CD8+ T cells fail in chronic infections and cancer. We currently are seeing major clinical breakthroughs in unleashing such killer cells from their inhibition and in engineering new killer cells for cancer and potentially in infectious diseases."

What made you choose for the Erasmus MC?

"I joined the Department of Immunology at Erasmus MC about a year ago. The vibrant research environment that centers around patient and disease attracted me to it. The Department of Immunology has a long history of supporting its three major missions of patient care, teaching and research. Our department continuously strives to develop and implement new diagnostics to improve patient diagnosis and treatment. It is committed to excellent teaching at all levels. Our mission is to maintain an exciting and open collaborative environment where basic and clinical researchers meet with Medical and Clinical Immunologists to synergize and innovate."

"The Department is currently undergoing major organizational changes. We are actively recruiting new staff to establish new lines of research and to strengthen current ones. Our goal is to explore fundamental immunology and to understand disease processes so that we can identify new diagnostic tests and biomarkers, therapeutic targets and interventions."

Do you have a message for the immunology community?

"Often in this competitive era of diminishing research funding and increasing use of productivity metrics, we tend to forget the real missions we have as scientists and educators. These are none other than to inspire the next generation of immunologists and through our basic and clinical research to shed light onto disease to ultimately benefit the patient."

Exercise immunology,

Dutch immunology stands its ground in science. The same goes for exercise physiology. But both fields hardly meet in The Netherlands. Where in some other countries exercise and immunology are integrated, in our country they remain like oil and water. How come? And, even more importantly, is this about to change? The importance grows now the field of exercise immunology expands from (elite) sports to the major health issue of fighting low rate inflammation and chronic diseases.

Karsten Krüge: "We know many single actors, but the actual interplay by signalling cascades in various tissues is unmapped territory."

Richard Jaspers: "The concept of exercise immunology has finally landed in The Netherland."

"ISEI? Never heard of it." You are likely to get this answer from 98.5% of Dutch immunologists. It is the International Society of Exercise and Immunology. The 12th ISEI symposium was held simultaneously with the ECI in Vienna, where a satisfying number of Dutch immunologists were among the lecturers. And on the ISEI symposium? No speakers, no poster presentations nor visitors from Holland – and no contributing authors to the journal Exercise Immunology Review either (see box). ISEI has 790 members from all major European countries and from all over the world. Only 12 of them are Dutch.

Dr. John Campbell PhD BSc HONs was a lecturer at the 12th ISEI Symposium: "I don't recall meeting a Dutch person, which is really a shame. Especially given the tremendous expertise that exists in the Netherlands in the fields of both immunology and exercise physiology." He is research fellow at the Institute of Immunology and Immunotherapy, College of Medical and Dental Sciences, University of Birmingham. "Exercise can impact almost every aspect of the immune system, in one way or another, so I am very motivated to promote this field to interested parties."

How can the absence of the Dutch in exercise immunology be explained? For one, immunology is hardly integrated into Human Movement Sciences curricula at the VU University Amsterdam, in Groningen, Nijmegen and Maastricht. The specialisation 'exercise immunology' officially exists in the UK and 'Sport Immunologie' is unofficially used in Germany, but is nonexistent in The Netherlands. Exercise physiologist Richard Jaspers PhD of the VU University Amsterdam: "Human Movement Sciences teach cardiology, orthopaedia and exercise physiology. Maastricht also focuses on nutrition and Nijmegen on lung diseases. Immunology has until now remained outside the scope. And if there is some knowledge, this only regards the innate immune system and hardly the adaptive immune system." On the clinical level, however, there is a link. Exercise is now recognized as a factor in immune-related diseases such as COPD and other inflammations and AIDS. Jaspers indicates that things are beginning to change: "Exercise against low grade inflammations is definitely on the radar. And yes, we have noticed that certain athletes are more prone to infections than others. We see things happening and begin to explore. In the master phase at the VU University Amsterdam we are about to start a course in exercise and clinical immunology, covering the basics of both the innate and adaptive immune systems."

The bus

Exercise physiology and immunology are two different worlds that both have to move in order to meet, according to Jaspers: "At the VU University Amsterdam this movement has now set in. We both have to invest in knowledge of each other's field to make it work." In the end it all comes down to personal interaction – which started in the bus to Haarlem where Jaspers

Marathon and free light chains

Campbell collaborated with Hans Jacobs from the Radboudumc in research around the Eindhoven marathon. Campbell: "Both in kidney disease and in levels of inflammation in general, the production of free light chains plays a key role. In that respect, we were curious what happens with these light chains in exercise – in this case a marathon. It was a good example of how exercise physiology can be paired with immunology."

a world to discover

met immunology professor Georg Kraal PhD. "This contact eventually led to a first joint animal model research project, in which immunologist Joke den Haan PhD was also involved. We intended to chart the effect of exercise on the animal immune system and are working on a publication."

"It is vital for the validity of exercise immunology outcomes to apply exercise in a well controlled fashion"

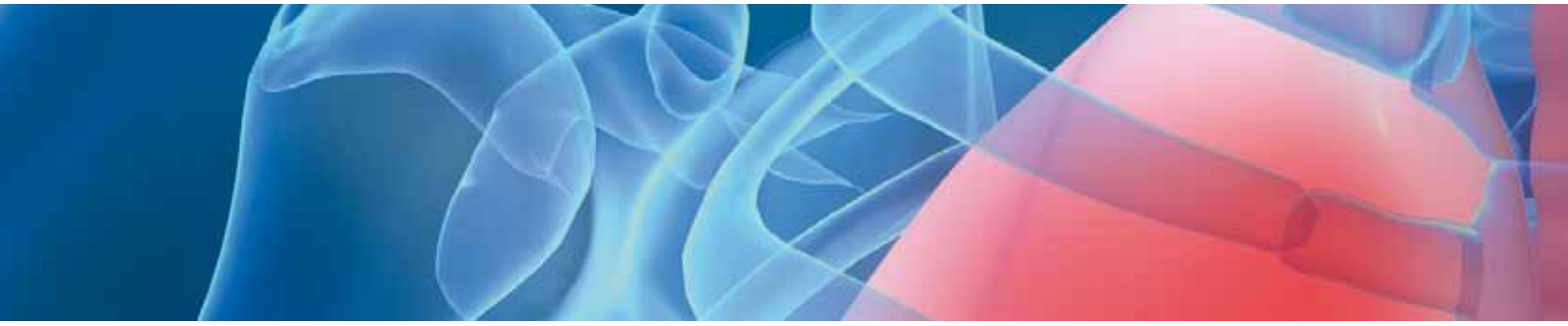
The animal model showed immune reactions taking place in response to exercise. Jaspers is determined to go deeper into the matter: "Whether the body is fit for heavy physical training is determined by more than just heart, lungs and muscles. So far, immunology research in this respect has led to detecting inflammation markers such as IL6. We know that during exercise signalling proteins enter the blood-flow. These intermediate indicators can have a beneficial or a detrimental effect, dependent on disease and context. At a certain point exercise can damage the muscles. It is all about the right time to stop training. The mechanisms to accurately determine timing are as yet uncharted. Muscles make up approximately 40% of body weight and they produce certain substances that play a role in the rest of the body, but there is far more to it. Recent evidence suggests that apart from signalling proteins, also certain vesicles are released into the blood-flow. These seem to have a beneficial effect on fitness, but the details are still unclear. We'd like to know what they do and why this beneficial effect occurs."
Scientific curiosity is aroused, says Jaspers, also in the direction of the interplay between vitamins and the immune system. "There is the personal interaction and willingness to explore things together. Of course we also need funding, but we now know there is a world to be discovered. The concept of exercise immunology has finally landed."

Exercise immunology in Europe

Germany already has a longer tradition in this field. The universities in Berlin, Paderborn, Freiburg, München, Giessen, Tübingen, Münster and Köln all have references to 'sport immunologie'. Dr. Karsten Krüger is biologist and sports scientist at the Department of Sports Medicine of the Justus Liebig Universität Giessen. He is also editor-in-chief of Exercise and Immunology Review: "It had already occurred to me that we never get contributions from Holland. The organisational situation in Germany, however, is quite similar to that in

(photo Mike Baird)

Holland; integration of immunology in sports medicine is also quite rare here. Institute directors are in most cases clinicians who operate at quite a distance from basic cellular or molecular science. Immunology is complex; it requires a lot of knowledge, methodology, animal models and advanced measurements to conduct proper research and many departments of sports medicine lack the knowledge as well as the devices. Tübingen, Mainz – with professor Pericles Siemon – and Giessen are the exceptions. A difference is maybe that immunology is integrated in the (clinical) exercise physiology master curriculum, for instance in Giessen and Frankfurt."
Krüger mentions Denmark, especially the large group of professor Bente Klarlund Pedersen at the University of Copenhagen, as a country spearheading in exercise



immunology. Besides that, he refers some groups in France/Monaco and especially the UK. That is where Campbell dedicated his PhD-research to the benefit of exercise and the immune system: "In the UK exercise immunology knowledge has traditionally been concentrated in the universities of Loughborough and Birmingham, and is now also being developed in the universities of Bath, Edinburgh, Napier and Bristol. When you do a three year master in exercise sciences, immunology lectures are included in the first two years of the curriculum. The final year contains an optional three months immunology module. Furthermore, there is the opportunity to conduct a dissertation project on exercise immunology" Outside Europe also Australia, the USA (for instance Houston in relation to cancer) and Japan are active in this field.

General Health

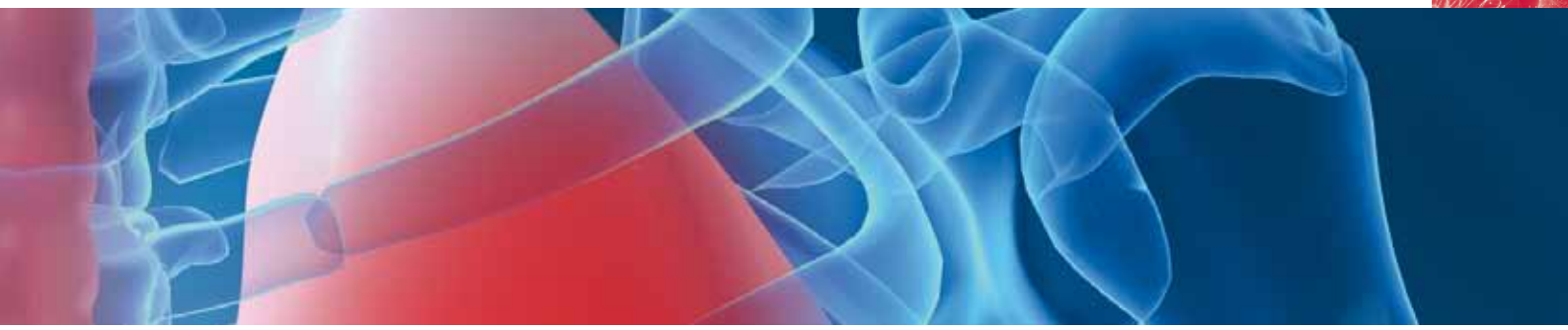
Maybe even more important than drawing the map of exercise immunology, is to describe the major shift this field is making at present. Krüger: "Exercise immunology started out by investigating the supposed higher infection risk in the upper respiratory tract in elite athletes." Campbell adds: "The field came up during the eighties and nineties, with the first dedicated conference held in 1990. The simple pioneering question got an equally plain answer: there is an increased risk of infection, but only in over-reaching or over-trained, physically stressed athletes. In general, exercise is good for you."

The focus shifts towards chronic disease treatment in internal medicine departments

The focus now shifts towards chronic disease treatment in internal medicine departments, Krüger and Campbell both state. Campbell: "This is of special importance given the widespread incidence of low rate inflammation among elderly – in an ageing society. It is established beyond doubt that exercise boosts the immune system. Antibody titers are higher in people who exercise than in a control group. Some effects are pronounced: the number of Natural Killer cells in the blood increases by 1,000% after an acute bout of exercise and of CD8+ cells by 500%. Along the lines of the 'fight or flight' response, these cells – as shown by dr. Krüger – migrate to the lungs, the gut and the skin to conduct immunosurveillance. There is not only this short term effect: over a longer duration, there is no doubt that people who exercise are more healthy. That may be no news, but the relation to the immune system is. The field now moves from an athlete focus towards inflammation in

Exercise, immunology and cancer

In her research work at VU University Amsterdam EMGO+ Institute Laurien Buffart PhD coordinates several research projects on physical activity and exercise in cancer survivors:
the Alpe d'HuZes Cancer Rehabilitation (A-CaRe, www.a-care.org), the Predicting OptimaL cAncer Rehabilitation and Supportive care (POLARIS) study (www.polaris-study.org) and the MEchanisms of Training In patients with Cancer (METRIC) pilot study. Immunology is one of the approaches.



general health and disease, especially regarding both types of diabetes, Rheumatoid Arthritis and cancer. Here in Birmingham we try to chart the modifying effect of exercise in all three diseases."

A real specialisation

Krüger: "The big and complex question is now how these widespread low rate inflammations interrelate with exercise. Another interconnection is that between vaccination and moderate exercise, especially in elderly. Generally, the immune response to vaccines decreases with age. It has now become clear that the effect of vaccination can be somewhat boosted by exercise before or after vaccination. These thematic connections open opportunities for collaboration with the institutes of internal medicine, which are very strong in Germany."

The actual interplay by signalling cascades in various tissues is unmapped territory

Exercise immunology offers real added value, says Krüger: "Although it is vital for the validity of outcomes to apply exercise in a well controlled fashion. It requires a well known previous training status of the research subjects and a carefully controlled and documented training regime with regard to intensity and duration. It is quite a difference whether the exercise is done at 60 or 80% of VO2max – the maximum volume of oxygen consumption. Another pitfall is to measure the effect of stress rather than exercise, which is what happens when you put test animals in a tub to swim."

Future research

Can you train your immune system? Will it work better in different pathogens? Krüger: "The answers are still under discussion, but some effects have become quite clear by now."
Campbell: "Very large studies have reliably shown that IL-6 and C-Reactive Protein (CRP) are lower in physically active people than in people with sedentary lives."
Moderate exercise suppresses infections and there is also an anti-inflammatory effect. This can, according to Krüger, apart from IL-6-suppression probably also be concluded from a cascade-effect during the contraction of muscles, resulting in less meteorin-like factors. This leads to the following situation, he says: "We know many single actors, but the actual interplay by signalling cascades in various tissues is unmapped territory. Exercise induces many signals, which makes it a lot of work to draw these maps. Immunology is one step ahead of exercise immunology; immunology discovers new factors, we then develop ideas about what they do."
Campbell: "Exactly. Insight into the effects of exercise has grown tremendously over the last five years. In general, the notion dawns that moderate exercise is extra beneficial to already weakened immune systems. Exercise induced immune system activation could be used to support treatment as well as to prevent relapse, for instance in certain cancers. Exercise is furthermore a cheap and easily implementable approach with multifactorial benefits. Besides the immune system, also the cardiovascular system and the renal function are enhanced."
Some more specific recent findings regard the effect of exercise on memory T-cells and the fact that exercise can induce apoptosis of highly senescent cells to prolong the life of beta cells in for instance type I diabetes. Campbell: "New discoveries like these give the field of exercise immunology momentum, but at the same time they create demand for more immunology expertise in our field. The next challenging step is to explain why the effects occur. Good news for immunologists: the field of exercise immunology is open to collaboration and the ISEI and the ISEI conference provide excellent opportunities to get things started."

Leendert van der Ent

ISEI and EIR

Membership of ISEI (www.isei.dk) is free and includes reception of the journal Exercise Immunology Review (EIR). Exercise Immunology Review (EIR) is the official publication of the International Society of Exercise and Immunology and the German Society of Sports Medicine and Prevention. It is committed to develop and to enrich knowledge in all aspects of immunology that relate to acute exercise and regular physical activity. EIR publishes review articles and papers with new, original data including an extended, review-like discussion. In recognition of the broad range of disciplines that contribute to the understanding of immune function, the journal has adopted an interdisciplinary focus, which allows dissemination of research findings from disciplines such as exercise sciences, medicine, immunology, physiology, behavioural science, endocrinology, pharmacology and psychology. ISSN: 1077-5552, Impact factor: 4.176 (2014). Editor: PD Dr. Karsten Krüger

Youth? It's in the blood!

One thing leads to another. A 2006 heatwave eventually led to immunology research among elderly participants of the Nijmegen Four Days Marches. This march unleashed unimaginable dynamics within the walker's aged immune systems. The results from this and similar research strongly suggests that immunosenescence, an important factor in ageing, can be slowed down by exercise.

The Nijmegen Four Days Marches (4DM) is a famous - or maybe infamous for some – hiking event in The Netherlands. 42.000 participants annually walk distances of thirty, forty or fifty kilometres for four days in a row. The 90th edition in 2006 starting on July 18 coincided with a heatwave. During the first marching day temperatures rose to 34 degrees Celsius in the shade. The consequences were grave: several hundreds of people fainted, 69 persons from 17 to 89 years of age were hospitalised and two males of 65 and 68 died. The 2006 edition was cancelled thereafter.

These dramatic events gave rise to the installation of a commission with among others a psychologist, a weather expert and an exercise physiologist as members. Their task would be to advise the board of the event and to think up measures to prevent future incidents. The exercise physiologist involved was professor Maria Hopman MD, PhD from the Radboud university medical center: "The Four Days Marches is quite an extraordinary activity, with up to ten or twelve hours of exercise each day. Such characteristics had been studied physiologically in military cohorts, but these studies only included healthy young males. In this case, the population is fit, but not necessarily healthy or young. It turned out there were hardly any relevant research data available at all."

Real-time measurements

Hopman jumped to the opportunity. From 2007 onwards, she and her team began to study the Nijmegen Four Days Marches population before, during and after each edition. Several parameters such as fluid balance and body temperature were measured in one hundred random volunteers to get insight into what actually happens inside the body. Hopman introduced a thermos-sensor and transmitter in a pill for the volunteers to swallow, in order to log real-time body temperature data. Apart from that, mobile labs were installed at the start, the finish and every five kilometres in between.

A predominant question was of course, what could have caused the two fatalities. "Two potential causes are hyperthermia, a dangerously high core temperature, and dehydration, which according to text book physiology are the most likely causes of death in this scenario", Hopman says. "It turned out that the participant's core temperature rose by one degree on average, independent of outside temperature. The conclusion must be that core temperature is hardly a risk factor for fatal incidents."

The fluid balance, however, proved to be a major problem. Hopman: "Twenty percent of the hikers crossed the line dehydrated, especially overweight males." During editions after 2007, the organisation therefore invested a lot of effort in preventing dehydration. From 2008 onwards, Hopman also started measurements during the Zevenheuvelenloop, the Seven Hills Run, a race over fifteen kilometres, organised half November. "Results are completely different here", she comments. "Most runners are well aware of dehydration risks and the duration is much shorter. But in 15% of our measurements, unrelated to performance, we noticed a surprisingly high core temperature of over forty degrees. Apparently most people have a warning mechanism or safety valve, as further rise of core temperature is blocked at the expense of performance. But in a certain percentage, such a mechanism seems to be lacking."

Immunosenescence

In 2010 Hopman replaced the random approach by a thematic one by targeting special cohorts such as people with diabetes, overweight or heart diseases. The 2013 theme was people over eighty years of age. Three hundred people in this category

Hans Jacobs
Photos Radboud UMC

participated and fifty of them agreed to be included in the study. Hopman likes to call this special cohort '*The Golden Oldies*'. This intriguing category of people combining high age with endurance exercise attracted the attention of medical immunologist Hans Jacobs MD, PhD: "Maria Hopman communicates the initiative well within the hospital and is very open to collaboration, which enabled us to join."
Jacobs, in turn, got Groningen UMCG Healthy Ageing researchers professor Mieke Boots PhD and Niels van der Geest MD interested. Their special interest lies with immunosenescence and the relation with late onset autoimmune diseases. Immunosenescence is used to describe the ageing-associated decline in the normal functioning of the immune system.
In no time it was decided to come together and brainstorm about the possibilities. Hopman: "A win-win situation was created with a highly interesting cohort as added value for the immunologists and an extra set of test parameters as added value for us." Jacobs: "Only then we realised what an enormous team and elaborate logistics Maria Hopman had in place to take questionnaires on the participant's diet, health, medical history, medication and mind-set, to assess physical fitness of each participant and perform all kinds of measurements in mobile labs, etc. etc. She is also very good in her feedback of results to participants, who highly value this effort."

General health condition

The researchers were interested in a comparison between the immune system condition of a general cohort of elderly, remarkably healthy elderly within the Groningen Healthy Ageing database and the very fit cohort in Nijmegen. And what would four days of walking do to the immune system of already well-trained elderly people? Boots could add an extra dimension to that with her knowledge of the ageing immune system.
Jacobs: "The role of immunosenescence in morbidity and mortality is still underrated; immunosenescence contributes to poorer vaccine responses and the increased incidence of infection and malignancy seen in the elderly. Exploring the positive impact of regular exercise on the ageing immune system is relevant for our society as it may provide simplistic and inexpensive methods to combat immune degradation."
The Swedish longitudinal OCTA/NONA studies looked at parameters that negatively influence the immune system's condition and established an 'Immune Risk Profile'. "It would be good to assess which of these parameters can be slowed down or even halted by exercise", Jacobs comments. The general thought was beforehand, that the walking elderly would represent a minority with an above average constellation.
Hopman: "Surprisingly, this proved not to be the case. It turned out that they were not considerably more healthy – physically nor cognitively – than their non-walking peers, but that they had the mind-set not to consider themselves ill, despite sometimes severe health limitations."

Maria Hopman

Elaborate test array

Immunosenescence is characterized by a variety of changes in the immune system. Jacobs: "An increase of fully differentiated T cells is combined with a lowering output of naive T cells in the elderly. On a functional level poor T cell proliferation and cytokine responses to mitogens are observed. Data suggest that these phenomena can be countered by regular exercise. A second relevant aspect is the association of ageing with a more permanent form of low-grade chronic inflammation, so called 'inflammaging'. Inflammaging is recognizable by higher IL-1, IL-6 and TNF-α levels and is thought to play a central role in the development of many chronic diseases in the elderly such as cardiovascular disease, vasculitis, diabetes, Alzheimer's disease and certain cancers. When you train, temporarily higher levels of these inflammatory cytokines are followed-up by a lower base level. The netto result is that regular exercise reduces circulating levels of inflammatory cytokines. Regular exercise could be an efficient intervention to prevent or delay the chronic diseases associated with inflammaging."
Long story short: for The Four Days Marches immune study, a broad range of parameters was charted, ranging from classic inflammation parameters such as CRP, antibody titers and white blood cell counts to extensive phenotyping and functional analysis of the white blood cell subpopulations. Jacobs: "This elaborate test array couldn't of course be carried out on the spot. A whole logistic set-up of its own, with a sample shuttle service from the city center to the Radboudumc, was put in place to isolate white blood cells from all participants and to guarantee that these were secured in our freezers within six hours after taking the blood sample."

Solid conclusion

At the moment the last results are being analysed to affirm functional immune parameters for a second publication that is upcoming. The first conclusions could be drawn rather quickly. They found their way to a first publication in Clinical Chemistry and Laboratory Medicine. Jacobs: "In-depth immune-analysis brings enormous dynamics to light, which surprised us, given this trained cohort. During the course of the event, certain parts of the immune system are activated for deployment. Immune cells over the entire range of white blood cells are transferred from peripheral tissue to the blood. Comparatively, we saw a significant relative increase in the amount of naive T-cells. From this we conclude that exercise rejuvenates the immune system in the blood. We didn't notice increased B-cell activation nor increased antibody production."
During the review phase of the first publication, the added value of teaming up with exercise physiologists was fully proven, says Jacobs: "The journal came with critical questions on fluid balance, suspecting that the shifts we noticed were due to differences in hydration status. Hopman's data enabled us to compensate for dehydration, so that our conclusion remained solid."
Comparison of the Nijmegen data with the data from the Groningen healthy elderly cohort proved difficult. "We could conclude that 'fit' in our cohort is far from synonymous with 'healthy'. Differences in pre-analysis further complicated a proper comparison between both cohorts."

Longitudinal research

Apart from scientific conclusions, the Nijmegen 'immunology dynamics measurements' gave rise to a number of suppositions and future research questions. "The challenge will be to shift from cross-sectional to longitudinal studies. The inherent flaw of cross-sectional research is, that lifestyle factors cannot be ruled out", says Jacobs.
Myriads of hidden and unexpected factors can have an unknown influence. Jacobs: "Attention for longitudinal intervention research is therefore increasing. This might indicate which kind of exercise positively contributes to slowing down immunosenescence, and may further unravel the underlying mechanisms. By now there is little doubt that immunosenescence can be slowed down. Prevention or reversion is another matter. We would like to learn the effect of training schedules in terms of the right endurance and intensity mix."
As a further topic for the future Jacobs mentions the relation between microbiome and immune system. "Both are affected by exercise. The current literature only reports isolated results on the impact of exercise on either immune system òr microbiome. Microbiome diversity is beneficial for proper functioning of the immune system and the microbiome's diversity is enhanced by exercise. The triangle microbiome – immune system – exercise is still largely terra incognita."
Mobilisation of immune cells from peripheral tissue was a significant finding in the Nijmegen 2013 measurements. Jacobs: "Research from the UK shows that exercise also induces a transient shift of haematopoietic stem cells into the blood. This suggests that exercise could be used to enhance the apheresis yield of stem cells from donors. This example shows that results from exercise immunology might be applicable to many fields. There's a world to be won here."

Leendert van der Ent

Links:
www.vierdaagseonderzoek.nl
www.immunityageing.com

Longfonds goes for 'dots on the horizon'

The immunology field is a stakeholder in the supply chain from fundamental science to health solutions for patients. A charity fund such as the Longfonds (Lung Foundation Netherlands) in Amersfoort is another stakeholder in that same chain. How do director Michael Rutgers and Research Coordinator Dorothee Laan regard this supply chain – and the immunologist's position in it? With a mix of surprise, criticism and praise, it turns out.

"There is no doubt that immunology is very relevant and important to our field", Rutgers states. "As an illustration: one of our most ambitious, high profile and long term projects, the development of a vaccine against asthma, is entirely based on immunology. The same goes for another dot on the horizon, the regeneration of lung tissue. Apart from asthma, also COPD and a number of more rare lung diseases find their basis in a dysfunctional immune system. Basic knowledge of immunology provides the "rails the research train rides on". That is why fundamental immunology research is included in a lot of research we fund."
Laan adds: "Therefore it is only logical that immunology is well represented in our scientific advisory board. Among its twenty-two members are LUMC lung immunologist Pieter Hiemstra, Sanquin executive board member and research director René van Lier, Erasmus MC allergist Roy-Gerth van Wijk, AMC Lung immunologist René Lutter and immunotoxicologist Henk van Loveren of RIVM and MUMC.
Apart from that, research proposals are assessed by reviewers from abroad. Also on that level immunology is well represented."
Rutgers smiles: "So we believe there is absolutely no need for the immunology field to have a feeling of inferiority about their position and relevance."

Societal relevance

This being said, Laan remarks that the organisation of research has changed profoundly over the last years. "In general there is more emphasis on added societal relevance of research, on translational research and on clustered research in large consortia. We hear from researchers that this leaves little room for fundamental research. Is this really the case? Fundamental research is part of the research infrastructure and should contribute to solving problems, as many fundamental researchers do amazingly well. A smart consortium will include fundamental research to be able to tackle fundamental problems."
Rutgers comments on the Longfonds viewpoint: "As far as we are concerned, our focus is completely on the end result, on problem solving. As to how that goal is achieved, that is not our prime concern. If the answer lies in immunology research, that is fine with us. If not, that is also okay. But the role of the immune system as prime mover in many of our patients' problems shouldn't be underestimated. Large part of our patient's problems originate from external damage inflicted to

Michael Rutgers: "That is how we do it now: as a solid societal party with a plan, the funding and the determination to go for result." (photo Longfonds)

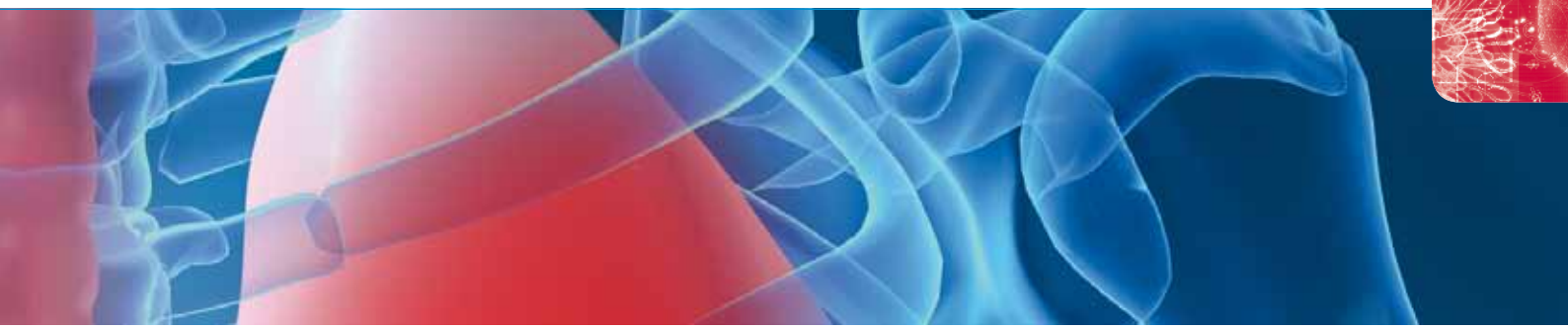
the immune system – with smoking as the strongest example. But it is the societal angle that triggers us: we analyse and present the patient's problem and present this problem as an open question to science: can you solve this?"

Marketing rules

Asked how the immunology field could gain in position and relevance, Rutgers indicates that this would need a strong marketing approach. "When the general audience is the target group, one needs expertise, money and a different name. If immunologists want to reach a larger audience, they have to get rid of their 'difficult' image and of the name 'immunology' which does not ring a bell among the general public. In his view, however, it would be a 'long shot' to promote a scientific field - in this case immunology – among the general public for fundraising purposes. The cost is enormous and the chance of failure huge. By the way, we had similar problems with the word 'exacerbations'. Too difficult for the general public. We changed it into 'lung attack'. That makes things clear in one word. Don't make it more complex than necessary. Everything is about storytelling, about framing a subject."

Realising a dream

The Longfonds has also focussed its research agenda. Laan: "Formerly, the agenda used to be quite open and bottom-up. Now we cluster it around less (and more focussed) themes, both in scope and in time, such as the asthma vaccine, prevention of lung diseases, treatment and care of lung diseases and lung tissue regeneration.
These themes are part of an long term road map. It contains the 'dots on the horizon' we are heading for, provided the scientific progress continues and financial means are available. It will take a decade or so before the 'asthma vaccine' – in whichever form - will be clinical reality. Such a theme can easily be communicated. It is inspiring and makes people eager to be part of it."
Rutgers explains: "We aim to realise a dream. There are many scientific and empirical clues that indicate that asthma can be prevented. We will direct the programme and contract the people who can help us realise that dream. A clear view and determination are appealing to the public."
In this way, Longfonds can be regarded as a marketing influencer at the end of the scientific supply chain. Rutgers:



"We translate scientific opportunities in such a way that they encourage the public to support this research financially. This enables us to (re)organise the supply chain from the patient's perspective. It enables us to transform the supply chain into a closed loop, as this funding is used to keep the scientific supply chain going from fundamental research to clinical application."

A magnet

The dream becomes more and more concrete now the first trials in Munich and Wageningen lay ahead. Rutgers: "Hermelijn Smits at the LUMC is working on protective proteins from parasites, Christian Taube at the LUMC brings in protective proteins from the heliobacter bacteria , Huub Savelkoul from the WUR is involved with proteins from raw milk. Also Bart Lambrecht at Ghent University is involved. It might well be that a vaccine takes the shape of a food supplement. We don't know yet. The question is: how can we influence the immune system in such a way that suspected asthma doesn't develop? There are several routes that may provide answers to this question and we don't know yet which one proves to be the best. Maybe ingredients from different routes can be combined."

"Our focus is on the end result, on problem solving"

There is a healthy rivalry between the several promising research lines. This rivalry is healthy, because parties involved need to keep in touch and need to share information to learn from each other for their own project's good. Rutgers: "Mind the phrasing: 'they need to'. Such a collaboration is not necessarily born out of personal sympathy, but is managed in such a way that this doesn't matter, as long as we provide the support and funding to enable it. This combination of collaboration and rivalry works stimulating, period. What's more, it attracts additional funding. Huub Savelkoul received a STW grant for fundamental work and a trial with proteins delivered by the food industry to produce proof of concept."
Everybody recognises the asthma vaccine as the major breakthrough it really represents, Laan adds: "Such a theme works as a framework for the scientific community. Within this framework there is room for the community itself to present the best means to the end. We are not the only ones to organise research along these lines; the EU framework programmes and NWO funding follow the same principle. And – as the STW example makes perfectly clear – there is also clustering between funding bodies. When others notice our effort and determination to turn this programme into a success, this determination works as a magnet."

Collaboration is everything

Rutgers reveals that the approach followed in the asthma vaccine project is not entirely new. "We actually build on what the Vereniging Spierziekten Nederland (Muscle Disease Society Netherlands) already did back in 1984 in its Duchenne's campaign: to gather scientists behind one banner in order to fight a disease. That is how we do it now: as a solid societal partner with the plan, the funding and the determination to go for result."

Laan: "While immunology might be known to medical researchers it isn't known to the general public. As research coordinator however I see immunology everywhere. Collaboration is everything: do it together or don't do it at all. If you want to get somewhere, show your added value and connect to the relevant colleagues in the relevant fields.

Leendert van der Ent

Sjaak Neefjes, Van Loghem Laureate 2015

Back to the future; bridging disciplines

From cell biology into chemical biology to translate chemistry into immunology and oncology: Sjaak Neefjes' lab is continuously evolving. This year's Van Loghem Laureate is always open to bridging scientific fields. He strongly supports the combination of disciplines in order to develop new and original insights and solutions to auto-immune diseases, infectious diseases and cancer.

His staff describes Neefjes as a kind, caring and down-to-earth-type of person with a passion for science. He also is inspiring and demanding, and an inexhaustible source of ideas. He has a keen eye for what's upcoming and is always prepared to enter a new direction. "He's a big picture person with an amazing capacity to connect the dots. He sees or senses things before others do and it's remarkable how often he's right", says postdoctoral fellow Ilana Berlin.

Scientific contributions

These capacities have certainly not been wasted. Up to this date, Neefjes (1959) has made many contributions to the understanding of the cell biology of MHC class I and II antigen presentation. He was involved in the development of chemical biology approaches to generate inhibitors for the peptide transporter TAP, to track peptidases in cells, and to develop the first antibiotics targeting host proteins and acting against a series of intracellular bacteria including Salmonella. He used this information to show how Salmonella can induce cancer, especially gallbladder carcinoma in India and Pakistan. He was amongst the first to use GFP in biology and pioneered in the application of a green fluorescent protein for intracellular tracking of molecules and vesicles and developed these to identify the mechanism of selective motor-driven transport of late endosomes. The Neefjes lab identified the first enzyme involved in multi-vesicular body formation, the biology and rearrangements within this compartment, the peptide transporter activity and specificity, DRiPS, peptidases and processes that –collectively- yielded a detailed understanding of antigen presentation by MHC molecules. In many cases, Neefjes and his team managed to solve outstanding cell biological issues in cell biology/immunology by integrating chemistry, genetic screens, cell biology, biophysics and immunology, thereby establishing a line of productive interdisciplinary research. "Innovation is to be found at the interface of different disciplines", he stresses.

ICI

Last year, Neefjes was the main applicant of a Gravitation grant for the Institute of Chemical Immunology (ICI). Together with his fellow applicants Figdor, Gros, Heck, Overkleeft and Schumacher, he secured a subsidy of 27.6 million euros. ICI aims at innovative, interdisciplinary research, conducted

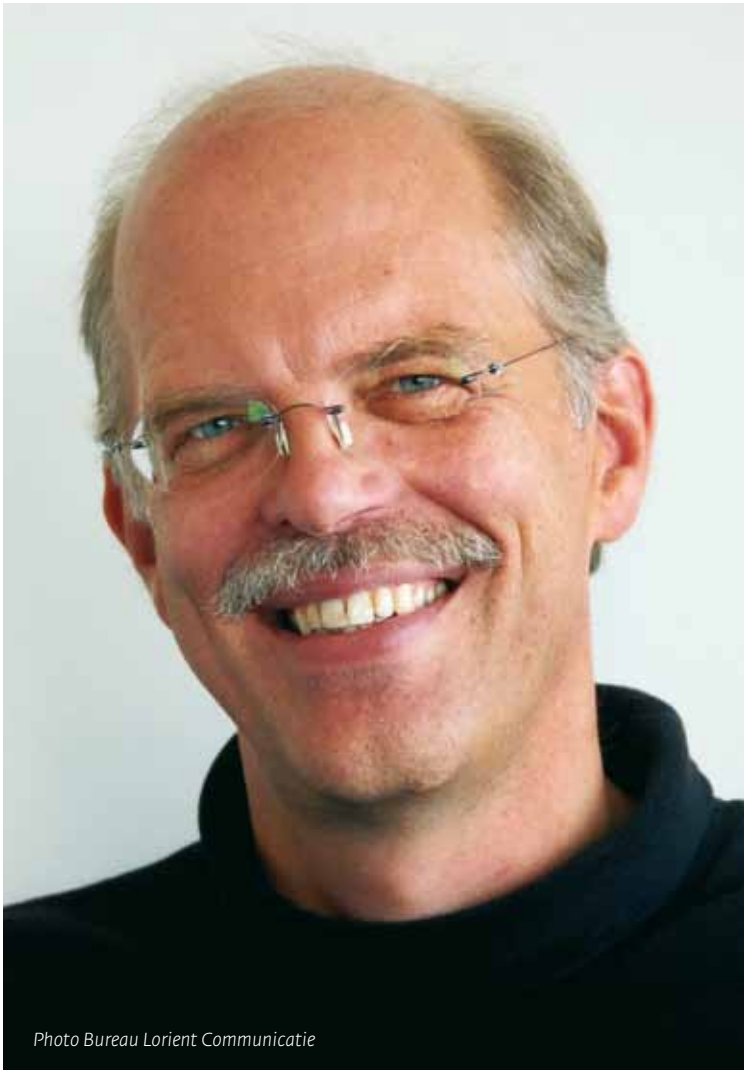


Photo Bureau Lorient Communicatie

by scientists from Dutch universities and institutes in the fields of immunology and chemistry. "The immune system is a fantastic system, involved in almost all diseases. In the Netherlands, the quality and quantity of immunological research is extraordinary high. But, if we want to translate this knowledge into real solutions, drugs will have to be developed. This can only be done by chemists, and it requires the two disciplines to really understand each other well. Bridging the gap between chemistry and immunology is quintessential for

the development of new and innovative ways to deal with auto immune diseases, infectious diseases and cancer."

Movement

Neefjes himself graduated as a chemist at VU University Amsterdam. He was interested in cell biology and moved as a student to Hidde Ploegh at the NKI. Ploegh asked Neefjes to start his PhD in his lab and sent him to the lab of Prof Jacques van Boom in Leiden to make iminosugars that inhibit so-called glycosidases. He then combined that with microscopy and employed the GFP molecule and chemical tricks to follow the dynamics of molecules in cells. "You can use lasers to activate processes or to bleach fluorescence which allows the visualization of dynamics. The diffusion of molecules has in fact been described by Einstein and explains how to interpret differences. We have used that to show that the peptide transporter TAP moves differently in the ER when actively pumping peptides or when inactive. This resulted in the identification (along with Jon Yewdell) of the DRiPs and in showing the potential of combining radiotherapy with immunotherapy to boost immune responses against cancer. We have used similar tricks to show that cytosolic peptides can move from one cell to the next when they are connected by gap junctions. Gap junctions are central in cardiotoxicity but poorly known in immunology although many immune cells express these when activated and then connect to tissue their cytosol. We used peptides synthesized such that they could not be destroyed to follow these peptides moving to other cells and then other tricks to confirm that peptides made by one cell can in fact be presented to the neighboring cells or a dendritic cell, thus illustrating another form of cross-presentation. This work would not have been possible when we would have stayed in the field of immunology only."

Cross-disciplinary research

The findings illustrate the importance of cross-disciplinary research. "Hidde Ploegh already combined many disciplines and inspired me to broaden my interest in the cell biology of the immune system. Over the years I experienced the explosion of new technologies in both domains and integrated these in my work in an attempt to understand and visualize the process of MHC class I and MHC class II antigen presentation. Cell biology and biophysics have solved many immunological questions, improving our molecular understanding of antigen presentation and other immunology related issues. At the same time, we need new tools for further manipulation of the MHC class I and MHC class II antigen presentation pathways. These tools would be applicable in a host of immunology-related disorders, including auto-immune diseases, cancer and infectious diseases." The latest research activities integrated drug screening, genetic screening and cell biology with the aim to find new targets and new lead structures that control the expression of MHC class II molecules, which may be of interest in case of many auto-immune diseases. This integrated approach may also yield new biology and then compounds to manipulate this.

Be curious

And this is where ICI comes in: chemists and immunologists from different universities joining forces and integrating their research. This is fostered by setting up PhD proposals with two PhD students working in two labs on the same topic, one the chemist and the other the immunologist. Important to the ICI is it's Junior Faculty. Neefjes: "I strongly support the goal of strengthening the competence of junior postdoctoral researchers in their career. Whereas I could become a group leader at the age of thirty, this is almost impossible today. This is a bad development as young independent scientists are critical for original research." In addition, the ICI aims to establish a school for chemical immunology.
His general motto in science and life is 'be curious always'. "If you come across a fact that puzzles you, do not ignore it; explore it! Even when it leads you into new fields. We for instance found an explanation for the link between Salmonella Typhi infection and the prevalence of gallbladder cancer in a specific area in India and Pakistan. This research took us really out of our comfort zone. We combined organoid cultured, mouse infection models, pathology of Indian samples, genetics, infection models and even epidemiology with help of labs in three countries including India. But when you find something that might be important to patients, you are obliged to take the next step."

Blessed

Neefjes considers himself fortunate that he has always been able to follow his research instincts. "My work is my hobby, I'm blessed. Immunology is endlessly fascinating. "
Now he has 'finally been accepted as an immunologist', Neefjes jokes, the Van Loghem Laureate ventures a few words of advice to immunologists. "Immunological research is evidently important. If immunologists would more often join forces with other disciplines, they would definitely be more successful in securing a share in large research infrastructures and networks. Also, be open to new technology for it is key to advancing immunological research. And finally, of course, marry a pathologist, like I did. It will keep your feet firmly on the ground and face facts."

Alinda Wolthuis

Mady Hornig: The battle against

Recently a sharper understanding of ME/CFS has emerged. Mady Hornig, MA, MD is Director of Translational Research at CII and associate professor of Epidemiology, is lead author of the publication in Science Advances: "Our findings suggest that objective diagnostic tests for ME/CFS may be possible. We also believe that the patterns of immune disturbances we uncovered may spur the discovery of new, effective treatments that can be tailored to different stages of the disease."

Mady Hornig

Myalgic Encephalomyelitis or Chronic Fatigue Syndrome or (ME/CFS) is a debilitating disease that by some estimates affects 4.5 million individuals in the USA alone. Symptoms include extreme fatigue, difficulty concentrating, headaches and muscle pain. There are no lab tests for ME/CFS. The disorder remains mysterious and sometimes controversial. As a consequence, people with ME/CFS often feel stigmatized.

Around 2010 the suggestion that two viruses might be implicated in the disease led to renewed interest. And although the two suspected viruses were eventually ruled out, recently a sharper understanding of ME/CFS has emerged. Researchers at the Center for Infection and Immunity (CII) at Columbia University's Mailman School of Public Health in New York have published research findings that identify distinct immune changes in patients with ME/CFS. They show distinct phases in the trajectory of the disease. The work provides perhaps the strongest support yet that ME/CFS is a biological illness and not a psychological disorder.

Hornig: "ME/CFS patients often report first getting sick with illnesses that are time limited, such as infectious mononucleosis, with swollen glands in the head and neck, sore throat and fever. However, unlike most patients, they never fully recover. Our research suggests that in these patients, the immune response to the initial infection-like illness may get stuck in 'high gear', with cytokine levels remaining very high for around three years. After the three year mark, the levels of most of the cytokines we studied begin to drop, with the immune system beginning to show evidence of exhaustion. Rapid detection of these immune changes may both facilitate early diagnosis and open up unique opportunities for initiation of treatments."

Improved detection

Hornig: "The study we published in February 2015 used immunoassay testing methods to determine the levels of 51 immune biomarkers in blood plasma samples collected through two multicentre studies.

Chronic Fatigue Syndrome

These represented 298 ME/CFS patients and 348 healthy controls. Patients at three years or less had increased amounts of many different cytokines. Notably, even small increases in interferon gamma, an immune molecule linked to the fatigue that follows infections with viruses such as Epstein-Barr, the cause of infectious mononucleosis, were more common in the early phase of illness. These discoveries are closely linked to the improved sensitivity of our immunoassays. Even small increases in immune molecules could be detected."

"A month after our first study came out, we published a second paper in Molecular Psychiatry that reported our discovery of another unique pattern of immune molecules among people with ME/CFS, this time in their cerebrospinal fluid. The group of ME/CFS patients we examined in this study were largely further along in the course of their illness. Not unexpectedly, the immune patterns we found for these patients were quite similar to those we found in the plasma of long duration ME/CFS patients. This discovery provides insights into the basis for cognitive dysfunction in ME/CFS, 'brain fog', as well as offering new hope for improvements in diagnosis and treatment."

Discovering signalling pathways

Hornig: "Technological advances have enabled us to discover many more immune molecules and their signalling pathways and to understand how essential these are to brain development and brain function. Improvements in the sensitivity and reliability of multiplexed immunoassays such as the ProcartaPlex® immunoassay from Affymetrix are accelerating our ability to discover new biological markers of disease based on samples that are easily accessible, such as peripheral blood. These new capabilities at the lab bench herald exciting new directions for research into various brain disorders."

"Brain-immune interactions are at the heart of the disease process we study. Disturbances among the many microbes that inhabit our intestinal tract disrupt the balance of the so-called metabolome. The metabolome comprises the bacterial and host metabolites present in blood and other biological samples, including amino acids, neurotransmitters, short chain fatty acids, and a host of other inflammatory and neuroactive molecules. Distortions in an individual's metabolome can skew their immune molecules, some of which interact with brain receptors. Through immune profiling of blood samples from patients diagnosed with ME/CFS, we have detected distinct changes in these immune molecules, identifying patterns in the immune system that have important relationships with different phases of the disease. Different mechanisms appear to be active in different stages of the illness; where patients lie along their disease trajectory may help predict which treatment will be most effective to them."

Immune profiling for brain disorders

Hornig: "The new lines of research emerging from our group and other research groups around the world hold great promise for changing mainstream conceptions about ME/CFS and accelerate investigation into its biological underpinnings."

"Beyond ME/CFS, I believe that there will be great utility, as yet untapped, in applying immune profiling to achieve a better understanding of a whole host of brain disorders that may be initiated or exacerbated by environmental factors such as infection, diet, xenobio/toxicology, extreme psychosocial stressors. These then exert their influences on the innate or the adaptive arms of the immune system and/or oxidative or nitrosative stress response machinery. These approaches may ultimately help us to understand the pathogenesis of disease among subsets of patients with depression – which is now thought to have an inflammatory subtype -, bipolar disorder, schizophrenia, OCD, ADHD, mild cognitive deficit, Alzheimer's disease and autism."

The contribution of eBioscience / Affymetrix

Hornig: "We've been working with the eBioscience unit of Affymetrix for about ten years. For these recent studies, in which we used the ProcartaPlex® Immunoassay to analyse both blood and cerebrospinal fluid samples, we were impressed with the reliability of the assay as well as the diversity of the analytes we could include – specifically 51 immune molecules. The early adoption of the magnetic bead format by Affymetrix helped immensely. We also value the very real connection that we have with respect to product development. We have developed customised products with their team; they have partnered with us to ensure that the solutions available to us match our research needs. This active engagement has helped us not only to troubleshoot technical issues, but has also accelerated our ability to establish a firm foundation for ongoing research into ME/CFS and other immune mediated brain disorders."

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Towards a more effective pharmaceutical pipeline

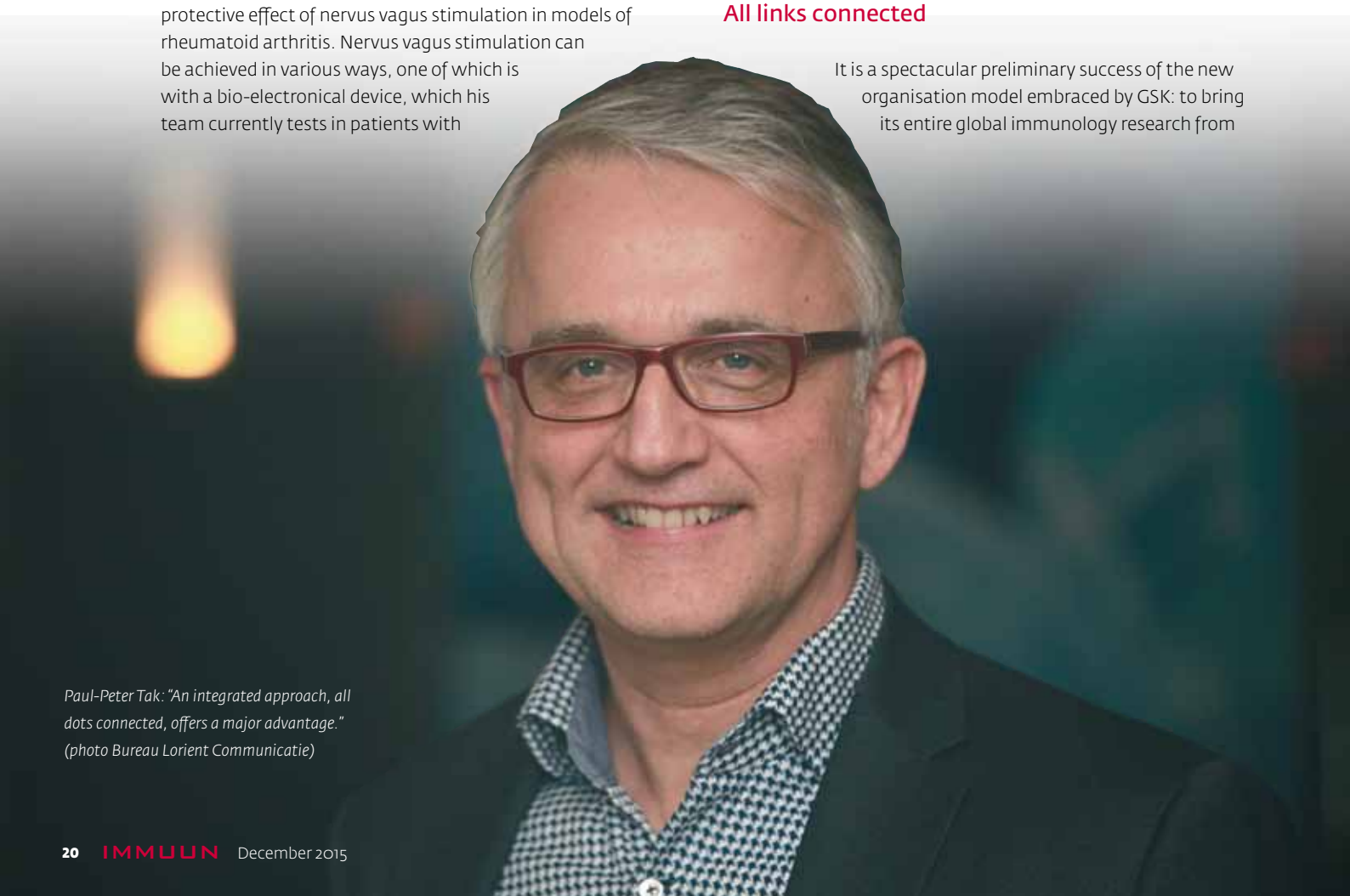
Paul-Peter Tak wishes to bridge the gap

The powerful effect of TNF inhibitors set Paul-Peter Tak on the track of immunology. Some years ago he made a second major move: he chose for a position in the pharmaceutical industry to maximize his impact on patient's lives. As Global Head of ImmunoInflammation at GSK he explains his research focus on a disease transcendent approach and GSK's collaboration model. Tak strives to overcome misunderstanding between academia and pharmaceutical industry by stimulating collaboration. "A better mutual understanding would be beneficial for both sides and will enhance the effectiveness of the pharmaceutical pipeline and the delivery of medicines to patients."

The first part of this story, published in the previous issue of Immuun, already gave witness of a lot of changes taking place. There is even more about to change, Tak reveals. "A radically different approach would be to study the relationship between different systems in the body, for instance the influence of the neurological system on inflammations." Neurosurgeon Kevin Tracey of the Feinstein Institute for Medical Research has shown a beneficial effect of nervus vagus stimulation in a model of sepsis. Tak and colleagues have demonstrated a remarkably protective effect of nervus vagus stimulation in models of rheumatoid arthritis. Nervus vagus stimulation can be achieved in various ways, one of which is with a bio-electronical device, which his team currently tests in patients with rheumatoid arthritis. Tak: "In one patient, all other treatments had failed. But she showed complete remission after nervus vagus stimulation and could stop all other medication. At present, this approach looks encouraging, although it will be years before this therapy may become clinically available." The sponsor of this clinical trial, SetPoint Medical, has secured financing from a new GSK strategic venture capital fund for bio-electronic medicines to facilitate further development.

All links connected

It is a spectacular preliminary success of the new organisation model embraced by GSK: to bring its entire global immunology research from



Paul-Peter Tak: "An integrated approach, all dots connected, offers a major advantage." (photo Bureau Lorient Communicatie)

discovery and development to approval of a new medicine under one head. "This integrated approach, all dots connected, gives us a major advantage. When something is discovered, we immediately think of patients and also ask clinicians and payers for practical implications. The other way round, we ask patients and clinicians for unmet needs. The shortest route from fundamental science to the patient and back again, in an iterative process."

This sounds logical, but separation between 'Early Discovery & Early Development' and 'Late Stage Development' in other organisations may introduce a focus on more limited goals, with its own dynamics. "This sometimes causes promising activities to be cut off at the transfer point from early to late stage", Tak remarks. "Furthermore, we believe that the science should be leading during early discovery rather than commercial strategy. The logic is that once you focus on the best science and the unmet needs in an integrated way, commercial success, which is necessary for a sustainable model, will follow."

Types of collaboration

External collaboration is an important aspect of GSK's ImmunoInflammation Therapy Area Unit. "We collaborate with other pharmaceutical companies, biotech companies and academia. Academic collaboration is largely concentrated on the top ten universities in the UK and USA, although we also closely work together with centres in for instance continental Europe. The Dutch research infrastructure is good, immunology research is very good, and the Netherlands is especially renowned for its high quality clinical trials. It is unfortunate that the distance to the pharmaceutical industry is larger than in the English speaking world."

Tak made some changes to the nature of collaboration with academia. "I put a stop to just providing research budget. It doesn't lead to the development of medicines for patients who need them. It is better to have clearly defined goals, milestones and deliverables. A better mutual understanding would be also beneficial for both sides. Academic groups are not always aware of the high science level within pharmaceutical companies. And yes, just like scientists within the academia our scientists strive for publication in high impact journals, but for us it doesn't stop at that, in the end our goal is to develop medicines. Another aspect that isn't always understood, is the industry's portfolio management, which can lead to a no-go in spite of success. We have to prioritize continuously based on emerging data across the portfolio."

Tak strives to overcome misunderstanding by stimulating collaboration. One form of collaboration is to have pharmaceutical scientists closely work together with academic scientists in a joint project team. "There may be a discovery at academia that could potentially lead to a new treatment. This leaves the academic with a couple of choices: publication without further development or perhaps the start of a biotech company - which is not everyone's cup of tea."

"It is unfortunate that the distance to the pharmaceutical industry in the Netherlands is larger than in the English speaking world."

Therefore GSK introduced a third option called DPAC: Discovery Partnerschip with Academia. It stands for a fifty-fifty partnership between a university and GSK, with shared costs and benefits. It functions like a virtual biotech company, except that scientists don't have to become entrepreneurs and the scientific team has access to the technology and platforms of pharmaceutical industry. Tak: "We have several highly successful projects in the context of the DPAC model."

Strengthening the bonds

Two years ago, GSK initiated an open innovation campus in Stevenage, halfway between Cambridge and London, with incubator and accelerator facilities. Tak: "Spin off companies from universities can apply for space in the Stevenage Bioscience Catalyst. They have access to part of our facilities. We embraced this radically new model of IP-free collaboration to speed up progress. If start-ups eventually decide to work with other pharmaceutical companies, they are free to do so, but we believe we have a lot to offer to many of these

biotech companies. " Another very recent initiative to foster collaborations is GSK's Immunology Network. "We select rising stars in immunology who will be free to work in our laboratories in Stevenage for up to three years", says Tak. "They stay employed by their university and continue to publish. We reimburse the university, and provide support in terms of scientific personnel and bench fee. We do this to maintain a challenging culture with scientific debate and to offer these selected scientists an opportunity to develop their 'soft skills' in a way a university hardly does: to develop their leadership skills, excellence in project management and people development capabilities. They will get in depth knowledge of the discovery and development of medicines. It will result in new ideas and boost collaboration and mutual understanding. This is called the Elion and Black Immunology Catalyst Sabbatical programme. We will give five immunologists at the associate professor level, selected by a world top level board, the opportunity to continue immunology research of their own at the multidisciplinary lab of the future together with chemists and biologists. They will be able to continue their academic career."

Attrition

To strengthen external collaborations is one means to enhance the effectiveness of the pharmaceutical pipeline. Tak: "The term 'attrition', once applied to the senseless charges of men against machine guns in World War I, summarizes what it means to get a drug on the market nowadays. Most candidates never make it to become a medicine. How can we change that? First, we need to select the best molecules. Second, it is important to select the best therapeutic targets, with a much stronger focus on human biology. The predictive value of animal models is limited and has sometimes been misleading. Third, we need to design smarter clinical trials with a stronger focus on experimental medicine during early development: small, high density of data studies in humans, in which the basics can be established." Is there target engagement, does the medicine hit the pathway, does it translate to effects on relevant disease mechanisms, are there trends towards clinical improvement? Tak: "In immunology, it is still hard to predict for which disease a medicine works best. This means: extensive exploratory studies to screen for the best disease to go after. Together, these strategies should help to reduce attrition and lower the costs of drug development."

Leendert van der Ent

Aspergillus fumigatus is one of the hundreds of variants in the aspergillus family of fungi. Its spores are very common in the air around us. They are harmless to healthy people, but in patients with a weakened immune function these spores can cause a possibly lethal infection. Mark Gresnigt PhD wrote the story of the encounter between Aspergillus fumigatus and the immune system entitled 'Recognition and cytokine signalling pathways in host defence against Aspergillus fumigatus', which won him the NVVI Thesis Award.

Mark Gresnigt wins NVVI thesis award 2015

The encounter between Aspergillus fumigatus and the immune system

Aspergillus fumigatus spores frequently enter the human respiratory tract. They are recognised by Pathogen Recognition Receptors (PRRs) and are subsequently killed by macrophages and neutrophils. Simultaneously, these innate immune cells produce cytokines (such as Interleukin IL-1 or IL-36) to also induce an adaptive immune response against the trespasser. This defence mechanism is highly effective - except when the immune system is weakened by for instance stem cell transplantation, corticosteroid or chemo therapy. Estimates indicate that 200,000 people worldwide annually struggle to overcome aspergillosis. As under-diagnosis is quite a problem, the real numbers are probably higher.
Furthermore, Th2 helper cells can induce an allergic reaction against *Aspergillus fumingatus* in severe asthma patients: Allergic Broncho-Pulmonary Aspergillosis (ABPA). "It turned out that, in contrast to T-cells in mice, there was little known about the human T-cell response against *Aspergillus fumigatus*", says Gresnigt.

Protective deficiency and other approaches

An amazing find featured in the thesis is that the NOD1 pathway, involved in the protection against bacteria and mutated in individuals with inflammatory bowel disease, interferes with aspergillosis. A study in mice at the Paris Institut Pasteur confirmed that NOD1 deficiency actually protects against aspergillosis. Gresnigt: "This led to the idea to develop a receptor-inhibiting drug for treatment of aspergillosis. In patients with aspergillosis the main question is, whether their immune system can recover quickly enough to beat the fungus. Inhibiting NOD1 could tip the balance positively."
Another approach is offered by immuno therapy with interferon-gamma (IFNγ), a cytokine with known antifungal properties. Gresnigt: "In a series of cases of invasive fungal infections we showed that IFNγ indeed strengthened patient cells against fungi." The role of the cytokine IL-1, another actor in the complex interplay between fungus and immune system and known for its attraction of neutrophils after infection, was also taken into account by Gresnigt. "Boosting IL-1 in aspergillosis patients could have a decisive impact against the fungus. We also found that a new member of the IL-1 family, IL- 36 which is known to play a role in psoriasis, is also induced by *Aspergillus fumigatus*. It could in this case take over IL-1's role when that interleukin is lacking, as it seems to manage the *Aspergillus-induced* T-cell responses."

Colitis

Gresnigt and researchers at the Institut Pasteur found in another collaboration project that a polysaccharide molecule in the cell wall of *Aspergillus fumigatus* induced the anti-inflammatory cytokine IL-1Ra. This anti-inflammatory effect correlated with a poor outcome of aspergillosis. The researchers hypothesized that the anti-inflammatory properties of this polysaccharide could be put to good use. "It could help to boost an anti-inflammatory response in Colitis Ulcerosa patients", Gresnigt comments. "Preclinical research in this direction is now carried out at the Institut Pasteur. If the present expensive recombinant receptor antagonists could be replaced by drugs cheaply synthesized by fungi, this would be great."
Gresnigt is presently working on postdoc research about reprogramming of cells during sepsis. But fungi have captured him and he is applying for a VENI on mucormycosis, a type of fungal infection with even more severe infective impact. "My preliminary data suggest that the immune reactions are entirely different from that to *Aspergillus fumigatus*. There is hardly any other research published to corroborate this, so I would very much like to chart this terra incognita."

Leendert van der Ent

Teaming up to mine the imm

The fight against disease during the last 125 years has taught us that we can prepare and tune the immune system in its reaction against pathogens or other disease-causing agents. Indeed the insight that we do not need to put up with a failing immune system carries a huge health care potential, says Paul Parren during his inaugural speech as professor of Molecular Immunology at Leiden University. Immuun summarized his inaugural speech.

"The immune system creates antibodies that bind foreign structures with great strength and specificity in their important 'seek and destroy' mission. Antibodies are produced by B-cells, which represent small factories that produce many copies of a single, unique, antibody molecule. The DNA of the B cell provides a very large number of puzzle pieces to assemble novel antibody molecules. In order to achieve immune protection against a pathogen, the body harbors up to a billion different antibody specificities, at any time, that attempt to seek a foothold on the pathogen. The immune system thereby detects partial matches and stimulates B-cells to optimize the specificity of their antibody by replacing building blocks to eventually obtain antibodies with a fully matching binding surface. During infection this mechanism creates a fair chance for the host to generate a protective antibody response to the pathogens before time runs out. The B-cell is then encouraged to continuously produce large numbers of this specific antibody to secure long term immunity.

Vaccines and HIV

Unfortunately, clever pathogens can beat or deceive the immune system. Vaccines (i.e. pathogen-derived antigens in an immune stimulating formulation) aim to prevent this via the induction of sufficient titers of protective antibodies, thereby giving the immune system a head start. Smallpox, as an example, caused one in ten children to die, until the smallpox vaccine changed this dramatically, leading to a total eradication of the disease by 1980. Vaccination programs against diphtheria, measles, rubella and polio, such as in the Dutch Rijksvaccinatieprogramma, have also been highly successful, and the WHO has now set the ambitious worldwide goal to eliminate measles and rubella altogether.

The pathogen HIV-1 is a master of deceit. Its genetic information evolves very rapidly, which makes it very hard for the immune system to keep track and produce effective antibodies against the contemporary virus. This failure of natural immunity makes the availability of a vaccine a matter of great urgency. Ipso facto, the highly changeable virus also makes it difficult to develop an effective vaccine.

Research performed at the Scripps Research Institute in collaboration with Tulane, Rockefeller and Cornell Universities, showed that active antibodies against HIV-1 exist in some long-term infected patients. Interestingly, we demonstrated that a laboratory version of such an antibody can provide effective protection against HIV challenge in an animal model. The experiment shows that a failing immune system indeed does not have to be taken for granted. A vaccine that would elicit sufficient amounts of the right antibodies may be protective, even for a smart and evasive pathogen as HIV-1. During the past decade, studies have therefore focused on identifying the Achilles heel(s) of HIV-1 by determining the structure of antibodies with broadly protective potential. The design of vaccines on the basis of this information has recently begun to bear fruit.

Therapeutic antibodies

The vast body of work on antibody- and vaccine-mediated protection against infectious diseases taught us some of the tricks of the trade of immune protection. Modern technologies which allow us to effectively generate human antibodies against self-antigens, has allowed us to translate this knowledge into the development of a strong arsenal of antibody therapeutics for the treatment of many other important human diseases. Similar to the fight against pathogens, researchers often look for antibodies with neutralizing activity. Neutralization takes place because the antibody binds at exactly the right spot to disturb an essential process in the lifecycle of a tumor cell, for instance the inhibition of a growth factor to which the tumor has become addicted. Neutralization alone however is not the whole story. Antibodies may also function as a weapons system with an ability to trigger various types of ammunition (e.g. complement proteins and proteolytic enzymes) and to attract auxiliary troops (e.g. white blood cells).

Currently there are about forty different antibodies registered as drugs for the treatment of cancer, inflammatory diseases, autoimmune diseases, cardiovascular diseases, bone diseases, infectious diseases and eye diseases. Several hundreds of antibodies are in various stages of drug development. The superb pharmacology and safety profile of antibodies and their strong potential in combination treatments has made them a preferred ingredient for many drug regimens.

une system for novel drugs

Collage van de instituten waarmee is samengewerkt. Figuur door Joost Bakker (Scicomvisuals).

Effector functions

Some antibodies effectively kill target cells because they activate proteins of the complement system. An academia – industry collaboration between the biotechnology company Genmab and a number of academic groups from Utrecht University, LUMC, the Scripps Research Institute and the University of Virginia recently yielded important new insights into this activation mechanism. It turned out that antibody molecules need to collaborate to activate the complement system. Six antibodies form a platform (hexamers), by joining their tails (Fc fragments), which functions as a launchpad for activating the complement system. Interestingly, antibodies are constantly accompanied by complement molecules in the blood. The concerted molecular sequence of events ensures that immune activation is only initiated when multiple antibodies simultaneously bind to the same recognition structure. Hexamer formation and complement activation provide a danger and mobilization signal which attracts and activates white blood cells. These help troops employ a number of clean-up mechanisms, including antibody-dependent cellular cytotoxicity and phagocytosis, to kill the pathogen or tumor cell.

Inspired by nature: ideas into applications

Despite the many successes, the work is not done. For each therapy, there are groups of patients who do not respond. In addition, it is often observed that after an initial response, patients become refractory to treatment and the disease progresses. New, better and more potent drugs are therefore urgently sought after. In our search for novel, more effective

treatments, we like to be inspired by the molecular principles of biological processes as they occur in nature. A number of examples, representing the fruits of such inspiration, include the antibody-toxin conjugates, bispecific antibodies and effector function-enhanced antibodies. These examples, described below, in addition highlight the strong potential of academia-industry collaborations in translating inspiration -- into ideas -- into applications.

Firstly, antibody-toxin conjugates. The recent progress in antibody-toxin conjugates, which bring together a strong poisonous substance with an antibody, is driving the development of new cancer drugs. The antibody is used to target the cancer cell after which the toxin kills it. This precise and specific approach increases the therapeutic window in which much stronger toxins than in traditional chemotherapy can be safely applied. The tubulin destabilizing agent auristatin represents one of the more successful toxins used in this approach. This technology builds heavily on the work performed at the Arizona State University and joins two natural defence methods. Interestingly, during a diving expedition in the Indian Ocean, it was observed that a sea slug known as Dolabella auricularia was completely avoided by an abundance of predators, without any obvious means of protection. From this creature, they isolated dolastatin, a substance that was found to inhibit the division of cancer cells with unprecedented potential. Researchers from the American biotech company Seattle Genetics used this compound as a prototype to develop auristatin which is currently widely used in research into new antibody-toxin conjugates. We combined auristatin with an antibody against TF, an antigen which is expressed on many cancers and which, by virtue of its rapid turnover, is highly suited for shuttling toxins into tumor cells. The antibody-drug-conjugate showed impressive potential against a broad spectrum of cancers in preclinical models and is now in clinical development for the treatment of solid cancers.

Secondly: bispecific antibodies. The dogma that antibodies are always produced by single B cells and represent symmetric, highly stable molecules ruled immunology for a very long time. A close collaboration between Sanquin Research, University of Maastricht, the VUmc and Genmab however surprisingly demonstrated that IgG4 antibodies are dynamic molecules that generate bispecific antibodies in man. These antibodies combine the binding site of one antibody with that of another and therefore bind two different recognition structures. The binding sites are produced in different B cells and were shown to recombine in the blood in a post-production process. In follow up research we elucidated the molecular mechanisms of this process. Based on this knowledge, we developed a new technology for the production of stable therapeutic bispecific antibodies in the lab. By targeting multiple antigens, these antibodies have the potential to target multiple pathways, inhibit tumor growth more effectively and to prevent escape. A second application employs bispecific antibodies to connect cancer cells to cytotoxic white blood cells, which engages these cells for indiscriminate tumor cell killing.

Thirdly: antibody hexamers. Understanding the molecular mechanism of complement activation was used to build a platform to potentiate antibody effector function. It was found that single amino acid mutations in the antibody Fc fragment enhance the ability of antibodies to form hexamers conditional on cell-surface antigen binding. This technology is resulting in new opportunities for enhancement of the efficacy of antibody-based drug development.

A vision of future immune-based drug development

Let it be clear that this is a personal and very antibody-centric vision of the field of immune therapy. If we should learn one thing from antibodies, than it is their outstanding capability to focus and to work together. Antibodies constantly exist in an environment that provides vast distractions. Antigens of limited interest that try to interact with low affinity, myriads of proteins and different kinds of cells offering all kinds of receptors, all mixed up at a pleasant biological temperature. Nevertheless, antibodies succeed in binding their cognate antigen and work together to specifically activate the immune system where it is needed. Understanding the molecular mechanisms of antibody effector mechanisms is key in further unlocking the potential of these versatile molecules.

The mechanisms of research and drug development find a surprising analogue in the molecular mechanisms of my favorite molecule. Indeed, any breakthrough can only be made by working together as it, in my experience, always requires the merging of minds with distinct expertises. Focus, trust, transparency, flexibility and communication are central ingredients in forging such collaborations. Alliances between academia and industry provide particular potential in the translation of ideas into novel platforms and drugs. The sharing of ideas, know-how, knowledge, resources and reagents provides a basis for extracting synergy from such partnerships, with results that benefit academia, industry as well as society. Indeed, it is time to set aside our focus on individual achievements and replace it with celebrating team work. Personally, none of the major advances in my career would have been possible without the hard work of my many exceptional colleagues and collaborators."

Paul Parren,
edited and summarized by Leendert van der Ent.

"When the balance is gone"

Marjolein van Egmond: "Now we have discovered the underlying mechanism of cancer metastasis after surgery and have the theoretical models to prevent this metastasis, the obvious next step is to apply this knowledge in a clinical study." (Photo VUmc)

On September 10th Marjolein van Egmond PhD held her inaugural speech as professor in Oncology and Inflammation at VU Medical Center Amsterdam. Her research started with the role of the Fcα receptor, which turned out to play an important role on Kupffer cells. Subsequently she investigated the effect of surgery on liver metastasis. This led to the question: can IgG induce Kupffer cells to eat cancer cells? Or does IgA induce neutrophils to kill cancer cells? IgA proved to work like a magnet, which leads to accumulation of neutrophils in chronic inflammations resulting in tissue damage. So what are the roles of IgA and the Fcα receptor?

Antibodies are proteins and part of the immune system. They bind to pathogens and these complexes are recognised by Fc-receptors on immune cells; thus they link pathogens to immune cells leading to their activation. Apart from receptors that activate, there are also receptors that inhibit; the immune system is all about balance. In case of infection with the flu-virus, the immune system is supposed to take action. Once the virus is destroyed, the system has to calm down again, as activation has nasty consequences.
There are several types of antibodies, such as IgG and IgA. IgG is mostly present in our blood and tissues and offers protection there. IgA predominantly acts in our mucous membranes, the places in contact with the outside world, such as the lungs and the intestines. When my research started, a lot was already known about Fc-receptors for IgG, the Fcα-receptors. A receptor for IgA had just been discovered, the Fcα-receptor. So my assignment was: 'Find the function of Fcα-receptor'. How hard could it be?

Kupffer cells

Actually, very hard, as it turned out during my research in the laboratory of Professor Jan van de Winkel at the UMC Utrecht. I encountered two major problems. The first one had to do with the location of IgA. The bowel can be seen as a hollow tube with folds. If the folds would be flattened, you find a surface with the size of a soccer field that is inhabited by 100,000 billion micro-organisms. A large part of these constitutes household bacteria that help to digest our food. Our food as well as these household bacteria are non-self, but it would be highly unpleasant if the immune system would respond to them. That is why it was thought that IgA's function was to keep the microflora in the intestinal cavity and safeguard the tissue of the gastrointestinal wall. An immune activating function wasn't expected, only an immune inhibiting function. In reality, the Fcα-receptor did actually give activating signals, which was really puzzling.
The second challenge was even harder, as no Fcα-receptors could be found in the gastrointestinal tract where they were expected. After three years of excluding possibilities, Cora Damen and I finally found the Fcα receptor on Kupffer cells in the liver. The handbook of cell biology reads: 'Kupffer cells are immune cells; they are the macrophages of the liver. The most important role of Kupffer cells is the destruction of bacteria from the blood that have penetrated from the bowel'.
That was the Eureka moment. What could be found in the bowel? IgA that patrols these tissues and sees to it that the

microflora stays in the intestinal cavity, but shouldn't activate there. But once bacteria penetrate our tissue, the IgA binds to them. Bacteria as it were pick up the key – and are transported to the liver via the blood. There the Kupffer cells express the 'lock', the Fcα-receptor, and are ready to break down the bacteria.

Metastasis

After this I started doing research in the group of professor Sybren Meijer of the Surgery Department at the VUmc. In close collaboration with professor Rob Beelen of the Molecular Cell Biology and Immunology Department, I joined the research team that investigated the consequences of colon cancer surgery. Surgery is the preferred treatment and offers patients the best chance of recovery. But as it is high impact surgery, the surgeons feared that the immune system would receive an inhibition signal, which would provide remaining cancer cells a 'carte blanche' to metastasise the liver. That is why research was aimed at switching to the immune system 'on'.
Our body produces antibodies against all kinds of pathogens. Since the eighties it however has become possible to produce antibodies against cancer cells in the laboratory. And as there is an Fcα receptor on Kupffer cells, it seemed logical to use IgA against cancer cells. Kupffer cells could then, apart from bacteria, also start eating cancer cells.
Unfortunately, this could not be tested as no large quantities of IgA could be produced at that time. Therefore we tried something else. Did colon cancer surgery actually induce immune system inhibition? No, discovered Steven Oosterling, Gerben van der Bij, Stephan Pouw, Gabor Abis, Nuray Gül, Simran Grewal and I, to the contrary, it induces an inflammatory reaction. That occurs because intestinal bacteria reach the blood circulation. Kupffer cells are not inhibited, but strongly activated. Unfortunately, this doesn't cause them to start eating cancer cells, but to excrete harmful substances that cause mild damage to the blood vessels of the liver. This in turn creates opportunities for cancer cells to adhere. This can lead to liver metastasis.

Clinical study

So what to do? Surgery is absolutely necessary, but however careful the surgery is carried out, it will always lead to a certain degree of tissue damage. Furthermore, it is not wise to turn the immune system off after such high impact surgery. But what if we could switch Kupffer cells on in a targeted way, with help of an antibody? We still did not have IgA but maybe IgG could do the trick as well. This is what Marielle Otten, Gerben van der Bij, Marijn Bögels, Nuray Gül and Rens Braster tried.
If there are no antibodies against cancer cells, macrophages try the best they can. They adhere to the cancer cells and try to fight it. But it doesn't bother cancer cells that a macrophage is connected to them. They escape and can divide into two daughter cells. Once IgG is present to act against the cancer cell, the macrophage makes contact. After some time the cancer cell is engulved by the macrophage and digested. To give IgG against cancer therefore seems to be a useful strategy.
Eventually, Gestur Vidarsson of Sanquin, among others, succeeded in developing and producing IgA. He helped us enormously and still helps us with providing new and better antibodies. At this point, however, it seemed rather useless to still find out whether IgA can induce macrophages to eat cancer cells, as IgG does that just fine.
But there are also other types of immune cells, such as neutrophils, 'the immune system's infantry'. Neutrophils are filled with toxic substances with the ability to destroy bacteria. Could neutrophils maybe attack cancer cells? This indeed turned out to be the case. Neutrophils don't really react to IgG, but they do react to IgA – even at some distance, and they even move towards IgA. It works like a magnet. It would of course be great if IgA would work like this in a tumour. Without the IgA neutrophils cannot do a lot, but with the IgA, more and more neutrophils are attracted that can attack the cancer cells.

Now we have discovered the underlying mechanism of cancer metastasis after surgery and have the theoretical models to prevent this metastasis, the obvious next step is to apply this knowledge in a clinical study. This will be a collaboration between the Surgery and Medical Oncology Departments of the VUmc together with the Surgery Department of the Spaarne Gasthuis hospital.

Long and winding

More in general we would like to apply this knowledge to restore the lost balance of the immune system. In the case of cancer we would like to switch it 'on' and on the other hand we would like to switch it 'off' in chronic inflammation and auto immune diseases. The bowel of someone with inflammatory bowel disease is ridden with neutrophils. We do not exactly understand why, but also in this case IgA in the gut functions as a magnet. And with their toxic substances neutrophils attack bowel tissue. The same process also seems to occur in other chronic autoimmune diseases. Along the same lines, patients with auto immune linear dermatitis produce IgA against their own skin: IgA attracts neutrophils that attack the epidermis. In these patients the balance in a in principle protective immune process has become lost.
What this protective role in this case would be? We don't know for sure, but we have a hunch. Neutrophils are the first to

"Everything starts with a fundamental finding, for instance the discovery of a new molecule." (Photo VUmc)

react against pathogens that invade our body. They also react extremely well to IgA that in this case works like a magnet. It is unlikely to be coincidental that IgA pops up at the places where we are most threatened by the outside world. But how the logic of these mechanisms actually works we still have to find out. Miel van Hout made the first step and Annelot Breedveld will continue to unravel this in the upcoming years. Who knows what will come out, except that it will likely be more complex than thought beforehand? As always in science.
The story of this long and winding quest illustrates how things work in biomedical research. This is how it goes in our field: everything starts with a fundamental finding, for instance the discovery of a new molecule. As related characteristics, functions and related mechanisms are still unknown, these all have to be charted. What is the role in normal processes? Is it related to pathology? Can the function be influenced by inhibition or stimulation? Could this lead to therapy? Preclinical models are elaborately tested to find this out in translational research. Then clinical studies follow and if all is well, the new finding is ready for application in clinical practice. It is not unusual for this process to take decades. What started with the fundamental question: 'what is the role of FcαRI?' now eventually leads to clinical application.

Societal relevance

The more you leave 'the big unknown' behind, the more you learn about a molecule, the easier it becomes to predict societal relevance. And as societal relevance has more and more become the driver for funding, translational and applied research has got more and more emphasis. But what about the long term? Just like the immune system, science also thrives on a balance, in this case on a balanced funding of fundamental and applied research.

Marjolein van Egmond,
summarized and edited by Leendert van der Ent

To witness the inaugural speech on video:

http://www.thesisapps.com/vanegmond/app/

NVVI

Dutch Society for Immunology

Welcome to the NVVI Winter School 2015

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Secretarial Office NVvI

Saskia ter Braak +31 (0)88 755 4306
(phone number not available during the NVVI Winter School)
nvvi@umcutrecht.nl

Welcome to the NVVI Winter School 2015

Dear colleagues,

Welcome to the NVVI Winter School 2015. As we have seen in the earlier Winter Schools, which are organised in the year that the European Congress of Immunology takes place (this year in Vienna), we will have no sponsors and only speakers from the Netherlands. This year's Van Loghem lecture will be delivered by Professor Sjaak Neefjes. Sjaak has contributed much to the field of antigen presentation by focussing on the cellular mechanisms of this process, and he has contributed with important insight to this field as well as to related fields. His lecture is entitled 'Can we understand the immune system? The cell biology of immunology' and you can find an interview with the laureate in this Immuun.
The year's winner of the NVVI thesis award is Dr. Mark Gresnigt, who was selected unanimously by the thesis committee as winner of 10 candidates. Mark performed his PhD with Prof. Mihai Netea , Prof. Leo Joosten and Dr. Frank van de Veerdonk at the Radboud UMC in Nijmegen. He reported his findings in his thesis entitled "Recognition and cytokine signalling pathways in host defence against *Aspergillus fumigatus*".

The program committee has put together a fantastic program with Karin de Visser (NKI, Amsterdam), Linde Meyaard (UMC Utrecht), Jacques van Dongen (Erasmus MC, Rotterdam), Maria Yazdanbakhsh (LUMC, Leiden) as keynote speakers. In addition, they have arranged an additional 9 invited speakers, who will give an introductory lecture to the various sessions.

This year 230 abstracts have been submitted of which 80 can be presented in the workshops. There are 4 abstracts selected for the Bright Sparks session. The 'brightest' spark 2015 will be announced at the end of the meeting. The other 150 abstracts will be presented in poster format and following the successes of previous years, poster walks will be organized on Wednesday and, Thursday around noon. Next year we will organize our Annual Meeting in Liverpool, together with the British Society for Immunology. Having this joint meeting will give us a great opportunity to get exposed to multiple outstanding speakers, which are only 1 hour by airplane away from Schiphol airport. The dates for this meeting will be December 6-9, 2016.

I wish you all an exciting and interactive meeting!

Reina Mebius
President of the NVVI board

GENERAL INFORMATION

Venue
Congress center NH Leeuwenhorst
Langelaan 3
2211 XT Noordwijkerhout

Secretariat of the conference
The registration and information desk for all registering procedures and distribution of badges and documents will be located in the Atrium Lounge (near Boston 10) at the ground floor.

Opening hours
Wednesday: 08:30 – 21:30 hrs.
Thursday : 08:30 – 16:00 hrs.

REGISTRATION FEES ONSITE
Two days
Member EUR 265
Non-member EUR 350
Master Student EUR 85

One day Wednesday
Member EUR 175
Non-member EUR 200

One day Thursday
Member EUR 125
Non-member EUR 150

The registration fee includes:
- Admission to all presentation and poster sessions
- Program book
- Coffee/tea for all conference days
- Buffet lunch for all conference days
- Drinks in Atrium on Wednesday December 16 from 17:00 – 18:30
- Dinner on Wednesday December 16
- Party on Wednesday December 16 (drinks not included)

The registration fee with hotel room includes:
- Admission to all presentation and poster sessions
- Program book
- Hotel accommodation for one night, December 16, at the conference venue (check-in from 14:00 hrs.)
- Coffee/tea for all conference days
- Buffet lunch for all conference days
- Drinks in Atrium on Wednesday December 16 from 17:00 – 18:30
- Dinner on Wednesday December 16
- Party on Wednesday December 16 (drinks not included)
- Breakfast on Thursday December 17

Abstracts
You can find the full text of the abstracts online, see our homepage, www.dutchsocietyimmunology.nl

Badges
For security and regulation reasons, please wear your name badge during the whole conference. It is your admission to all sessions as well as the various breaks and lunches. We kindly ask you to return your lanyard to the conference secretariat at the end of the conference.

Breaks and lunches
All breaks during the morning and afternoon even as the lunch will be held at the Atrium. Coffee & tea will be provided during both conference days.

Cloak Room
You will find the cloak room on level -1. (take the stairs in the Atrium Lounge).
A guarded cloak room is located in room Harvard 9.

Conference coach schedule
Wednesday evening: from 20:00 (after dinner) a bus will be available to bring you back to Leiden Central Station

Thursday morning:	between 08:00 – 08:30 busses are available to bring you to the conference venue.
Thursday afternoon:	from 16:30 busses will be available to bring you back to Leiden Central Station.

Conference dinner
On Wednesday December 16 a dinner buffet will be provided in restaurants 'Gaudi' and 'Dali' (inside the conference building). Dinner will take place from 18:30 – 19:45.

Conference party
After the 'Van Loghem Laureate' on December 16, there will be a party in Sorbonne from 21:30-0:30 hrs. Please note that drinks during the conference party are not included in the congress fee. Coins (for the drinks) can be bought (cash or bankcard) in front of the entrance of Sorbonne 2.

Lost and found
Found items should be returned to the Conference secretariat. You can bring those items to the registration desk.

Messages
You can leave messages for another participant on the information board near the registration desk.

Mobile phones
We kindly ask you to switch off your mobile phone in the conference rooms.

No Smoking Policy
Please remember that smoking is not permitted in the whole building.

Official language
The official language of the conference is English. No simultaneous translation will be provided.

Wifi
Free WIFI is available at the lobby of the hotel. If you booked a hotel room, you have access to free Wifi for the hotel and the conference venue. Please ask the front desk of the hotel for your personal login name and password. The capacity of the Wifi is suitable for checking email and visiting websites.

The poster sessions are scheduled as follows:
Wednesday, December 16: 17:30 – 18:30 hrs.
Thursday, December 17: 12:15 – 13:15 hrs.
Boston 12, Boston 14 and Atrium

Please make sure that you are present in advance to meet with your moderator. You can install your poster at the start of the conference and leave it until the end of the day that you are presenting.

NVVI Poster Awards*
The three best poster presentations will receive a Poster Award. The winner will be determined by an independent jury who will award the prize based on the research, poster composition and presentation.

NVVI Bright Spark Award*
The best Bright Spark presentation will receive a NVVI Bright Spark Award. The winner will be determined by an independent jury who will award the prize based on the research and presentation.

*The prizes will be presented on Thursday at 15:30. To be eligible of the prize, you must be present.

Liability and Insurance
The organization of the NVvI Winter School accepts no liability for any personal injury, loss or damage of property belonging or additional expenses incurred to conference participants either during the meeting or as result of delays, strikes or any circumstances. Participants are requested to make their own arrangements with respect to health and travel insurance.

Congress secretariat
P.O. Box 2428
5202 CK 's-Hertogenbosch
The Netherlands
Tel: +31 (0)73 700 35 01
Fax: +31 (0)73 700 35 05
E-mail: info@congresscompany.com
www.congresscompany.com

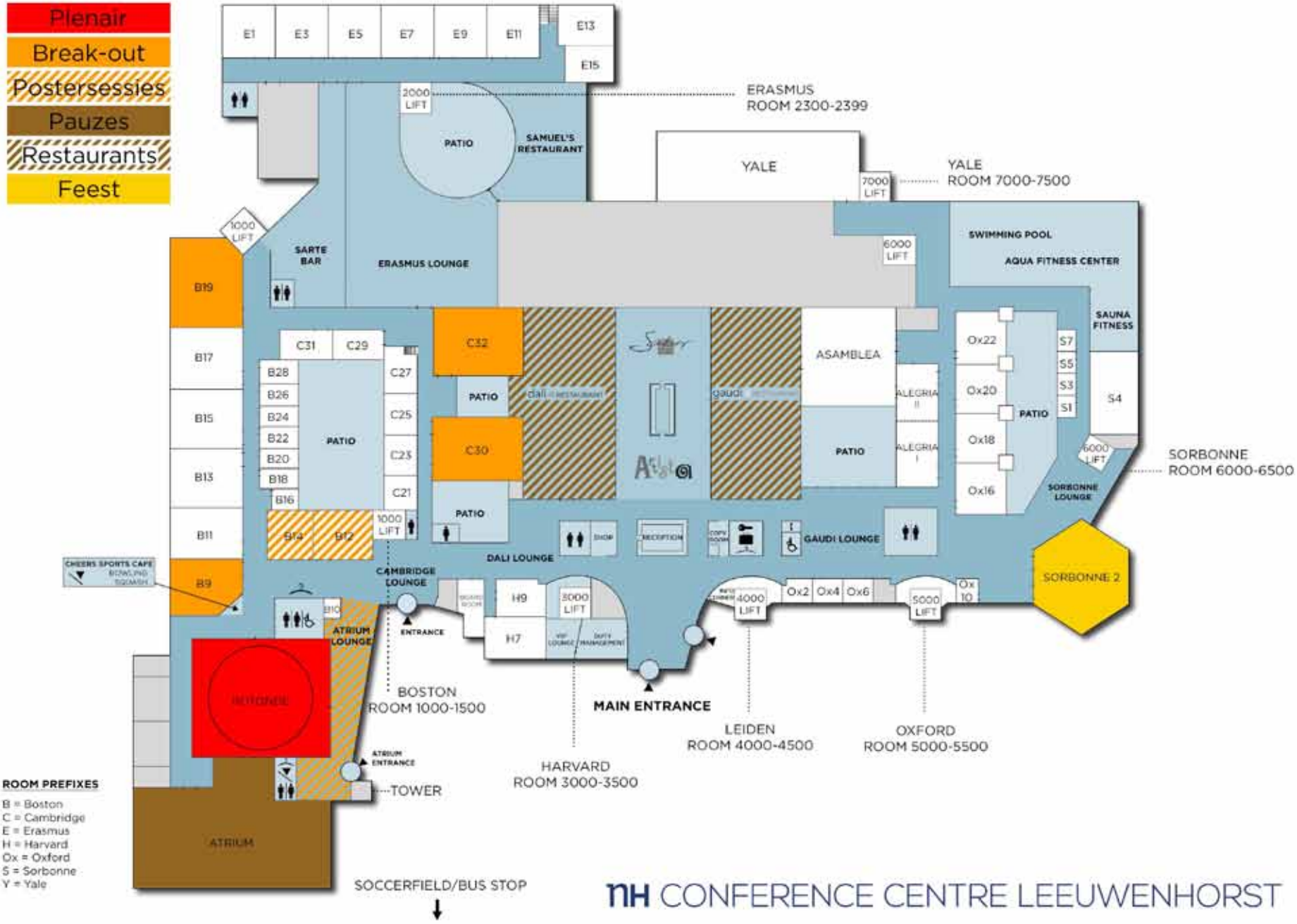
Program-at-a-glance

Wednesday, December 16

Time	Room	
09:00-09:45	*Atrium Lounge*	*Registration*
09:45-10:00	*Rotonde*	**Welcome by Reina Mebius (Chairman of the Board)**
10:00-11:00	*Rotonde*	**Keynote lecture by Karin de Visser**
11:00-12:30	*Boston 9*	**Parallel sessions**
	Rotonde	
	Boston 19	
	Cambridge 30	
	Cambridge 32	
12:30-13:30	*Atrium*	*Lunch*
	Boston 9	**'NVVI General Assembly' to be held during lunch time**
13:45-14:45	*Rotonde*	**Keynote lecture by Linde Meyaard**
14:45-15:45	*Boston 9*	**Parallel sessions**
	Rotonde	
	Boston 19	
	Cambridge 30	
	Cambridge 32	
15:45-16:15	*Atrium*	*Break*
16:15-17:15	*Boston 9*	**Parallel sessions**
	Rotonde	
	Boston 19	
	Cambridge 30	
	Cambridge 32	
17:00-18:30	*Atrium*	*Drinks*
17:30-18:30	*Boston 12 & 14 Atrium*	**Poster Walks**
18:30-19:45	*Gaudi & Dali Restaurant*	*Dinner*
20:00-20:30	*Rotonde*	**Winner Thesis Award – Mark Gresnigt**
20:30-21:30	*Rotonde*	**Van Loghem lecture by Jacques Neefjes**
21:30-00:30	*Sorbonne 2*	**Conference Party**

Thursday, December 17

Time	Room	
08:30-09:00	*Atrium Lounge*	*Registration*
09:00-10:30	*Boston 9*	**Parallel sessions**
	Rotonde	
	Boston 19	
	Cambridge 30	
	Cambridge 32	
10:30-11:00	*Atrium*	*Break*
11:00-12:00	*Rotonde*	**Keynote lecture by Jacques van Dongen**
12:00-13:30	*Atrium*	*Lunch*
12:15-13:15	*Boston 12 & 14 Atrium*	**Poster Walks**
13:30-14:30	*Rotonde*	**Bright Sparks - Plenary**
14:30-15:30	*Rotonde*	**Keynote lecture by Maria Yazdanbakhsh**
15:30-16:00	*Rotonde*	**Presentation of the Poster Award & Bright Sparks Award**
16:00-16:15	*Rotonde*	**Closing by Janneke Samsom, Chairman of the Scientific Committee**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H = Harvard
Ox = Oxford
S = Sorbonne
Y = Yale
SOCCERFIELD/BUS STOP
nh CONFERENCE CENTRE LEEUWENHORST

WINTER SCHOOL 2015

09:00-09:45	Registration - Atrium lounge
09:45-10:00	Opening - Rotonde
	Rotonde - Keynote lecture
10:00-10:55	**Karin de Visser**
Title	"The Immune System: A Double-Edged Sword in Metastatic Breast Cancer"
Chair	Mirjam Heemskerk

Location	Rotonde	Location	Boston 9	Location	Boston 19
Session 1	Autoimmunity & Allergy	Session 2	Innate Immunity	Session 3	Adaptive Immunity
11:00-11:30	**Dominique Baeten**	**11:00-11:30**	**Marco Schilham**	**11:00-11:30**	**Peter Katsikis**
Title	How innovations in immunology lead to value for patients	Title	Is there a role for NK cells in immunotherapy of cancer?	Title	"Aiding and abetting killer cells"
Chair	**René Toes** **Dominique Baeten**	**Chair**	**Jeroen van Bergen** **Marco Schilham**	**Chair**	**Debbie van Baarle** **Peter Katsikis**
11:30	Rogier, R.L. Toll-like receptor 4-induced interleukin-1 defines the intestinal microbiome and mucosal immune response in arthritis-prone IL-1 receptor antagonist deficient mice	11:30	Brandsma, A.M. Super-resolution imaging reveals enhanced clustering of the high affinity IgG-receptor FcγRI upon inside-out regulation	11:30	Behr, FM Metabolic features of CD8 tissue-resident memory Tcells
11:45	Maracle, C.X. Identification of new inhibitors of angiogenesis in a novel 3D model of rheumatoid arthritis synovial angiogenesis	11:45	Dingjan, I Lipid peroxidation causes antigen release from endosomes for cross-presentation	11:45	Nierop, G.P. van Characterization of local T-cell responses in multiple sclerosis patients
12:00	Roeleveld, DM Anti-GM-CSF Treatment Promotes Synovial Monocyte-derived Dendritic Cells and Increases Th17 Cells During Experimental Arthritis	12:00	Broeke, T. ten Regulation of the Fc α-receptor by Glycogen Synthase Kinase-3 and Protein Kinase C 7, during cytokine-mediated inside-out signalling	12:00	Hope, JL Enhancing acute anti-viral and anti-tumor CTL responses through specific microRNA modulation.
12:15	Kampstra, ASB The increased ability to present citrullinated peptides is not unique to HLA-SE molecules: Arginine-to-citrulline-conversion also enhances peptide-affinity for HLA-DQ molecules	12:15	Laar, L van de Yolk sac macrophages, fetal monocytes and adult monocytes all efficiently colonize an empty niche and generate functional tissue resident macrophages	12:15	Kragten , N.A.M. Hobit in contrast to Blimp-1 maintains cytotoxic T cell memory

12:30	Lunch - Atrium
12:30-13:30	General Assembly NVvI - Boston 9
	Rotonde - Keynote lecture
13:45-14:40	**Linde Meyaard**
Title	Prevention of collateral damage by immune inhibitory receptors
Chair	René Toes

Location	Rotonde	Location	Boston 9	Location	Boston 19
Session 6	Autoimmunity & Allergy	Session 7	Innate Immunity	Session 8	Adaptive Immunity
Chair	**Hermelijn Smits** **Niels van de Geest**	**Chair**	**Annemiek van Spriel** **Cees van Kooten**	**Chair**	**Marieke Griffioen** **Joke den Haan**
14:45	Hafkenscheid, L Extensive glycosylation of ACPA-IgG variable domains in rheumatoid arthritis	14:45	Goedhart, MJ Bone marrow harbors a unique population of resident DCs that is prone to induce Th2 and Th17 immune responses	14:45	Freitas Alves, C.H. Dendritic cell-specific deletion of ß-catenin results in fewer regulatory T-cells without exacerbating autoimmune collagen-induced arthritis
15:00	Kampstra, ASB Crossreactivity to vinculin and microbes provides a molecular basis for HLA-based protection against rheumatoid arthritis.	15:00	Pelgrom, L.R. Distinct metabolic requirements for T helper 1 and 2 polarization by dendritic cells	15:00	Karrich, Julien J. Plet1-mediated Cell Detachment Controls Steady State Migration of Intestinal Dendritic Cells.
15:15	Fabian, F.C. ADAMTS13 reactive CD4 T cells targeting CUB-2 domain derived peptides in autoimmune thrombotic thrombocytopenic purpura	15:15	Coorens, M Inhibitory effect of cathelicidins on macrophage activation by E. coli depends on bacterial viability	15:15	Pascutti, M.F. GITR-GITRL interactions boost humoral immunity by shaping follicular helper T cell-B cell responses
15:30	Hamburg, J.P. van IL-17A-low CCR6 Th cell populations of patients with rheumatoid arthritis are pathogenic, multidrug resistant and associated with DMARD/ glucocorticoid treatment response	15:30	Burm, SM Different IL-1ß expression patterns in multiple sclerosis and experimental autoimmune encephalomyelitis suggest a different role during disease course	15:30	Dunlock, V.E. Tetraspanin CD53 and PKC: partners in B cell signaling

15.45-16.15	Break - Atrium

December 16

Location	Cambrigde 30	Location	Cambridge 32
Session 4	Tumor Immunology	Session 5	Infection & Inflammation
11:00-11:30	**Jurgen Kuball**	**11:00-11:30**	**Frank van de Veerdonk**
Title	Utilizing gdT cells and its receptors for defined immune interventions	Title	"Novel concepts in Infection and Inflammation"
Chair	**Gerty Schreibelt** **Jurgen Kuball**	**Chair**	**Mirjam Heemskerk** **Frank van de Veerdonk**
11:30	Laghmouchi, A In vitro generation of HLA-DP-restricted donor T-cells with hematopoiesis specificity	11:30	Smits, H.H. B cells capture helminth antigens, develop regulatory function and drive Treg cell development
11:45	Cornelissen, L.A.M. Tumor sialylation negatively instructs T cell mediated anti-tumor responses while promoting tumor-associated Tregs	11:45	Yang, Y.Y.M Dynamics of anti-glycan antibody responses in Schistosoma japonicum-infected rhesus macaques studied by schistosome glycan microarray
12:00	Ahrends, T. CD4 T-cell help improves CTL priming, memory programming and anti-tumor efficacy via CD27-costimulation and PD-1-inhibition	12:00	Kuipers, K. Salmonella outer membrane vesicles displaying Pneumococcal surface protein A for broad protection against Streptococcus pneumoniae carriage
12:15	Kunert, A Intra-tumoral production of IL-12 and IL-18 by therapeutic T cells counteracts immune evasion of solid tumors	12:15	Pouw, R.B. Plasma levels of both the main human complement regulator and its proposed antagonist decrease during meningococcal infection

Location	Cambrigde 30	Location	Cambridge 32
Session 9	Tumor Immunology	Session 10	Infection & Inflammation
Chair	**Jeanette Leusen** **Reno Debets**	**Chair**	**Kiki Tesselaar** **Ramon Arens**
14:45	Matlung, H.L. Neutrophils kill antibody-opsonized cancer cells by trogoptosis	14:45	Cleophas, MCP Suppression of monosodium urate crystal-induced cytokine production via inhibition of histone deacetylases 1 and 2: Potential treatment of acute gout
15:00	Verboogen, D.R.J. Regulation of IL-6 secretion in dendritic cells	15:00	Aalst, S. van Adjuvant determines influx-profile, micro milieu and in vivo-antigen-loading of antigen presenting cells (APC) at injection site
15:15	Schetters, S.T.T. Towards glycan-based DC-SIGN-dependent anti-tumor vaccination	15:15	Brouwers, H The omega-6 fatty acid Adrenic acid acts as a pro-resolving mediator
15:30	Winde, CM de Protection against development of B cell lymphoma by tetraspanin CD37	15:30	Asten, SD van A high-content secretome screen uncovers new modifiers of arenavirus infections

Continue on page 38 >>

Wednesday, December 16

Location	Rotonde
Session 11	Autoimmunity & Allergy
Chair	**Esther de Jong** **Edward Knol**
16:15	Peeters, J.G.C. From bench to BET: Bromodomain (BET) inhibition reduces autoimmune disease-associated gene expression
16:30	Lummel, M van "Epitope stealing as mechanism of dominant protection by HLA-DQ6 in type 1 Diabetes
16:45	Huitema, L.F.A. CD40-mediated activation of noncanonical NF-κB signalling in dendritic cells induces AIRE expression, which is impaired in primary sjögren's syndrome
17:00	Vroman, H Activated CD103 conventional DCs dampen house dust mite driven asthma

Location	Boston 9
Session 12	Innate Immunity
Chair	**Leendert Trouw** **Leo Koenderman**
16:15	Bar-Ephraim, J.E. CD62L marks a population of naïve innate lymphoid cells in blood.
16:30	Vlugt, L.E.P.M. van der Farm dust extract increases the epithelial barrier function of human bronchial epithelial cells partly via MyD88 signalling
16:45	Geer, A van de The rare p40-phox deficiency causes a novel type of CGD with impaired bacterial but normal fungal killing capacity
17:00	Lagraauw, HM Stress-induced mast cell activation contributes to atherosclerotic plaque destabilization

Location	Boston 19
Session 13	Adaptive Immunity
Chair	**Mirjam Kool** **Klaas van Gisbergen**
16:15	Baliu-Piqué, M The bone marrow is not the preferential site for long-lived memory T cells
16:30	Zonneveld, M.I. Human breast milk-derived extracellular vesicles reduce CD4 T cell activation
16:45	Reijmers, R.M. Lymph node conduit composition determines efficiency and kinetics of T cell-dependent immunity
17:00	Oja, A.E. Human lung resident memory CD4 T-cells exhibit immediate but tightly regulated effector function

Location	Cambrigde 30
Session 14	Clinical Immunology
Chair	**Irma Joosten** **Arjan Lankester**
16:15-16:45	**Arjan Lankester**
Title	Progress in diagnosis and treatment of severe immune deficiencies
16:45	IJspeert, H Diversity of the naive B cell repertoire in normal in most CVID patients
17:00	Budding, K A CD59 promotor polymorphism in donor lungs correlates with a higher risk for chronic rejection after lung transplantation

Location	Cambridge 32
Session 15	Infection & Inflammation
Chair	**Cecile van Els** **Frank Verreck**
16:15	Jacobino, S.R. Recombinant human IgA antibodies of the monomeric, dimeric and secretory forms protect mice against infection with respiratory viruses
16:30	Sarrami Forooshani, R Activation of Langerhans cells facilitates sexual transmission of Hepatitis C virus
16:45	Ribeiro, CMS HIV-1 uptake by C-type lectin receptors drives human TRIM5a restriction
17:00	Geerdink, RJ Inhibitory collagen receptor LAIR-1 suppresses NET formation by airway neutrophils in RSV bronchiolitis

17:15	Drinks - atrium
17:30-18:30	Poster Walk - Boston 12-14 & Atrium
18:45-19:45	Dinner - Gaudi & Dali Restaurant
	Rotonde
Chair	Reina Mebius
20:00-20:30	**Thesis Award Winner - Mark Gresnigt**
Title	Recognition and cytokine signalling pathways in host defence against *Aspergillus fumigatus*
20:30-21:30	**Van Loghem Lecture by Jacques Neefjes**
Title	Can we understand the immune system? The cell biology of immunology.
21:30-00:30	**Congress Party - DJ Nancy - Sorbonne**

Thursday, December 17

Location	Rotonde
Session 16	Mucosal & other organ specific immunology
9:00-9:30	**Tom Cupedo**
Title	Bones, guts and strong black coffee
Chair	**Andreea Ioan Fascinay**
	Tom Cupedo
09:30	Liu, K Differential distribution and function of human fetal intestinal dendritic cell subsets
09:45	Veenbergen, S Interleukin-10 inhibits human IFNγ and IL-17-producing T helper cells indirectly by controlling antigen-presenting cell function
10:00	Pascutti, M.F. The bone marrow hosts unique memory T cell populations with characteristic expression of chemokine receptors and cytokine production
10:15	Monica, M ILC3 shape homeostasis of the intestinal stem cell niche

Location	Boston 9
Session 17	Chemical Immunology
Chair	**Sjaak Neefjes**
09:00	Albert Heck Using mass spectrometry to investigate immunology
09:45	Hermen Overkleeft Dissecting human proteasome composition and activities using subunit-selective inhibitors and activity-based probes

Location	Boston 19
Session 18	Immune Therapy
9:00-9:30	**Jolanda de Vries**
Title	Visualizing immune responses in cancer patients
Chair	**Astrid van Halteren**
	Jolanda de Vries
09:30	Xiao, Y A progenitor for MF/OC/DC discovered in human bone marrow and cord blood yields dendritic cells with T-cell priming ability
09:45	He, X. Anti-TNFR2 agonist facilitates expansion of human Treg for clinic purposes
10:00	Boross, P A monoclonal antibody against complement C2, as a novel complement inhibitor
10:15	Jahn, L TCR Gene Therapy Targeting the Intracellular Transcription Factor Bob1 for the Treatment of Multiple Myeloma and Other B Cell Malignancies

Location	Cambridge 30
Session 19	Clinical Immunology
Chair	**Martin van Hagen**
	Arjan Lankester
09:00	Chouri, E. MicroRNAs as novel potential biomarkers for the diagnosis of Systemic Sclerosis
09:15	Sonneveld, M.E. Unique glycosylation patterns of IgG alloantibodies against RBC correlate with clinical outcome in hemolytic disease of the fetus or newborn
09:30	Staveren, S van Using FLOOD, a new multidimensional analysis method for flow cytometry data, to identify different cell subsets in disease
09:45	Maracle, C.X. Non-canonical NF-κB signaling in microvessels of atherosclerotic lesions in coronary arteries is associated with inflammatory cell infiltration and myocardial infarction
10:00	Kamburova, E.G. Pretransplant donor specific HLA antibodies in 4770 renal transplant recipients: A preliminary analysis of the PROCARE cohort
10:15	Schie, KAJ van The biological effect of immune complexes in infusion reactions towards infliximab

Location	Cambridge 32
Session 20	Medical Immunology
9:00-9:30	**Ton Langerak**
Title	Chronic lymphocytic leukemia: new developments in prognostication and monitoring
Chair	**Kyra Gelderman**
	Ton Langerak
09:30	Hamann, D ELISA to measure neutralizing capacity of anti-C1-inhibitor antibodies in plasma of angioedema patients
09:45	Jacobs, JFM Quantitative measurement of immunoglobulins and free light chains using mass spectrometry.
10:00	Cor, C.H.J. Early CD4 T-cell reactivity towards mismatched HLA-class II alleles is associated with graft predominance after double umbilical cord blood transplantation
10:15	Schreurs, MWJ Determination of adalimumab, infliximab and etanercept trough levels: an assay comparison

10:30-10:55 Coffee/tea break - Atrium

Thursday, December 17

	Rotonde - Keynote lecture
11:00-11:55	**Jacques van Dongen**
title	"Dissection of immune cell maturation pathways: relevance for diagnostic patient care."
chair	Arjan Lankester
12:00-13:15	**Lunch - atrium**
12:15-13:15	**Poster Walk - Boston 12 - 14 & Atrium**
Location	Rotonde
Session	Bright Sparks
Chair	**Lotte de Winde**
	René van Lier
13:30	Szilagyi, K
	SIRPa is a novel inhibitory receptor on B1 cells controlling the production of natural antibodies and critical for atherosclerosis development
13:45	Sprokholt, JK
	Follicular T helper cell formation induced by Dengue virus through RIG-I like receptor and type I interferon receptor crosstalk
14:00	Salerno, F
	TLR-mediated innate production of IFN-gamma by CD8 T cells is independent of glycolysis
14:15	Bakdash, G
	A novel tumor-associated myeloid cell population inhibits antigen-specific immune responses in cancer patients
	Rotonde - Keynote lecture
14:30-15:25	**Maria Yandanbakhsh**
title	Parasitology in the limelight: what have we learnt about the immune system and beyond
chair	Janneke Samsom
15:30	**"Awards ceremony**
	Poster prize, Bright spark award & Best Medical abstract prize"
16:00	**Closing by Janneke Samsom**

Poster Walks

B

Wednesday, December 16 Time 17:30

topic	**Innate Immunity**
moderator	**Marjolein van Egmond**
Vlist, M van der	CD200R limits TLR responses by reducing PI3K activity
Heineke, M.H.	IgA and IgG Fc receptors on neutrophils: two sides of the same coin?
Schaper, F	High mobility group box-1 (HMGB1) skews macrophage polarization and negatively influences phagocytosis of apoptotic cells
Grievink, H.W.	Stimulation of TLR7/8 results in direct IL-1ß and IL-18 release in human, suggesting a novel pathway for inflammasome activation
Scheenstra, M.R.	Immunomodulatory capacity of porcine antimicrobial peptide PMAP-36
Thielen, AJF	The differential role of complement regulatory proteins investigated using CRISPR/Cas 9 generated human knockout cells
Does, A.M. van der	Cigarette smoke reduces the presence of host defence proteins by compromising bronchial epithelial cell differentiation
Beek, A.E. van	New insights in the physiological characteristics of complement factor H-related proteins 1, 2 and 5
Burm, SM	Inflammasome-mediated activation in the central nervous system is chronic and partially independent of inflammatory caspases.
Burm, SM	The effects of extracellular nucleotides on microglia reflect tissue-specific adaptations of innate immune responses

C

Wednesday, December 16 Time 17:30

topic	**Innate Immunity**
moderator	**Carla Ribeiro**
Lugthart, G	CD69 and CXCR6 identify a distinct population of tissue-resident NK cells in human lymphoid tissues
Sabogal Piñeros, Y. S.	Eosinophils rapidly degrade respiratory viruses and are mildly activated; its relevance in virus-induced loss of asthma control
Hertoghs, Nina	SAMHD1 Degradation Enhances Active Suppression of Dendritic Cell Maturation by HIV-1
Saris, A	Immune modulatory effect of paltelets on dendritic cells
Hovingh, ES	Modulation of human dendritic cell phenotype by the Bordetella pertussis virulence factor pertactin
Worah, K.	Human dendritic cell subset protein signatures reveal differential inflammasome function across subsets
Kraaij, MD	Immunomodulatory effects of chicken cathelicidin CATH-2
Schaarenburg, RA van	The production and secretion of C1q by human mast cells
Zaal, A	RNA-seq analysis reveals that C5a and LPS synergize at the transcriptional level in human dendritic cells
Groot Kormelink, T	Degranulating mast cells abundantly release extracellular vesicles containing mast cell-specific 'soluble' proteases

D

Wednesday, December 16 Time 17:30

topic **Auto-Immunity & Allergy**

moderator **Tanja Nikolic**

Jong, T.D. de	Physiological evidence for diversification of IFNa- and IFNß-mediated response programs in different autoimmune diseases
Wienke, J.	GALECTIN-9 is a robust biomarker for disease activity in juvenile Dermatomyositis and acts as a T cell activator
Garcia Perez, S.	Class 3 Semaphorins Modulate the Invasive Capacity of Rheumatoid Arthritis Fibroblast-Like Synoviocytes
Boltjes, A	CD141 conventional dendritic cells (cDC) are enriched at the site of autoimmune inflammation and display a regulatory phenotype
Kostadinova, A.I.	Prevention of cow's milk protein allergy in vivo by early exposure to beta-lactoglobulin-derived peptides and synbiotics
Kroef, M van der	Histone modifications are associated with aberrant expression of interferon responsive genes in monocytes of systemic sclerosis patients
Nadafi, Reza	The role of lymph node stromal cells in controlling the immune response in rheumatoid arthritis patients
Blokland, SLM	Increased CCL25 (TECK, thymus expressed chemokine) expression and CCR9-expressing T-follicular helper-like Cells in salivary glands of primary Sjögren's syndrome patients

E

Wednesday, December 16 Time 17:30

topic **Infection & Inflammation**

moderator **Pleun Hombrink**

Ekta Lachmandas, EL	Metabolic mechanisms underlying metformin therapy in tuberculosis and diabetes co-morbidity
Brouwers, H	Bioactive lipids in arthritis patients: A novel way to look at chronic inflammation
Jong, S.E. de	Immunological differences between European and African new-borns and young adults
Hilvering, B.	Severe eosinophilic asthma is characterised by high numbers of CRTH2 cells; a new target for treatment?
Wiekmeijer, A	MSCs demonstrate low intra- and inter-donor heterogeneity but show response-specific phenotypic and functional changes in response to pro-inflammatory stimuli
Dijkman, K	Disparate modulation of myeloid DC post-BCG in rhesus populations displaying differential M.tuberculosis susceptibility phenotypes.
Damen, MSMA	A single nucleotide polymorphism in IL-32 results in a higher cytokine production in RA patients.
Ruiter, K de	Effect of three-monthly anthelminthic treatment on the expression of granulocyte activation markers in a placebo controlled trial in Indonesia
Jans, J	Respiratory syncytial virus (RSV) induces IFNAR-mediated activation of human newborn and adult B cells

F

Wednesday, December 16 Time 17:30

topic **Medical Immunology**

moderator **Renate van de Molen**

Kroeze, A.	Unraveling the role of damage-associated molecular patterns (DAMPs) in acute graft-versus-host disease (aGVHD)
Turksma, A.W.	Immunomonitoring; detecting and characterizing antigen specific CD4 T cells
Meek, B	Rheumatoid factor isotypes and anti-Ro52/60 autoantibodies in primary Sjögren syndrome with extraglandular manifestations.
Cornelissen, A.S.	Mesenchymal stromal cells stimulate proliferation and cytokine production of group 3 innate lymphoid cells

G

Wednesday, December 16 Time 17:30

topic **Tumor Immunology**

moderator **Robbert Spaapen**

Doorduijn, E.M.	TAP-independent self-peptides for T-cell based immunotherapy of MHC-IIlow tumors
Beyranvand Nejad, E	T cell costimulatory pathways are required for cisplatin-based chemotherapy
Kroon, P	Concomitant targeting of PD-1 and CD137 improves the efficacy of radiotherapy in a mouse model of human BRAFV600-mutant melanoma
Kunert, A	Intermediate-affinity TCR for MAGE-C2, in combination with epigenetic drug treatment of target cells, yields tumor-selective therapeutic T cells
Nierkens, S	Early CD4 T-cell reconstitution as predictor for viral reactivations and associated complications following HCT in Children.
Dammeijer, F	Combination therapy with a CD40-agonist and dendritic cell immunotherapy has synergistic effects in a murine mesothelioma model
Nicolet, B.P.	Flow-FISH for IFNγ allows simultaneous analysis of mRNA and protein levels, and reveals divergent responses in human T cells
Klaver, Y	Plasma IFN-γ and IL-6 levels correlate with peripheral T-cell numbers in RCC patients treated with CAR T-cells

H

Wednesday, December 16 Time 17:30

topic **Clinical Immunology**

moderator **Virgil Dalm**

Aleva, F.E.	Patients with autosomal-dominant Hyper IgE Syndrome (AD-HIES) show non-transcriptional Signal Transducer and Activator of Transcription 3 (STAT3) activity in platelets.
Vissers, M.	Nasal IgG levels correlate better with respiratory syncytial virus load than plasma IgG levels
Timmermans, WMC	Changes in blood B and T-lymphocyte numbers as early markers for successful TNFa-blocking therapy in patients with sarcoidosis
Han, W.G.H.	Association of Vitamin D receptor polymorphism with susceptibility to symptomatic pertussis
Kemna, M.J.	Seasonal influence on the risk for a relapse at a rise of anti-neutrophil cytoplasmic antibodies in renal vasculitis patients
	Dissecting human proteasome composition and activities using subunit-selective inhibitors and activity-based probes
Theunissen, P	Kinetics and proliferation of regenerating B-cells in children treated for B-cell precursor acute lymphoblastic leukemia
Landman, S	Effect of 5-azacytidine on human preexisting CD4 CD25hiFoxP3 regulatory T cells
Berg, S.P.H. van den	Cytomegalovirus-infections do not impair antibody responses to influenza virus infection in elderly

I

Wednesday, December 16 Time 17:30

topic **Adaptive Immunity**

moderator **José Borghans**

Panagioti, Eleni	Synthetic long peptide vaccination elicits protective polyfunctional CD8 T cell responses against cytomegalovirus infection.
Aalderen, M.C. van	Characterization of Polyomavirus BK-specific CD8 T cells in Renal Transplant Recipients Suffering from viral reactivation.
Heijden, T van der	Interplay between CD4 T cells and lipid laden antigen presenting cells

Pieren, D.K.J.	The effect of age on the in vitro dynamics of murine T-helper and T-regulatory cell activation
Guichelaar, T	Interleukin-2 does not recover helper T-cell activation but extends activation of regulatory T-cells at old age
Brummelman, J	Shift in expression of T-helper signature genes in acellular pertussis vaccine-induced CD4 T cells after addition of a TLR4 ligand
Ioan-Facsinay, A	The fate of oleic in human activated CD4 T cells
Kallemeijn, MJ	Next-generation sequencing reveals novel insights in signaling, proliferation and apoptosis in TCRγδ T-cell large granular lymphocyte proliferations

J

Wednesday, December 16 Time 17:30

topic **Adaptive Immunity**
moderator **Ghaith Bakdash**

Grosserichter-Wagener, C	Shaping of human adaptive immunity by the intestinal microbiome
De Groot, NG	A Rhesus macaque MHC class I molecule with non-classical features has HLA-B*27-like peptide-binding characteristics
Dou, Yingying	A novel T cell model revealed cross-presentation of HBV antigens by human dendritic cells
Grein, S.G. van der	Immunogenic and tolerogenic dendritic cell subsets release phenotypically different extracellular vesicle populations with distinct immune-modulatory properties
Driedonks, T.A.P.	Immunogenic vs tolerogenic dendritic cells release extracellular vesicles that differ in small noncoding RNA content
Ruben, J.M.	Tissue priming of plasmacytoid dendritic cells enhances their phagocytosis and lowers the threshold for subsequent Toll-like receptor 7/9 activation
Hartholt, R.B.	Von Willebrand factor is not internalized by monocyte derived dendritic cells and modulates coagulation factor VIII peptide presentation by HLA-DR
Herwijnen, MJC van	In-depth proteomic analysis of human breast milk-derived extracellular vesicles reveals a distinct proteome with novel immuno-modulatory proteins
Wentink, MWJ	PI3Kd mutations affect both B-cell differentiation and maturation via multiple AKT-dependent pathways.

K

Thursday, December 17 Time 12:15

topic **Innate Immunity**
moderator **Jeroen den Dunnen**

Linden, M.A.M. van der	A Novel Live Cell Imaging Approach to Study Morphology, Kinetics and Mechanisms of Neutrophil Extracellular Trap Release
Van den Bossche, J.	NO production in inflammatory M1 macrophages blunts their mitochondrial function and prevents repolarization to M2
Haar, N.M. ter	The role of monocytes and neutrophils in the inflammatory cascade of systemic onset Juvenile Idiopathic Arthritis
Costes, LMM	Gliadin protein degradation and concomitant IL-27 production by macrophages drive oral tolerance to gluten
Grinsven, E van	A physiologically relevant assay for bacterial killing by neutrophils shows differences between CD16/CD62L subsets
Hiemstra, I.H.	Activated neutrophils suppress T lymphocyte proliferation by the production of ROS and the release of granules, in a CD11b-dependent manner
Meinderts, S.M.	Antibody-mediated phagocytosis of red blood cells by neutrophils in the human spleen
Huizinga, H.G.	Measuring human innate responsiveness to microbial ligands in vitro

L

Thursday, December 17 Time 12:15

topic **Immune Therapy**
moderator **Sandra van Vliet**

Nikolic, T	Tolerogenic dendritic cells induce three functionally distinct subtypes of antigen specific regulatory T-cells
Weiden, J	Activation and proliferation of primary T cells in three-dimensional microenvironments
Kritikou, E.K.	LPA1/3-receptor antagonism reduces atherosclerosis development
Fokkink, WJR	Neonatal Fc receptor promoter gene polymorphisms in relation to intravenous immunoglobulin pharmacokinetics and outcome in the Guillain-Barre syndrome
Eggermont, LJ	Polyisocyanopeptide nanoworms as artificial antigen-presenting cells: towards efficient cancer immunotherapy

M

Thursday, December 17 Time 12:15

topic **Auto-Immunity & Allergy**
moderator **Michiel van der Vlist**

Rijvers, L	Impaired control of the HLA-II pathway in B cells during multiple sclerosis development: implications for CLEC16A
Aleyd, E	IgA immune complexes present in rheumatoid arthritis patients activate neutrophils via FcalphaRI and induce release of neutrophil extracellular traps
Ramos, M.I	Altered CD200-CD200R signalling in sex-biased autoimmune diseases
Kempers, A. C.	Anti-Citrullinated Protein Antibody Immune Complexes Bind to Fc Gamma Receptor I and II on Human Neutrophils
Falkenburg, W.J.J.	Anti-hinge antibodies recognize IgG subclass- and protease-restricted hinge neo-epitopes and can serve as targets for Rheumatoid Factors
Wang, Q	Age determined severity of anti-myeloperoxidase autoantibody mediated glomerulonephritis in mice
Land, J	Pro- and anti-inflammatory B-cell cytokine production in relapsing granulomatosis with polyangiitis patients.
Verheul, M.K.	Anti-Carbamylated protein antibodies: fine-specificity and cross-reactivity

N

Thursday, December 17 Time 12:15

topic **Auto-Immunity & Allergy**
moderator **Jon Laman**

Wit, J de	Small molecule RORγt-inhibitors suppress Th17-responses in inflammatory arthritis and inflammatory bowel disease
Rijt, L.S. van	Subcutaneous immunotherapy for birch pollen allergy decreases recruitment of ILC2s in response to inhaled birch pollen in mice
Dankers, W	1,25(OH)2D3 induces a Tr1-like phenotype in human CCR6 T cells and promotes their migration to an inflammatory environment
Vroman, H	A20 levels in dendritic cells control Th17 driven neutrophilic lung inflammation in severe asthma
Borek, Z. A. B.	LncRNAs show dynamic response to stimulation in human gluten-specific T-cells
Mijnheer, G	Functional specialization of Regulatory T Cells in human autoimmune inflammation
Willemsen, LEM	Regulatory T-cell depletion abolishes the protective effect of dietary galacto-oligosaccharides on eosinophilic airway inflammation in house dust mite-induced asthma

O

Thursday, December 17 Time 12:15

topic	**Mucosal & Other organ specific Immunology**
moderator	**Sharon Veenbergen**
Feyaerts, D	Effect of microbiota on immunoregulation in reproductive tissues
Joosse, ME	"Bacterial flagellin-specific T-cell responses in pediatric inflammatory bowel disease."
Unen, V van	Tissue- and disease-specific signatures identified by mass cytometric analysis of the human mucosal immune system
Hombrink, P	Human CD8$^+$ lung resident memory T-cells: different populations with unique identities exhibit a controlled state of alert
Berge, JCEM ten	Prevalence and clinical impact of anti-retinal antibodies in uveitis
Jong, B.G. de	Dissecting abnormal immunoglobulin responses in destructive periodontal disease

P

Thursday, December 17 Time 12:15

topic	Clinical Immunology
moderator	Michael Eikmans
Budding, K	Retrograde flushing of the pulmonary vein during explantation: lymphocyte composition in the perfusate and impact on outcome after lung transplantation
Kamburova, E.G.	Pretransplant non-HLA antibodies in renal transplant recipients
Roex, MCJ	Multi-Antigen specific T-Cell Products for the Prevention of Viral Infections and Tumor Relapses Early after Allogeneic Stem Cell Transplantation
Budding, K	Serum miRNAs as potential biomarkers for the bronchiolitis obliterans syndrome after lung transplantation
Schreurs, I.A.A.M.	"Increase of Classical monocytes in LoTx patients diagnosed with Bronchiolitis Obliterans Syndrome, a pilot study
Geer, A van de	Characterization of buffy-coat-derived granulocytes for clinical use: a comparison with GCSF/dexamethasone-pretreated donor-derived products.
Bruggeman , C.W.	On the mechanism of IVIg-associated hemolysis by antibodies against A and B blood group antigens in IVIg products
Langelaar, J. van	Imbalances in Th1/Th17 cell subsets are associated with disease development in early multiple sclerosis

Q

Thursday, December 17 Time 12:15

topic	**Adaptive Immunity**
moderator	**Esther Nolte 't Hoen**
Bovenkamp, F.S. van de	Fab glycosylation represents an additional mechanism of antibody diversification that modulates antigen binding
Unger, P.A.	Cytokine requirements for homing of human IgG4 B cells differ from human IgG1 B cells
Dekkers, G	Elucidation of the functional consequences of naturally occurring glycan changes in humoral IgG responses through glyco-engineering
Unger, P.A.	Complement-opsonization enhances particle capture and B cell receptor-mediated phagocytosis by human peripheral blood B cells
Ahmadi, Fatemeh	Impaired B-cell memory from intestinal immune responses on patients with symptomatic IgA deficiency

R

Thursday, December 17 Time 12:15

topic	**Tumor Immunology**
moderator	**Marieke Griffioen**
Vliet, S.J. van	Tumor-associated glycans trigger the C-type lectin MGL on dendritic cells to dampen anti-tumor immunity
Guislain, Aurelie	Relieving post-transcriptional regulation of IFN-g increases anti-tumoral responses by TILs
Kleinovink, EJW	Combination of photodynamic therapy and immunotherapy efficiently eradicates established tumors
Braster, R	Evolutionary conserved anti tumor effects of low fucose antibodies in human and mouse
Benonisson, H	Monoclonal antibody therapy of established mouse melanoma depends on Fc receptors expressed by inflammatory macrophages and NK Cells
Eisden, TTHD	Harnessing melanoma-derived autophagosome formation and dendritic cell-mediated immune responses in melanoma vaccine development.
Duinkerken, S	Branched multiple antigenic peptides for the targeting of skin dendritic cells to treat cancer
Horrevorts, S.K.	Targeting skin-resident antigen-presenting cells for the treatment of cancer.
Dusoswa, S.A.	

S

Thursday, December 17 Time 12:15

topic	**Infection & Inflammation**
moderator	**Elena Pinelli**
Aa, E van der	Chronic hepatitis B virus infection affects BDCA3 dendritic cell frequency and interferon-lambda production
Verdijk, P	Intranasal administration of a new live-attenuated RSV vaccine is safe and effective in the cotton rat model
Nijmeijer, B.M.	Immune activation by HIV-1 enhances sexual transmission of HCV
Vissers, M.	High pneumococcal density correlates with more mucosal inflammation and a reduced respiratory syncytial virus disease severity in infants.
Teijlingen, N. van	A novel ex vivo HIV-1 vaginal transmission model: dysbiotic microbiota increase HIV-1 susceptibility.

A

Posters without presentation

Jansen, MAA	Tolerogenic dendritic cells as a vaccination strategy against Rheumatoid Arthritis
Li, RJE	A Single Molecule Vaccine against Melanoma: A Harmony between C-type Lectin Receptors and Toll-like Receptors
Chen, N	Pathogenic role of neutrophils during metastasis: in vivo imaging of the interactions between metastasizing tumor cells and neutrophils
Erp, E.A. van	The effect of Respiratory Syncytial Virus immune complexes on cytokine and chemokine responses
Baranov, M	Direct recruitment of SWAP70 to phagosomes is required for NOX2 activation
Stairiker, C.J.	Differential Gene Expression Profiles of Influenza Infected and Bystander Type 2 Alveolar Epithelial Cells.
Voskamp, A.L.	Specific allergen immunotherapy: dissecting the role of regulatory B cells
Damoiseaux, J.	Optimization of the ANCA detection algorithm: How do first-, second-, and third-generation ANCA assays relate in daily clinical practice?
Van't Land, B	Immunomodulatory effects of human milk oligosaccharides on influenza vaccination responses in mice

The Art of Saving a Life
The Unknown Health Worker

German painter Thomas Ganter introduces us to the 'everywoman' of health in this arresting portrait. Bringing a sensitive brush and a keen eye for detail, The Unknown Health Worker represents those women and men in every country who do their best to reach families and offer life-saving services including immunization. The portrait is inspired by a photograph of a health worker in eastern Nepal, who was in the midst of climbing up and down steep hillsides in the Himalayas to reach all children with measles, rubella and polio vaccines. She carries the vaccines in the cold box slung on her shoulder. Thomas spent countless hours tending to each detail of this piece, which measures about 5 feet in height.

The painting by Thomas Ganter is part of the 'Art of Saving a Life'-collection commissioned by the Bill & Melinda Gates Foundation. More than 30 world-renowned photographers, painters, sculptors, writers, filmmakers, and musicians tell the stories behind the success and the future promise of immunization. Stories of risk and bravery, passion and dedication of scientists, the love of parents, and the determination of health workers.
Hear, see and feel the tremendous impact of immunization!

www.gatesfoundation.org