Amsterdam UMC
University Medical Centers

Amsterdam Gastroenterology Endocrinology Metabolism

AGEM
Annual report 2020

Colophon

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AGEM directors looking back

2020 was a year like no other for everybody. As the lockdown measures designed to contain the Covid-19 pandemic were imposed from country to country Amsterdam Gastroenterology Endocrinology Metabolism (AGEM) was not spared. Laboratories shut, teaching shifted online, students flew home unable to continue oversees internships, academic friends could no longer travel to the Netherlands. The whole philosophy of sparking scientific inquiry through contact – physical contact - nurtured through the Institute's first three years, was put on hold.

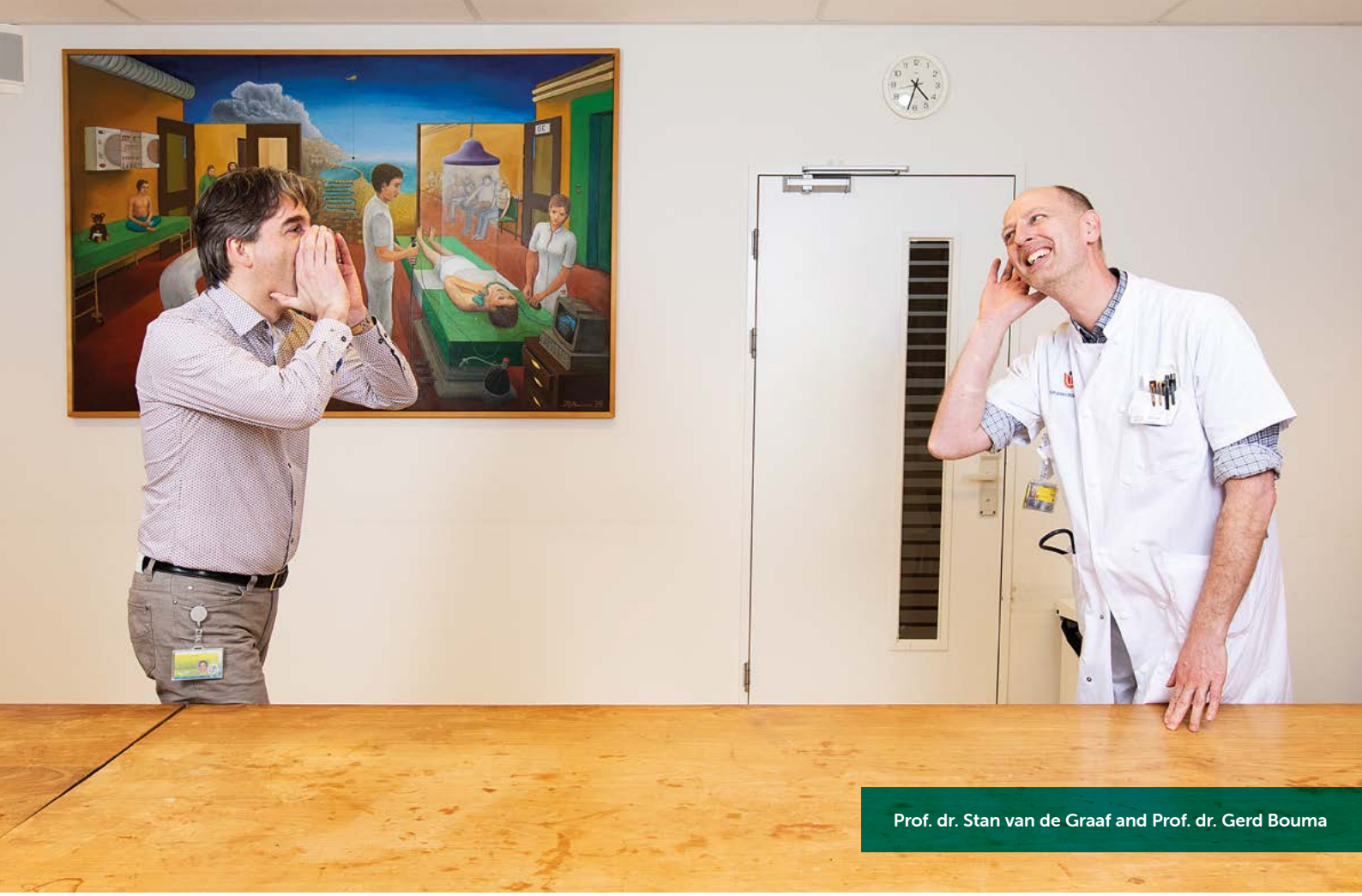
"Yes, it was heart breaking. It felt at some moments like the Institute was falling apart," recalled AGEM co-director Professor Gerd Bouma. His co-director colleague Professor Stan van de Graaf adds that one of the first blows was the cancelling of the annual two-day retreat where, only in 2019, more than 100 PhD students, postdocs and Principal Investigators had got to meet and share ideas. We are rather proud of this event, but a short online option was all that could be saved in 2020. "We simply couldn't have a meeting with 100 people any longer," he said.

Another huge blow to the AGEM was the announcement soon after the beginning of the Covid-19 pandemic of a large cut in clinical and laboratory research. Eventually laboratories almost closed completely. There were exceptions, but these were few. After the first wave of Covid-19 lockdown, the labs began to re-open but were much restricted. It was now possible to do some lab work but offices stayed empty and networking within and outside the institute suffered.

Professor Bouma: "Understandably the policy was to have as few people on Campus as possible, but also colleagues were needed elsewhere to work on the Covid unit. This was a blow to our clinical science. Trials were either put on hold or postponed as we painfully were forced to judge them as 'less essential'." One example was a trial being conducted among patients suffering from irritable bowel syndrome, a very common but not life-threatening condition. Here, patients were being given a fecal transplant where feces from a healthy donor is infused in the patient's intestine. It meant, with pressure on clinical work, it had to be postponed. "This has an impact upon science. Not least upon the PhD candidate who could not finish his research", said Professor Bouma.

And yet, looking back, even the "catastrophe" of 2020 may, in time, be shown to have a positive side. Professor Bouma: "Under pressure everything turns to a liquid. Academia just like many other organizations can be quite bureaucratic. This catastrophe forced us to organize things differently, very simple things, but things which may come to have a huge impact upon the efficiency of our work. It made us realize we have to continually re-think our processes."

Neither co-director is suggesting Covid-19 was good for the Institute but, says Professor Van de Graaf: "It did



Prof. dr. Stan van de Graaf and Prof. dr. Gerd Bouma

allow me the time to think bigger and better." Professor Bouma added: "We lost a lot during the last year, but we also gained things. The flexibility that we witnessed, that it is possible to change things to do things differently, that is something I learned."

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Although the PhD retreat in its very successful format, covering two-days in a residential setting, could not go ahead, it was possible, thinking creatively, to salvage the idea digitally and keep the tradition alive.
A one-afternoon retreat was held online which even managed to retain some social aspects, holding a pub quiz among those attending.

The symposia also moved online with sessions every Thursday for four weeks looking at fatty liver disease. In addition, we (co-)organized two symposia and two Tager Lectures. There was even a benefit to be recognized here because, being online, it was easier to attract keynote speakers. Professor Van de Graaf: "We often invite academics such as from the United States. Now, we no longer had to ask people to spend a lot of time on travel, and have a huge carbon footprint, just for a one-hour presentation. This also meant that we had more choice in who we could invite."

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Since the lockdown in March 2020, teaching generally suffered. Fortunately, the two-week PhD student course developed in 2019, coordinated by five AGEM members, Anje te Velde, Dries Kalsbeek, Sarah Siegelaar, Riekelt Houtkooper and Maarten Soeters, and with more than 40 teachers giving lectures during the course, took place before all teaching had to go online. This AGEM course was specifically developed for PhD students who conduct research in gastroenterology, endocrinology and/or metabolism, in order to include those topics not necessarily within the scope of their own research. It involves broadening perspectives through a whole program of lectures on diverse subjects and interaction among the participants. The series of physical daily lectures was first launched on 13 January 2020 with subjects ranging from the pathophysiology of oesophagal diseases from clinic to cell biology, to imaging techniques for insulin resistance, and from epigenetics, to macrophage metabolism. During the two weeks of the course, in small groups of 3 or 4 persons, the PhD students wrote a multidisciplinary grant proposal that was, well-prepared by the pitch workshop given in the first week, pitched to all participants on the last day of the course. In the course of the year it became clear that the 2021 course, would have to move online.

The extraordinary circumstances of 2020 also affected the awarding of AGEM grants and fellowships. The International Student Fellowships program was severely affected. Students who went abroad to study at the start of the year were forced to return home, even from countries such as the US or Sweden which did not yet have restrictions. Dutch universities wanted their students back so many internships were halted. Later on as restrictions eased demand for these grants remained dramatically low as students were either unaware or unwilling to take up the fellowship. As also internships within the Netherlands were affected, this may have worrying consequences for the talent pool we recruit PhD students from, as these may have had less laboratory experience than those in the past.

In 2020 we had the Consensus Grants, which were very vulnerable to the exigencies of 2020. Professor Van de Graaf explained these were an interesting idea in which experts could be brought to the Netherlands from across the world to discuss a clinical problem. Agreement could then be reached and a consensus paper written defining the new disease and proposing a good therapy and strategy for clinical research. Van de Graaf: “the problem is, it involves travelling. We managed to award two of these grants but these were the ones heavily affected by Covid.”

The Talent Development and the Innovation grants however continued with researchers applying for grants and launching projects. With labs closed, progress was often slow but the AGEM helped by giving extensions. In addition both co-directors were very proud of results related to grants awarded in previous years. These included Michel van Weeghel’s report on tracer-based metabolomics to analyze metabolic flexibility and dynamics, which had benefitted from an Innovation Grant in 2018. And too, the work of Maartje Singendonk into Peroral Endoscopic Myotomy (POEM) as opposed to Endoscopic Balloon Dilation EBD for the treatment of idiopathic achalasia in children, which was supported by a Talent Development Grant in 2018.

In 2020 actually extra grants were being awarded to boost clinical research. These grants included those awarded for the work of Hans Waterham, Ronald Wanders, Frits Wijburg, and Clara van Karnebeek into a rare genetic disease Gyrate Atrophy (GA) of the choroid and retina - an autosomal recessive metabolic disorder caused by a deficiency of ornithine δ-aminotransferase. Also benefitting from these grants was the work of Jeroen den Dunnen, Riekelt Houtkooper, Marjolein van Egmond, and Manon Wildenberg which investigated whether C-reactive protein is not only a marker, but also a cause of inflammation in Crohn’s Disease.

A further 10 smaller clinical research grants of €15,000 were awarded too. Professor Van de Graaf explained: “This was all seeding money to enable people to speed up their research, to give it a boost, and be more competitive.”

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There were several aspects of the work of the AGEM where 2020 was business as usual or even better. The official name change from AG&M to AGEM, with its recognition of the importance of endocrinology, went ahead in April with the launch of an animation which was reported in the media. Scientific publications too was an area in which work continued. Professor Van de Graaf: "During the time people were in lockdown, one had the opportunity to write. So I would not be surprised if our total output increased not reduced this year."

Looking back over an extremely challenging year, Professors Bouma and Van de Graaf speak of dramatic changes, ways of working that were not thought possible, tremendous challenges, but also the realization that it is possible to adapt, to be flexible in response to unimaginable circumstances. Professor Bouma: "I'm sitting here staring out of the window of my spare bedroom exactly a year since it all started. Before March 2020 it was supposed to be impossible to work from home. I just went into work five days a week. That's now changed and we have online working for scientists." Bouma recently took part in an online international symposium comprising speakers and participants from 30 different countries from right across the world. "Until one year ago that would not have been imaginable, you would not have attempted an online symposium. So that has changed dramatically."

He recognizes that symposia are not just about the transmission of knowledge but also the crucial role of networking which cannot happen so easily online. However, the advantages are clear it is easier to participate, there is no travelling, no sitting around losing time in hotels. "You just plug in, spend two hours in a symposium and you are updated. I can't imagine we will go back to exactly how it was before. I think there will be hybrid forms in future, there will definitely be physical symposia just for networking, coming together, brainstorming, but I think we will continue to host online symposia and a whole range of other meetings.

He sees the same as true for patient care which has been transformed by the necessity of Covid distancing. "We have had to continually re-think our processes, me going to the hospital in the morning, the patient coming to the clinic, the patient being sent for tests, this all takes time and there was an environmental impact as everyone had to travel. Now we have learnt that in a significant proportion of cases you can also do it by telephone or video conferencing and that works pretty well. It may not be perfect yet, but it is evolving and will continue to evolve. It forces us to look at ourselves in the mirror and question our processes. Of course Covid-19 was a tragedy, it is a tragedy, it is terrible but there are also positive things that have come out of it too."

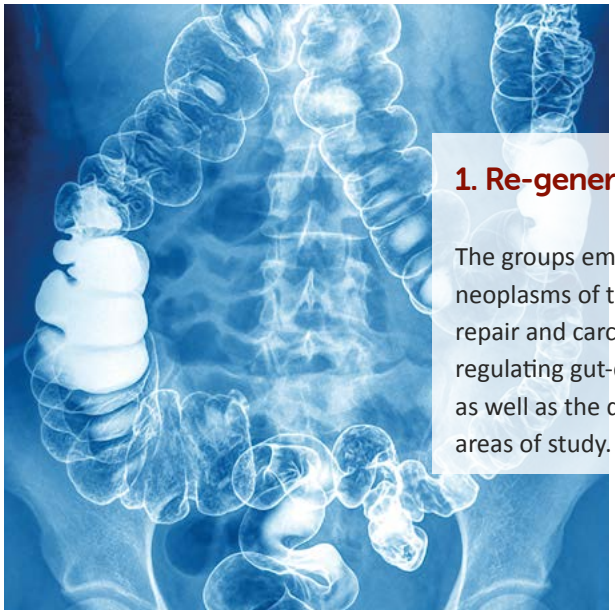
So while both co-directors accept the damage that has been done, there is a positive side too to be taken from this experience. Professor Bouma: "We still managed to organize meetings with some sense of common being, of acting together in a social way. One year ago would have seen as impossible. I hope we can remember that and remain flexible under so-called normal conditions. If everyone agrees it would be better to change we should not be held back by doing it how it always was done. That is one of the fascinating things I have seen happening over the last year."

"We still managed to organize meetings with some sense of common being, of acting together in a social way. One year ago would have seen as impossible. I hope we can remember that and remain flexible under so-called normal conditions."

Professor Van de Graaf agrees: "A year ago we could not even attempt a digital meeting such as the two-weeks' training course. The fact that that this is feasible surprised me." But he also valued the opportunity to take stock. "People outside of academia may think we have all the time in the world to think, to reflect, but this is not the case, we are often interrupted by other tasks. At home, I don't get interrupted by so many phone calls, by problems to solve, so Covid did allow me to step back a little bit and think things through bigger and better. That has been an advantage of the last year. That said, I am really looking forward to a situation with colleagues together again in the same room, to have fun and get inspired".

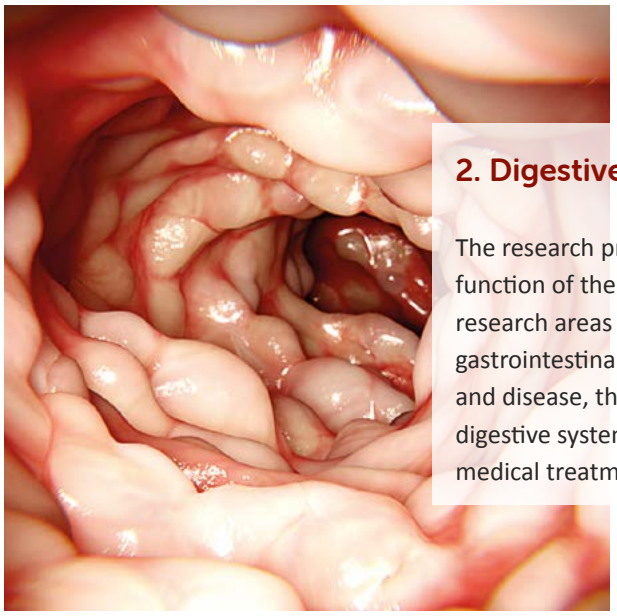
AGEM Research Programs

Based on an inventory of the strengths of the research in gastroenterology, endocrinology and metabolism conducted at the Amsterdam UMC, the following four research programs have been specified. Our aim is to stimulate research in these 4 themes, and also multidisciplinary research that bridges them.



1. Re-generation and neoplasms of the digestive system

The groups embedded in the research program “Re-generation and neoplasms of the digestive system” focus on the postnatal development, repair and carcinogenesis of the digestive tract. The mechanisms regulating gut-development, post-surgical healing, and tumorigenesis, as well as the development of novel treatment strategies are important areas of study.

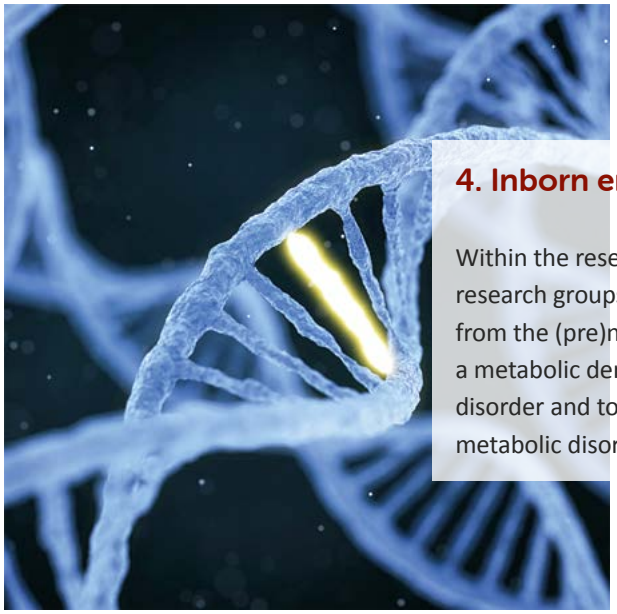


2. Digestive function and pathology

The research program “Digestive function and pathology” focusses on the function of the human digestive system in health and disease. The main research areas are: (patho)physiology of the digestive tract, including gastrointestinal motility, the role of the microbiome in digestive health and disease, the mechanism of action of therapies of diseases of the digestive system, nutrition, and the development of novel surgical and medical treatment strategies.

3. Endocrinology, metabolism and nutrition

In the research program “Endocrinology, metabolism and nutrition”, the effect of lifestyle, diet and malnutrition on metabolism and hormonal regulation plays a central role. The ultimate aim of this research program is to improve metabolic health of patients with metabolic and endocrine pathologies.



4. Inborn errors of metabolism

Within the research program of “Inborn errors of metabolism” the research groups investigate rare inborn errors of metabolism manifesting from the (pre)neonatal period into adulthood. To unravel the cause of a metabolic derangement in patients suspected of a genetic metabolic disorder and to develop and improve treatment for patients with a genetic metabolic disorder are the main areas of focus in this research program.

The AGEM Research Board 2020

The AGEM research board consists of two AGEM directors, seven members (at least one representative from each of the four AGEM research programs), the AGEM policy officer and the AGEM secretary. The research board meets approximately once per two months and discusses the AGEM policy.

The AGEM research board 2020

New to the AGEM Research Board

Hilde Herrema

Since September 2020, Hilde Herrema, joined the AGEM research board. Hilde is assistant professor and PI at the department of Experimental Vascular Medicine. She studies development of cardiometabolic diseases with a particular interest in the gut microbiome.

What I want to achieve with the AGEM research institute…

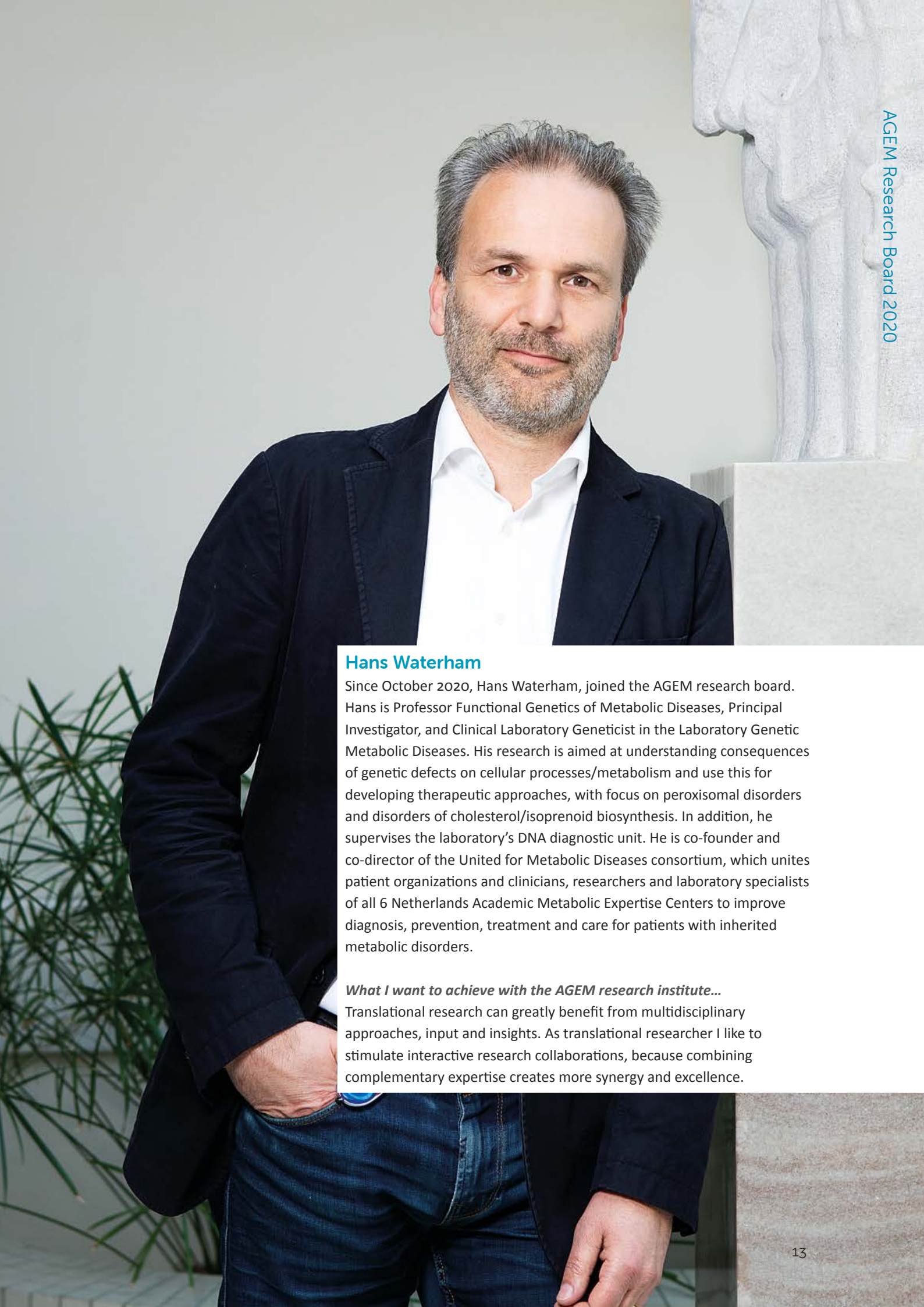
In addition to bridging clinical and basic scientists, AGEM can enable interactions between senior and junior scientists and contribute to societal and industry outreach. This will enhance research opportunities and academic excellence while disseminating and creating knowledge.

Richard IJzerman

Since April 2020, Richard IJzerman joined the AGEM research board. Richard is an internist-endocrinologist at the Amsterdam UMC, location VUmc. He studies the influence of the hormonal and microbiota gut-brain axis on the regulation of food intake and the development of obesity. In addition, one of his other main tasks concerns clinical assessments and scientific advice for the Medicines Evaluation Board (CBG) / European Medicines Agency (EMA).

What I want to achieve with the AGEM research institute…

Last year, the E for endocrinology has been added to the name of the research institute. This was an important step, but now this needs to be put into practice. As a endocrine researcher, I consider it important to improve the involvement of clinical and preclinical endocrine researchers from both locations. In addition, I hope we will be able to organize physical meetings for all AGEM researchers in the near future!



Hans Waterham

Since October 2020, Hans Waterham, joined the AGEM research board. Hans is Professor Functional Genetics of Metabolic Diseases, Principal Investigator, and Clinical Laboratory Geneticist in the Laboratory Genetic Metabolic Diseases. His research is aimed at understanding consequences of genetic defects on cellular processes/metabolism and use this for developing therapeutic approaches, with focus on peroxisomal disorders and disorders of cholesterol/isoprenoid biosynthesis. In addition, he supervises the laboratory's DNA diagnostic unit. He is co-founder and co-director of the United for Metabolic Diseases consortium, which unites patient organizations and clinicians, researchers and laboratory specialists of all 6 Netherlands Academic Metabolic Expertise Centers to improve diagnosis, prevention, treatment and care for patients with inherited metabolic disorders.

What I want to achieve with the AGEM research institute…

Translational research can greatly benefit from multidisciplinary approaches, input and insights. As translational researcher I like to stimulate interactive research collaborations, because combining complementary expertise creates more synergy and excellence.

AGEM directors

Prof. dr. Gerd Bouma

Department of Gastroenterology and Hepatology

Professor of Gastroenterology and Hepatology
Specialization: Gastroenterology
Research subject: Mucosal immunology

Prof. dr. Stan van de Graaf

Tytgat Institute for Liver and Intestinal Research & Department of Gastroenterology and Hepatology

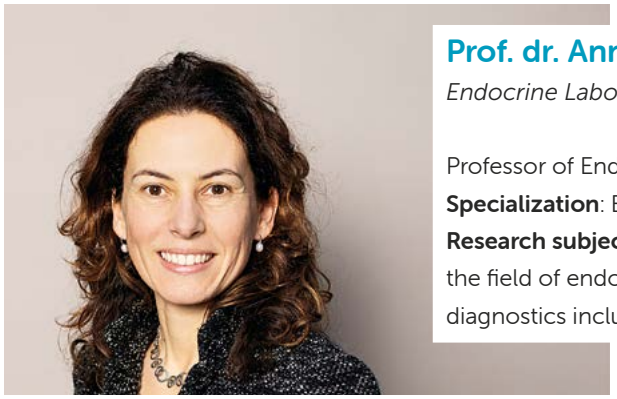
Professor of Experimental Hepatology and Metabolism
Principal investigator at Tytgat Institute for Liver and Intestinal Research
Specialization: Biochemistry/Physiology
Research subject: Targeting metabolite dynamics to treat metabolic and liver diseases

AGEM Research Board members

Dr. Anje te Velde

Tytgat Institute for Liver and Intestinal Research & Department of Gastroenterology and Hepatology

Principal investigator at Tytgat Institute for Liver and Intestinal Research
Specialization: Immunology
Research subject: Study of chronic intestinal inflammation (inflammatory bowel disease, IBD): pathophysiology and therapeutic interventions



Prof. dr. Annemieke Heijboer

Endocrine Laboratory & Department of Clinical Chemistry

Professor of Endocrine Laboratory Medicine
Specialization: Endocrinology/Clinical Chemistry
Research subject: To study physiology and pathophysiology within the field of endocrinology and to make the translation into endocrine diagnostics including the use of biomarkers

Prof. dr. Marc Besselink

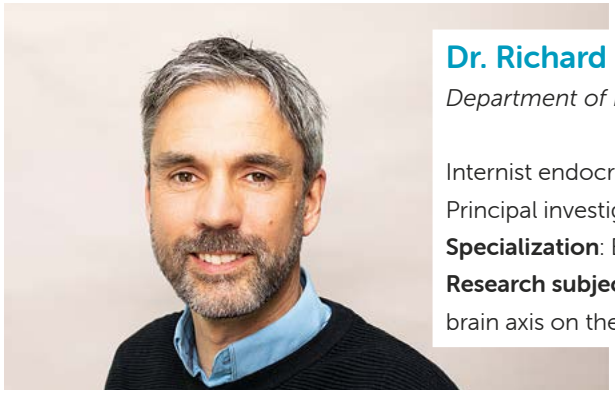
Department of Surgery

Professor of Pancreatic and Hepatobiliary (HPB) surgery
Specialization: Pancreatitis, pancreatic cancer, pancreatic cysts, HPB surgery, robotic and laparoscopic HPB surgery
Research subject: Improving clinical treatment and patient outcomes for pancreatitis, pancreatic cancer, pancreatic cysts

Prof. dr. Annet Bosch

Department of Pediatric Metabolic Diseases

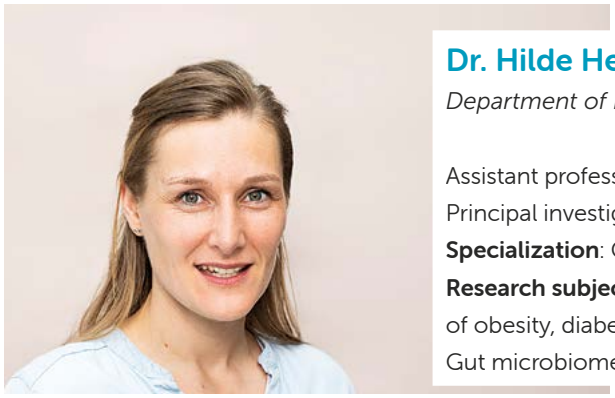
Professor of Pediatrics, Metabolic Diseases
Specialization: Metabolic Diseases
Research subject: Diagnosis and Treatment of Galactosemia, Phenylketonuria, Riboflavin Transporter Deficiencies



Dr. Richard IJzerman

Department of Endocrinology

Internist endocrinologist
Principal investigator at the department of endocrinology
Specialization: Endocrinology, diabetes
Research subject: The influence of the hormonal and microbiota gut-brain axis on the regulation of food intake and the development of obesity



Dr. Hilde Herrema

Department of Experimental Vascular Medicine

Assistant professor
Principal investigator at the department of Experimental Vascular Medicine
Specialization: Cardiometabolic disease
Research subject: Translational and integrative research into development of obesity, diabetes and fatty liver disease
Gut microbiome

Prof. dr. Hans Waterham

Laboratory Genetic Metabolic Diseases

Professor Functional Genetics of Metabolic Diseases
Principal investigator at Laboratory Genetic Metabolic Diseases
Clinical Laboratory Geneticist (VKGL and EBMG)
Specialization: Molecular biology/Genetics/Metabolic disorders
Research subject: Functional genetics of metabolic disorders in a broad sense with special focus on inherited defects in peroxisome biogenesis/function and cholesterol/isoprenoid biosynthesis

AGEM office

Dr. Eva Dirkx-Beuling

Amsterdam Gastroenterology Endocrinology Metabolism (AGEM)

Policy officer AGEM

PhD-thesis: GATA transcription factors and the regulation of intestinal development, differentiation and function

Yvonne van Beusekom

Secretary AGEM

January 2020 – July 2020

Linda van den Noord

Secretary AGEM

October 2020 – present

AGEM Science Impressions 2020

To give an impression of the research conducted in the AGEM research institute, eight couples of young investigators and their supervisors were invited to present the research projects they worked on in 2020.

A gene heavily methylated with age appears crucial in metabolism - meet FHL2!

Carlie de Vries and Maria Clemente

In crime scene investigation it is important to determine the age of an individual based on a single spot of body fluid. When DNA is present in such a spot this is relatively simple, because there are specific DNA-methylation marks that increase with age. One of the genes that gets heavily methylated when we grow old encodes 'Four and a Half LIM-domain 2' (FHL2). The expression of FHL2 also increases with aging, which has been demonstrated in multiple tissues among which the pancreatic islets of Langerhans. These islets comprise beta-cells that release insulin when glucose levels rise in the circulation upon intake of carbohydrates. In type 2 diabetes, which is a typical disease of the elderly and obesity, insulin plays a critical role. Based on this information, we asked ourselves whether FHL2 may actually be involved in metabolism, diabetes and obesity. For these studies we made use of publicly available human expression datasets and FHL2-deficient mice.

It has been a long and winding road to unveil the functional connection between FHL2 and metabolism, but with a lot of help from metabolic researchers within our Institute and from elsewhere we managed. We found that human FHL2 expression associates with body-mass-index and HbA1c; the latter is an important marker to measure whether an individual has diabetes. Next, we challenged FHL2-deficient mice with a high dose of glucose and demonstrated that these mice clear glucose faster than their wild-type littermates. At baseline the concentration of insulin is the same but FHL2-deficient mice release more insulin in the circulation in response to such a glucose dose. At that point we were lucky because PhD candidate Torsten Scheithauer from the group of Daniel van Raalte was already skilled in isolating islets from mouse pancreas and he taught PhD candidate Jayron Habibe the secrets of this technique. This allowed us to very efficiently assess that also isolated islets express more insulin under high glucose conditions when FHL2 is deficient. But what is the underlying mechanism? Working with cultured beta-cell like cell lines it turns out that FHL2 modulates a number of intracellular signaling pathways in such a way that it inhibits the expression of specific genes thereby obstructing insulin release from the cells.

To assess the role of FHL2 in obesity, FHL2-deficient mice were placed on a high-fat diet. In the absence of FHL2 mice eat the same as wild-type mice, but they move less and gain less weight. What is going on in these mice? Coming to a detailed understanding of this interesting phenotype turned out to be a rather tough project and it took several years of the PhD trajectory of Maria Clemente. Maria originally comes from Madrid, she did her Master in the UK and joined the group in 2017 to tackle FHL2 in obesity. It turns out

Maria Clemente and Carlie de Vries

that FHL2-deficiency in mice mildly affects multiple, metabolic tissues altogether generating a favorable metabolism. FHL2-deficient mice generate more heat as revealed by experiments in metabolic cages at our mouse facility. This may be explained by enhanced activity of their brown fat; indeed, there is a trend towards enhanced expression of the uncoupling protein UCP1. In collaboration with Patrick Rensen from Leiden, we demonstrated that in line with this trend brown adipose tissue changes its substrate preference upon FHL2 deficiency. Also, the white adipose tissue is different in FHL2-deficient mice in such a way that it expresses genes that are typical for brown adipose tissue; the so called 'browning' of white adipose tissue. Based on all our data, Maria concluded that low FHL2 expression is beneficial in diabetes and obesity.

AGEM had a serious role in Maria's scientific life, providing excellent PhD candidate retreats where she got to know many other scientists interested in metabolism, diabetes and obesity. These were great opportunities to learn from each other's project and hear about innovative techniques and available equipment. She was also involved in organizing one of the retreats, which was great fun. Unfortunately, there was no live retreat last year, so we missed the interaction with fellow scientists during the scientific sessions, but also in the workshops, at the party and the early morning boot camp session.

We hope to use our newly gained knowledge to understand why some individuals are 'healthy obese' and do not develop diabetes whereas other obese humans become sick. Our data suggest that high FHL2 expression is a marker for those who are at risk to develop diabetes. Ideally, we can treat the growing number of people with obesity-induced type 2 diabetes by inhibiting FHL2 expression specifically in adipose tissue. For sure, Maria will write everything we learned on FHL2 in metabolism and all her dreams on application of this knowledge in clinical practice in her thesis, which she will defend this year.

Neurons that Fight (or Flight) Inflammation

Wouter de Jonge and Anne ten Hove

The intestinal mucosa is home to an immune cell network that delicately needs to balance responses to microbiota in the gut lumen. Some 90,000 people (in the Netherlands only) suffer from Inflammatory Bowel Diseases (IBD), a chronic inflammation of the intestinal mucosa (colitis) in which immune cells get viciously activated by gut microbiota for unknown reason. It is a complex disease that is not always easily treated. Despite decades of research and investments in treatment, no cure for IBD exists thus far. Current therapies only focus on suppressing the inflammation, and are only partially effective, often leading to further extra intestinal manifestations or fistulae, and in the end, surgical removal of bowel which is highly debilitating.

Several projects conducted in the Tytgat Institute are aimed at gaining a better understanding of cellular interactions in the intestinal mucosa. We feel that each IBD patient is different and thus we also aim to tailor therapies to an individual level to enhance their effectiveness before start of therapeutic route. Together with prof. dr. Geert D'Haens, we developed several research projects that explore intestinal inflammation at single-cell level, focusing on epigenetic regulation of tissue cells in patient biopsies.

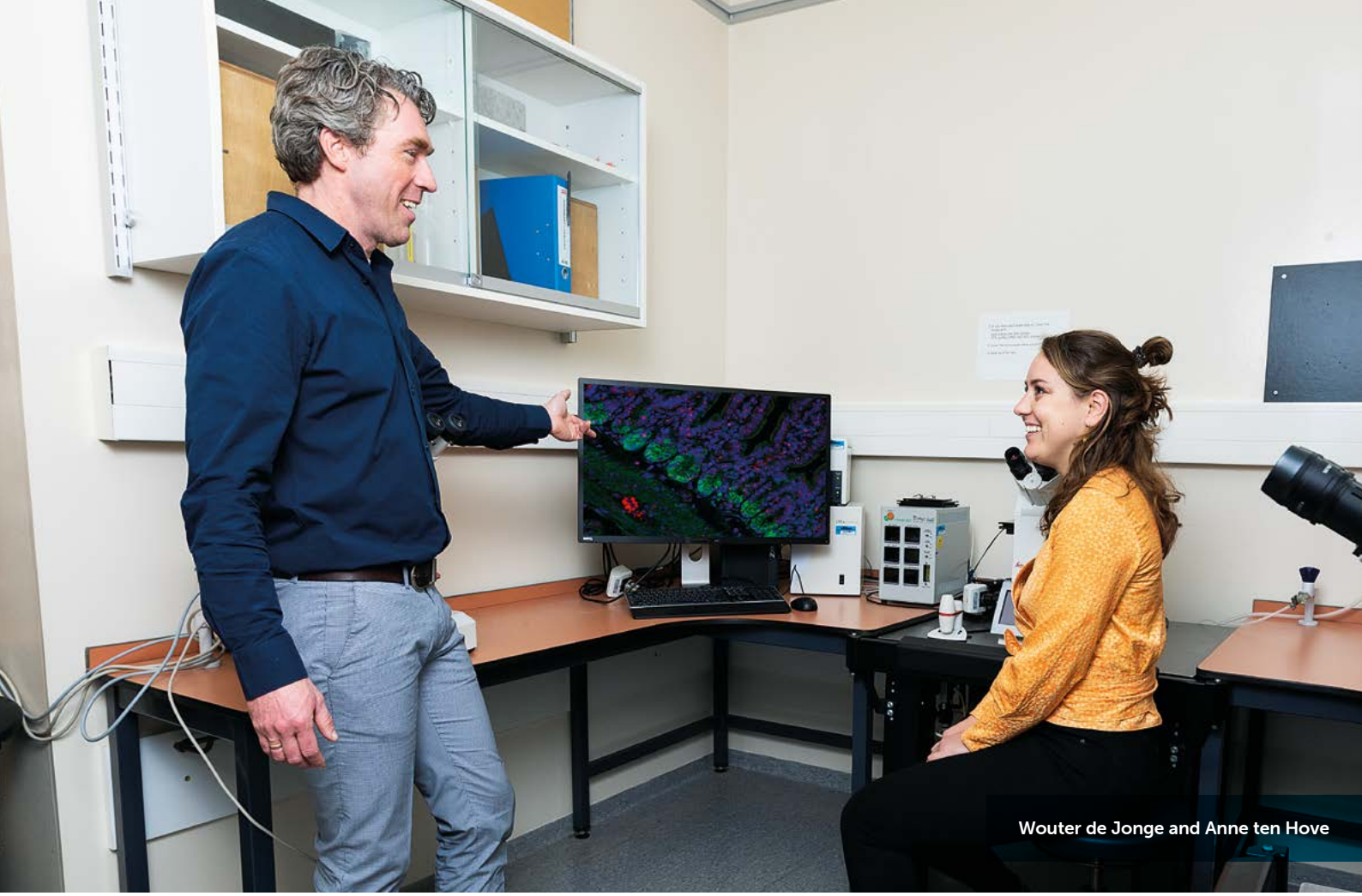
Maybe one of the more unconventional approaches for IBD treatment is based on recent recognition of the nervous system as an integrated regulator of inflammatory processes. The magnitude of an inflammatory response is crucial as insufficient responses can lead to infection and cancer, while excessive responses cause morbidity and mortality. The regulation of this reaction has long been viewed as autonomous, mediated by interactions between immune cells in a largely self-regulated system. However, we now have substantial evidence that in this balance, the nervous system has an active regulatory function. In 1929 the neurotransmitter acetylcholine was firstly isolated from the spleen, a typical primary lymphoid organ. This may seem surprising to the lay observer, but by now we have come to appreciate that all lymphoid organs, including bone marrow, thymus, and lymph nodes, receive neuronal input at a level far more advanced than originally documented. We are beginning to identify how a broad range of body functions can be influenced by interfacing with the nervous system. This extends from the control of appetite and blood pressure, to the production of destructive cytokines in patients with IBD and rheumatoid arthritis.

Anne ten Hove's project on innervation of the intestinal crypt stem cells

Anne started in a MD-PhD combined trajectory in 2015. The area of the neuronal innervation of the intestinal crypt immediately caught her eye. This enigmatic area of research is largely overlooked by many in the past. Autonomic neurons of the enteric and sympathetic nervous system innervating the intestinal crypt can be an underestimated factor in mucosal healing through the effect on intestinal epithelial cell growth. This is, as in intestinal inflammatory conditions, autonomic neuronal innervation and its coding is dramatically diminished. The finding of this loss is important since the autonomic nervous system was introduced as a mediating factor in intestinal epithelial cell growth.

Her ultimate research aim is to reduce chronic colitis by the targeted intervention in neuronal signaling to the intestinal mucosa and the spleen. For this we can make use of unique neural implantation devices we developed with the help of several partners such as Cortec Corporation and Galvani Bioelectronics, a spin-off company of GSK. With their technical and financial help, we identified sympathetic nerves that are surprisingly potent in regulating severity of intestinal inflammation.

In previous studies we already showed that by using bioelectronic medicine we can target specific nerve bundles improving disease in models of intestinal failure and inflammation. Also, preliminary data from clinical trials has shown the potential of nerve stimulation in reducing inflammation in human as it being safe and effective.



Wouter de Jonge and Anne ten Hove

Yet, Anne's current work is more fundamental; it is based on single-cell expression profiling in organoids of mouse and human intestine to find receptors for neurotransmitters on stem cells. She has identified adrenergic receptor α2A as unique intestinal epithelial adrenergic receptor, expressed in both Paneth cells and stem cells (see figure below). Activation of this adrenergic receptor affects a variety of epithelial functions, including proliferation, host response, and effects on the microbiota. With the bioelectronics technology in modulating innervation patterns of the intestinal crypt, she is currently studying the role of innervation in epithelial cell growth and differentiation, in mice and men. Anne is studying this in relation to colitis, but also to anastomotic leaks, seen in approximately 15% of colorectal surgeries. Here, we closely work with pediatric surgeon dr. Joep Derikx and his team.

From a more clinical perspective, together with Catherina Hospital Eindhoven (surgeon dr. Misha Luyer), we have applied specific neuronal stimulation in several human settings including abdominal surgeries, to study how innate and adaptive immune responses are modulated by neuronal signals at the level of the spleen lymph nodes and gut lymphoid organs in human. These results are tremendously exciting, and we really hope to deliver more understanding of the mechanism by which neuronal innervation could stimulate epithelial cells function, and mucosal healing, a critical end point of IBD remission.

Thyroid hormone: a key player in innate immune cell function.

Anita Boelen and Anne van der Spek
Anita Boelen, PhD - Endocrine laboratory, Department of Clinical Chemistry
Anne van der Spek, MD PhD - Endocrinology & Metabolism, Department of Internal Medicine

Anita Boelen is a professor of Thyroid Hormone Metabolism at the Endocrine Laboratory. Her research is focused on thyroid hormone metabolism and action during illness and inflammation. She is in charge of the regional Dutch Neonatal Screening laboratory, situated in the Endocrine Laboratory and a former member of the board of the European Thyroid Association (ETA). Historically Amsterdam UMC has a longstanding tradition in both academic thyroid patient care as well as basic thyroid research. Following the merger of the endocrine laboratories of the VUmc and AMC, the novel Amsterdam Center of Endocrinology at the Meibergdreef has been set up so that clinicians, laboratory specialists and basic scientists, from different departments, work closely together in the same location, creating a unique environment for translational research.

Thyroid hormones (TH) play a key role in the metabolism and function of an ever-expanding range of tissue and cell types. Circulating TH concentrations in the blood do not necessarily reflect intracellular TH bioavailability. This is tightly regulated by TH transporters, TH receptors, and enzymes that convert TH into active or inactive metabolites, the deiodinases. Due to this system, effective TH concentrations can differ significantly between, and even within, tissues. This tight regulation of the cell-specific bioavailability of TH is crucial for optimal cellular metabolism and function.

In recent years our work has focussed on the role of TH in innate immune cells. The link between the endocrine and immune system is well established. Profound changes occur in the regulation of TH bioavailability during illness and inflammation. These changes are collectively known as non-thyroidal illness syndrome (NTIS) and include disruption of the classic endocrine negative feedback loop that governs serum TH concentrations and changes in cellular TH metabolism thereby affecting cellular TH bioavailability. NTIS is characterized by low serum TH concentrations which correlate with disease severity and outcome in a broad range of illnesses from sepsis to stroke and is part of the acute phase response during illness. Work from our group has demonstrated that the function of innate immune cells is highly responsive to changes in cellular TH metabolism as occurs during NTIS.

Anne van der Spek performed her PhD in the Endocrine Laboratory, supervised by Anita Boelen and has continued her work there as a postdoc after defending her thesis in 2018. During her PhD she focussed on the role of TH in neutrophils and macrophages. Neutrophils and macrophages are highly specialized cells of the innate immune system that are capable of identifying and killing pathogens, initiating an inflammatory response and recruiting other immune cells to the site of inflammation. While neutrophils are generally very pro-inflammatory cells, macrophages are capable of a wide range of phenotypes from pro-inflammatory to more immunomodulatory. Anne's thesis cemented the idea of innate immune cells as TH target cells, by demonstrating an important role for intracellular TH metabolism in neutrophil and macrophage function. In neutrophils a lack of the TH inactivating type 3 deiodinase (D3), meaning the cells are unable to degrade cellular TH, results in impaired reactive oxygen species generation by NADPH-oxidase and reduced neutrophil migration to the site of infection in vivo. D3KO animals also demonstrate reduced bacterial clearance and higher mortality during bacterial infection. In macrophages changes in TH action also affect cellular phenotype. High intracellular TH levels have a pro-inflammatory effect whereas reduced intracellular TH action skews the cells to a more anti-inflammatory phenotype including impaired phagocytosis and enhanced expression of markers associated with immunomodulatory (M2) functions.

Anita Boelen and Anne van der Spek

Our current work further explores the effects of TH in the regulation of macrophage function and phenotype. We are currently studying macrophage function and phenotype in cells derived from patients with resistance to TH due to a mutation in thyroid hormone receptor α (RTHα) in collaboration with Prof. Chatterjee at the University of Cambridge. RTHα is a genetic disorder resulting in severe hypothyroidism in tissues in which TRα is expressed (including the heart, central nervous system and myeloid cells such as erythrocytes and macrophages).

Our work will make clear whether disturbances in TH availability lead to disturbances in macrophage function and what the consequences are for innate immunity in general. Improved understanding of macrophage function will be valuable to researchers and physicians, as it will ultimately contribute to new and improved treatment strategies for bacterial infections and diseases that are associated with macrophage dysfunction such as cancer, atherosclerosis and diabetes. Thyroid disease has a high prevalence in the general population and is associated with adverse metabolic effects. The role of TH in macrophages could be an important part of the puzzle in understanding the immunological, metabolic and cardiovascular effects of thyroid disease.

Non-alcoholic fatty liver disease: a translational research program in Amsterdam UMC for an ever more prevalent cardiometabolic liver disease

Onno Holleboom and Anne-Marieke van Dijk

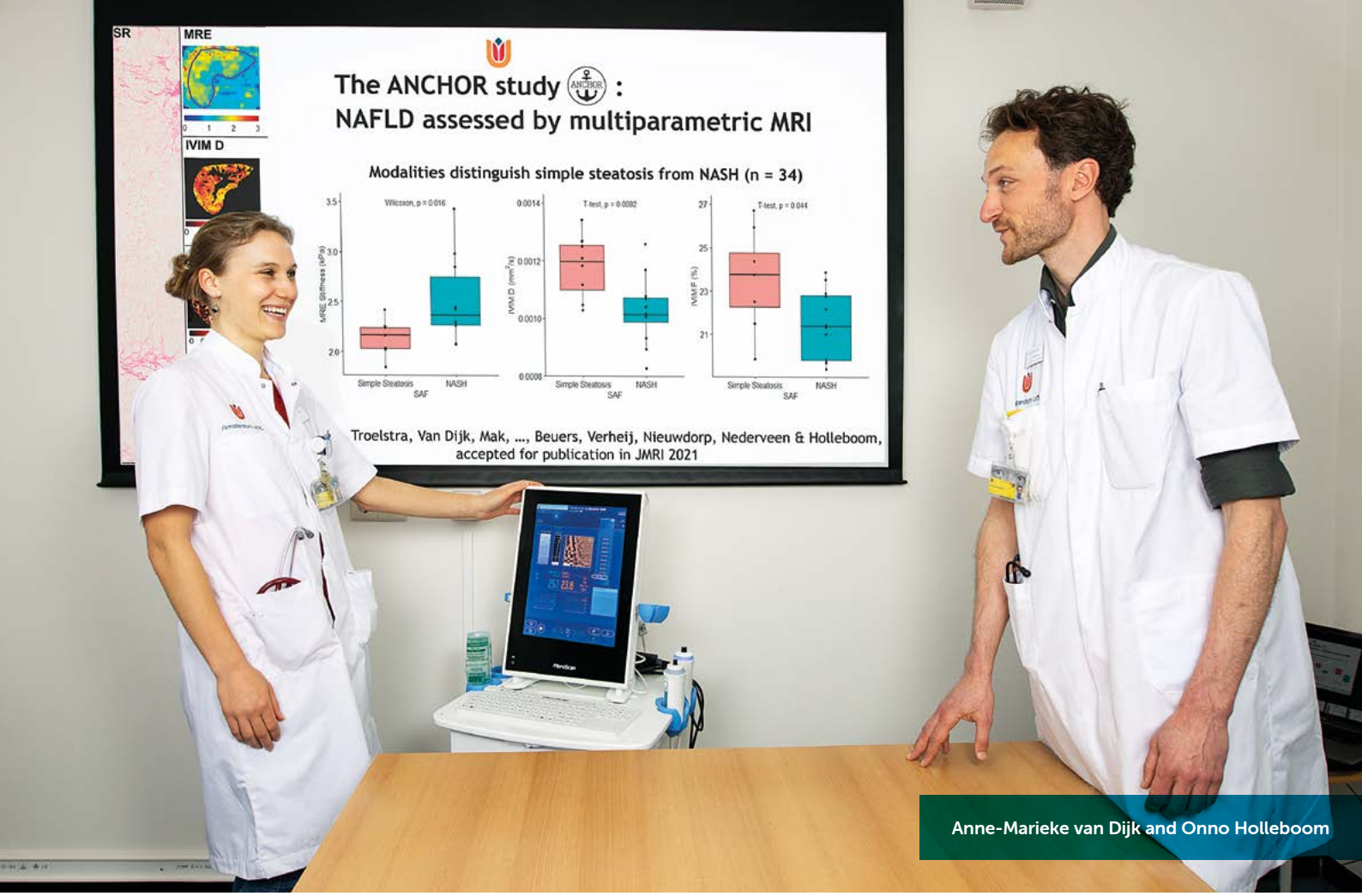
Science impression Onno Holleboom and group

In my group, we focus on non-alcoholic fatty liver disease (NAFLD). In my NAFLD clinic at Vascular Medicine in close collaboration with Hepatology, I aim to offer a platform to identify patients at risk for advanced stages of this ever more common metabolic liver disease. NAFLD often occurs in patients we see at Internal Medicine, i.e. those with obesity, type 2 diabetes mellitus, hypertension and cardiovascular disease. My aim is to investigate the efficiency of a new clinical care path for NAFLD, together with dr. Tushuizen from LUMC and prof. Drenth from Radboud UMC. In this effort, we seek guidance from the NAFLD-NASH workgroup from the Dutch hepatology society NVH.

In our clinic, we offer lifestyle programs to patients with progressive stages of NAFLD, and on occasion, we refer for bariatric surgery and treat patients with progressive and severely fibrotic NASH with vitamin E, pioglitazon or a GLP1 receptor agonist, taking into account that phase 3 evidence for these treatments is currently lacking, and thus we will also participate in selected clinical trials to assist in providing this evidence in the near future. Dr. Van Dijk, MD PhD candidate in my group, has a monthly NAFLD clinic at Flevoziekenhuis in Almere, to which she takes our FibroScan machine to go on an identical mission in Almere, i.e. to timely identify patients at risk for a progressive disease course of NAFLD.

Together with Anne Linde Mak MD and Julia Witjes MD, Anne-Marieke van Dijk also runs our growing prospective Amsterdam NAFLD-NASH cohort study into genetic and metabolic drivers of NAFLD, in a collaboration with prof. Nieuwdorp and prof. Beuers and. In this ANCHOR study, we have found, together with Marian Troelstra and prof. Nederveen, that multiparametric MRI can distinguish patients with simple liver steatosis from those with active steatohepatitis, which may reduce the need to stage this liver disease with invasive liver biopsy in the future. The ANCHOR study also recruits in location VUmc, Flevo and Rijnstate hospital Arnhem, and will now also expand to Amstelland hospital and Spaarne Gasthuis, which will provide to power to increase our insights into the progression of NAFLD. In addition, we participate in the EU IMI LITMUS NAFLD registry, set up to identify and validate the optimal biomarkers for NAFLD progression, the biggest challenge being a biomarker for active disease, i.e. NASH.

Next to her clinic and the ANCHOR study, dr. Van Dijk has initiated the NILE study, a NAFLD substudy in the HELIUS cohort, in which she investigates the values of non-invasive liver tests for steatosis and fibrosis in a multiethnic setting, with the goal to map the NAFLD epidemic in Amsterdam. In a subgroup of this population, she has already found a strong and positive relation between the presence of T2DM and FIB4, a validated score for liver fibrosis, and this relation was independent of ethnic background. The ultimate aim of NILE is to define new genetic susceptibility loci for NAFLD, which may serve as future therapeutic targets. Such new leads can be validated in our disease models for NAFLD: hepatoma cell lines, iPSC-derived hepatocytes in collaboration with dr. Bruinstroop and the Endocrinology lab, and our newly established diet-induced obesity mouse model by Anne Linde Mak and dr. Aldo Grefhorst in our lab of Experimental Vascular Medicine, which is also used for probiotic development for NAFLD. We have recently demonstrated the potential of our candidate gene approach in a collaboration with the University of Pennsylvania in Philadelphia and with prof. Hans Jonker from UMCG. In our disease models, my PhD candidate Lars Larsen showed that defects in two new genes, both involved in the assembly of the transmembrane proton pump V-ATPase, cause severe steatohepatitis by a defective lysosomal turnover of lipid droplets. This most likely occurs via abberant autophagy of these lipid droplets, shedding light on the understudied and as of yet untargeted processes of lipophagy and lipotoxicity in steatohepatitis.



Anne-Marieke van Dijk and Onno Holleboom

Taken together, our group runs a translational research program for NAFLD, in which we help each other forward by sharing and collaborating within our team and other groups, supported by the current momentum for NAFLD, which is fully justified given the clear increase in prevalence and severity of this metabolic liver disease, as we highlighted during the AGEM NAFLD & Obesity webinars we organized late 2020. This allows for lots of opportunity to actively build and contribute to new cohorts, intervention studies and molecular analyses, as exemplified by the rapid MD PhD tracks of Anne-Marieke van Dijk and her colleagues.

Combining dedicated patient care and research - Teamwork is key

Roos Pouw and Esther Nieuwenhuis

The mission of the esophageal research team is to optimize management of patients with Barrett's esophagus and Barrett's neoplasia. Around 2000, prof. Jacques Bergman started the then very small esophageal research team, studying endoscopic imaging and treatment of early Barrett's cancer. Roos Pouw started her PhD in Jacques' group in 2006, focusing on endoscopic treatment in patients with Barrett's neoplasia. After her cum laude PhD defense in 2011, she continued as a postdoctoral researcher in the esophageal research team, next to her clinical training to become a gastroenterologist. After finishing her specialty training, Roos started working as a gastroenterologist at the Amsterdam UMC. Her focus is on management of patients with early upper GI neoplasia in her clinical work as well as in research. Next to Jacques Bergman and Roos Pouw, the esophageal research team currently consists of 10 research fellows, two nurse practitioners and two doctors' assistants, taking care of patients with Barrett's esophagus and early neoplasia, and running multiple research projects.

The work of the esophageal research team is characterized by a multicenter approach leading to fruitful collaborations in the Netherlands and abroad. The group focuses on several research lines such as endoscopic imaging and artificial intelligence in partnership with TU Eindhoven, risk-stratifying patients with Barrett's esophagus at risk for esophageal cancer using biomarker panels, optimizing surveillance intervals, quality of life, and improving endoscopic therapy for dysplasia and cancer arising from Barrett's esophagus.

In the Netherlands, endoscopic therapy for Barrett's related neoplasia is uniquely organized. Treatment of patients with early Barrett's neoplasia is centralized in nine Barrett Expert Centers. According to the Dutch Barrett's esophagus guideline, all patients with dysplasia or early cancer in a Barrett's esophagus are referred to one of these centers, where care is provided by experienced endoscopists and specialized pathologists. This collaboration was initiated by the Amsterdam esophageal research team, and has led to joint protocols, training programs and multicenter studies.

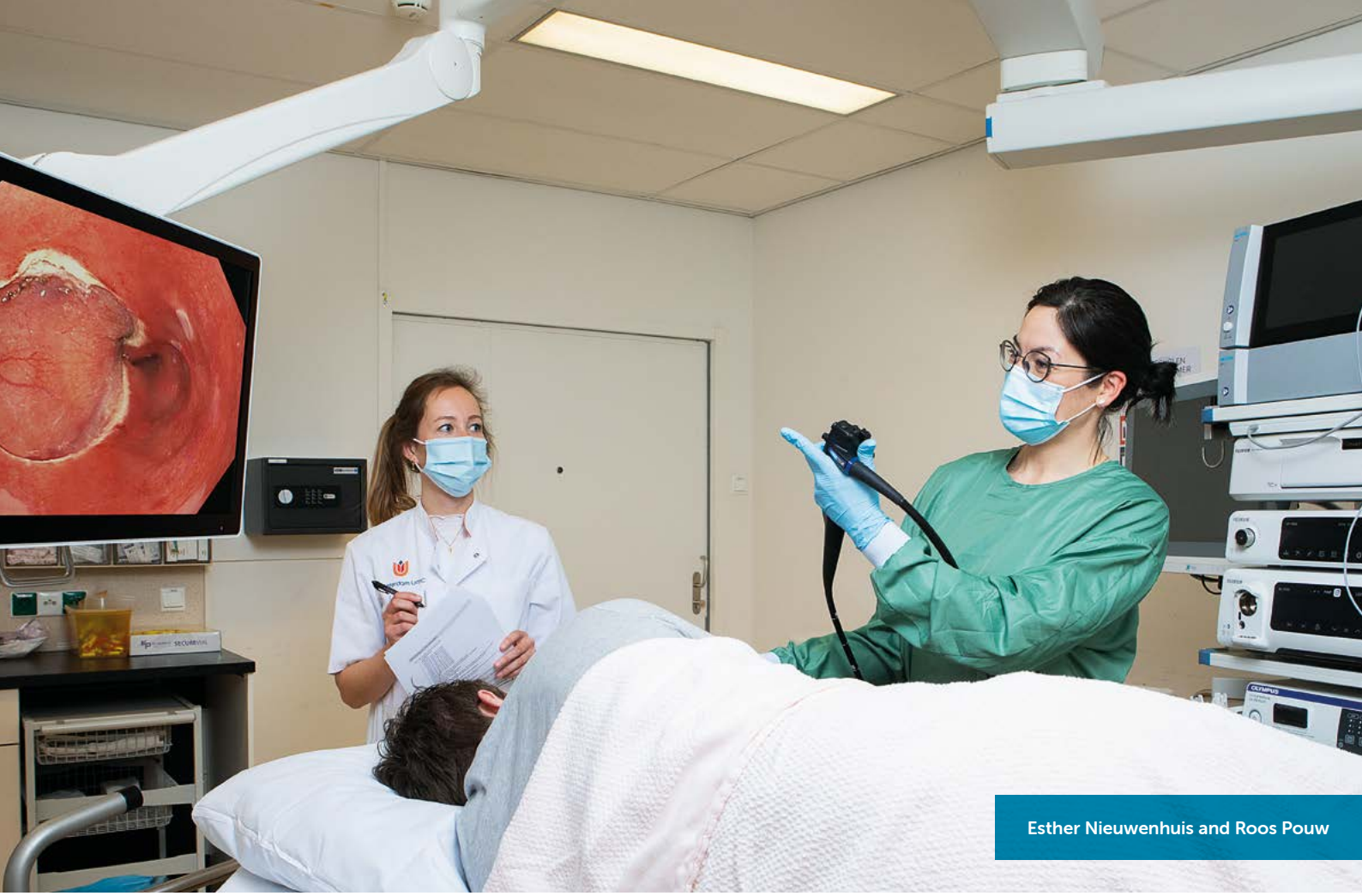
Endoscopic management of early Barrett's carcinoma

The esophageal research team has been involved in standardizing endoscopic therapy for Barrett's esophagus containing low-risk early carcinoma, as first choice treatment. Since the risk of lymph node metastasis in these tumors is negligible, local treatment is considered sufficient. For this indication lymph node dissection and invasive esophagectomy have become abundant. These low-risk carcinomas include tumors limited to the mucosa or superficial submucosa (<500µm), with a good to moderate differentiation grade of tumor cells, without lymphovascular invasion, which were radically resected.

Tumors with high-risk features

Traditionally, the lymph node metastasis risk for more advanced stages of early carcinoma (i.e., deeper submucosal invasion ≥500µm, and/or poor differentiation, and/or presence of lymphovascular invasion), is considered too high to offer these patients curative endoscopic treatment. Only in elderly patients with comorbidity, more often a less invasive endoscopic protocol was chosen. However, the risk of lymph node metastasis associated with submucosal Barrett's carcinoma is mainly based on old surgical studies. In these studies, the invasion depth and other risk features of tumors may have been underestimated due to thicker cuts of the surgical specimen. A number of more recent endoscopy-based studies showed lower lymph node metastasis risk than previously assumed, making an invasive esophagectomy possibly unnecessary in a subset of patients.

Esther Nieuwenhuis started her PhD in 2018. Supervised by Roos she is working on an ambitious project trying to push boundaries in endoscopic management for more advanced stages of early Barrett's carcinoma. With an international, prospective cohort study Esther is evaluating the safety of endoscopic treatment followed by watchful waiting instead of surgery, in patients with a submucosal



Esther Nieuwenhuis and Roos Pouw

Barrett's carcinoma (i.e., PREFER study). Follow-up consists of frequent gastroscopy and endoscopic ultrasound to inspect the esophagus for residual or recurrent neoplasia, and to detect metastatic lymph nodes at a still curable stage. This way, adjuvant treatment is reserved for those patients in whom it is really indicated, while the majority of patients who will not develop lymph node metastases is saved from unnecessary invasive treatment. Endpoints of the study are disease specific survival and mortality and quality of life. Furthermore, the study may help to identify certain risk factors, which may influence risk of lymph node metastases. This project received a grant from KWF.

Due to Esther's commitment and organizational skill, by now the study is running in all Dutch Barrett Expert Centers, as well as in 9 international sites in Germany, Switzerland, Belgium, France, the UK and Australia. The aim is to include 141 patients who will be followed for 5 years. At the moment, 60 patients have been included.

Future prospects

As our research team is always focusing on improvement by conducting research and applying the outcomes into clinical practice, we hope we can work towards a more patient tailored treatment approach for patients with high-risk early Barrett's carcinoma.

Galactosemia, elucidating the spectrum

Annet Bosch and Mendy Welsink

There is a long history of research of inborn errors of metabolism in the AMC. Research of peroxisomal disorders was started by Prof. dr. H.S.A. Heijmans more than 50 years ago. Dr H.D. Bakker was the first pediatrician specialized in metabolic diseases in the AMC, and Prof. dr. F.A. Wijburg was appointed as the first professor of Clinical Metabolic Diseases in 2004. In cooperation with the world renowned lab of Genetic Metabolic Diseases (head Prof dr. G. Salomons) a large number of long lasting research lines are in place. There is close cooperation with the departments of Internal Medicine Metabolic Diseases and Pediatric Neurology.

Prof. dr. Annet Bosch is professor of Pediatrics, Metabolic Diseases. Her research focuses in particular on three inborn errors of metabolism: Classical Galactosemia, Phenylketonuria and Riboflavin transporter deficiencies with a strong translational approach. Another focus of her research is newborn screening for inborn errors of metabolism in close cooperation with Prof. dr. Anita Boelen, of the Laboratory of Endocrinology.

Classical Galactosemia

Classical Galactosemia (CG) is one of the more frequent inborn errors of metabolism. A severe deficiency of the galactose-1-phosphate uridyltransferase (GALT) enzyme which is essential for the conversion of galactose into glucose results in the accumulation of toxic substrates upstream of the GALT enzyme, such as galactose-1-phosphate (Gal-1-p), and a shortage of substrates downstream of the GALT enzyme, which causes galactosylation abnormalities.

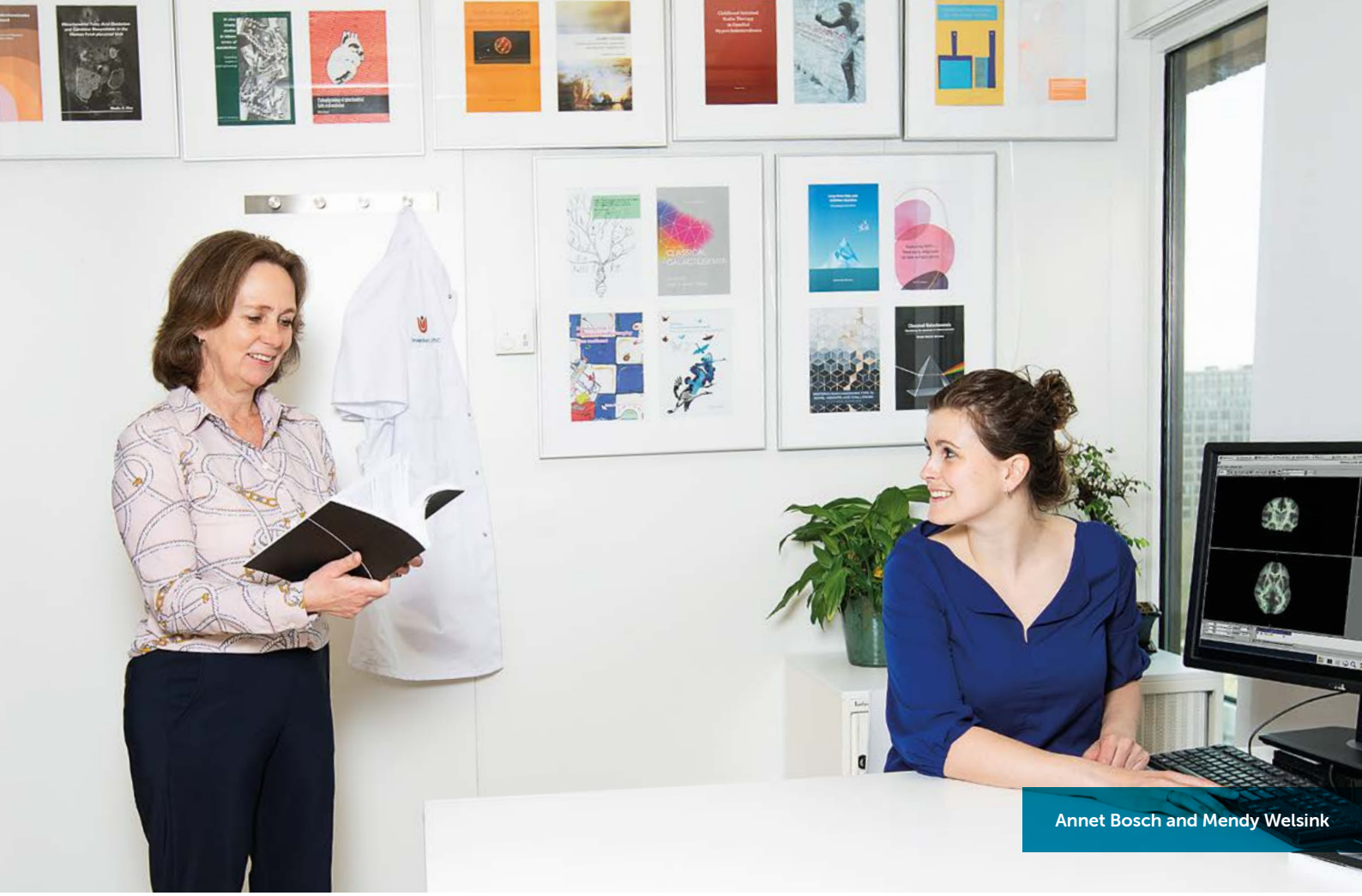
The only available treatment is a galactose-restricted diet. An early initiation of the diet (newborn screening was started in The Netherlands in 2007) prevents severe illness in the neonatal period but not the long-term complications observed in patients such as a below average IQ, cognitive impairment, movement disorders and premature ovarian insufficiency in females, which are thought to be caused by both the toxic metabolites and the galactosylation abnormalities.

The long-term outcome of patients is highly variable, ranging from fully normal to severely impaired even in siblings with the same genetic variations and comparable enzyme activities. This unexplained high variability has been the main focus of the galactosemia research in the past years. Dr. Mendy Welsink successfully defended her thesis “Classical Galactosemia, elucidating the spectrum of clinical outcome” on January 22 2021.

Elucidating the spectrum

The AMC is a nationally recognized Galactosemia center of expertise. Patients are evaluated according to the 2017 International CG guideline and invited to participate in research and the galactosemia biobank. We evaluated the neurological, neuropsychological, endocrinological and biochemical outcome of patients and used these outcome measures in our search for biomarkers of clinical outcome. Our deep phenotyping study demonstrated the high variability of outcomes: the IQ ranged from 45-103 (with a mean of 78) and movement disorders were present in 47% of the patients. In our search for predictive biomarkers we evaluated the extent of galactose intoxication and galactosylation abnormalities (as indicated by Gal-1-p and N-glycans), performed metabolic profiling to measure the galactose oxidation capacity in fibroblasts (in vitro) and used a non-invasive 1-13C galactose breath test to determine whole body galactose oxidation capacity (in vivo).

In our patient cohort we were able to distinguish two different groups, based on outcomes as well as the investigated biomarkers: patients with severe enzyme deficiencies who presented with CG related symptoms at the time of diagnosis (clinical or newborn screening) called classical patients and patients detected by newborn screening with previously unreported genotypes, residual GALT enzyme activity in red blood cells up to 10% and no symptoms at diagnosis (hereafter variant patients). Future studies are needed to demonstrate whether the variant patients are true patients in need of a strict and life-long diet.



Annet Bosch and Mendy Welsink

Within the group of classical patients, the studied biomarkers Gal-1-p and N-glycans were not associated with the occurrence of long-term complications. Also, both the in vivo and in vitro galactose oxidation capacity were not able to differentiate between classical patients with a poor and good clinical outcome.

The brain in Galactosemia

As the long-term complications mainly involve the brain, the brains of CG patients were studied in more detail with the use of MRI. We evaluated white and gray matter volume, white matter integrity in the whole brain and corticospinal tract and myelin content in gray matter, white matter and the CST and found significant differences between patients and controls. Moreover, these neuroimaging parameters were associated with the neurological and intellectual outcome of patients as gray and white matter volumes, white matter integrity and myelin content were lower for patients with more severe movement disorders and/or a lower IQ when compared to patients without long-term complications. The finding that the structural changes in the brain of CG patients were associated with neurological and intellectual outcome indicate that MRI could be of use to further unravel the disease mechanism of CG. More research is needed in a larger cohort in which the course of gray- and white matter should be investigated by repeating the MRI over time.

Reshaping macrophage metabolism and function

Jan Van den Bossche and Sanne Verberk

Macrophages and Jan Van den Bossche: a common thread throughout his career

Jan Van den Bossche is Assistant Professor at the Department of Molecular Cell Biology and Immunology at the VUmc location of Amsterdam UMC. He obtained his PhD in the VIB Myeloid Cell Immunology lab of Prof. Jo Van Ginderachter in Brussels, where he studied macrophage activation and heterogeneity in cancer. In 2012, Jan joined the group of Prof. Menno de Winther as a postdoc at the AMC to investigate the epigenetic regulation of macrophages in atherosclerosis.

The study of macrophages, their regulation, markers and functions in disease has been the common theme throughout the career of Jan Van den Bossche. Macrophages are innate immune cells that secure the first line of defence against a broad range of pathogens. However, unbalanced macrophage responses play a perpetuating role in diseases that massively impact society.

Pro-inflammatory macrophages drive chronic inflammation and the progression of diseases like atherosclerosis, obesity, diabetes and rheumatoid arthritis. Conversely, cancer cells can hijack the immunosuppressive and reparative functions of anti-inflammatory macrophages to support tumour growth. A better understanding of how macrophages are regulated will pave the way for reprogramming aberrant macrophage activation and development of novel therapeutics.

Entering the wonderful world of immunometabolism

In the last decade, immunometabolism research highlighted the critical role of cellular metabolism in regulating macrophage functions and disease progression. Jan entered this flourishing field when he observed that inflammatory “M1” macrophages failed to convert into anti-inflammatory “M2” cells. He identified disturbed mitochondrial function in inflammatory macrophages as the culprit factor responsible for preventing macrophage repolarization.

Macrophages can be compared with different types of runners. Inflammatory “M1” macrophages are fast, but short-lived, sprinters that rely on glycolysis for their energy supply when fighting pathogens. Conversely, anti-inflammatory “M2” macrophages are the marathoners of the macrophage activation spectrum and depend on mitochondrial respiration for long-term energy production to support their reparative functions during tissue repair (Off-note: Jan is an enthusiastic marathon runner himself). While you can force a marathoner to do a last sprint at the end of his marathon, a sprinter will never finish a marathon after an all-out 100-meter sprint. Accordingly, M2 macrophages can be converted to M1 macrophages, but the inverse is impossible.

By inhibiting nitric oxide production, a key factor that enables microbial killing, the M1 macrophage’s energy status could be restored and this improved their reprogramming into an M2 polarization state. Therapeutically restoring the macrophage’s energy metabolism might be useful to improve the reprogramming of inflammatory macrophages into anti-inflammatory ones to control diseases such as atherosclerosis and rheumatoid arthritis.

Macrophage Immunometabolism Lab

The Macrophage Immunometabolism Lab consists of 6 young and enthusiastic researchers and studies how specific metabolic enzymes and intermediates control macrophage phenotype, function and disease progression.

Sanne Verberk works as a PhD student on a senior grant from the Dutch Heart Foundation and aims to understand how specific metabolic enzymes can be targeted to redirect macrophage activation. Her work is divided into different projects all aiming to better understand how cellular metabolism can be used as a tool to combat chronic inflammatory disorders. Sanne just finalized a project on the role of ATP citrate lyase (Acly) in macrophages during atherosclerosis. This work was conducted in close collaboration with Jeroen Baardman and Menno de Winther at the AMC, where the study was initiated by Jan as a postdoc. The study

Jan Van den Bossche and Sanne Verberk

revealed that deletion of Acly in macrophages during atherosclerosis increased plaque stability. This means that plaques were less prone to rupture and hereby the risk of a heart attack or a stroke was decreased. To analyze the applicability of these findings in future drug development, she tried to unravel the underlying mechanisms. Analysis of macrophages lacking Acly with RNA-sequencing showed altered transcription of genes involved in lipid metabolism and programmed cell death. These findings were recently published and are now being utilized in follow-up studies into using Acly as a potential target.

A second main research line involves **“immunometabolites”** and particularly Karl Harber and Kyra de Goede focus on this exciting aspect of immunometabolism. Upon activation, immune cells undergo extensive metabolic rewiring to support the production of immune mediators and to provide energy for survival. Meanwhile, immune activation results in intracellular accumulation of metabolic intermediates with many roles beyond energy production. So-called immunometabolites function as signalling molecules that regulate immunity via distinct mechanisms. Jan recently discovered a metabolite that is massively induced in macrophages. Xanthe van Dierendonck just joined the lab as a postdoc and will study the regulation and function of this newfound immunometabolites with the support of a fundamental ENW-Klein-1 grant. More translational future projects aim to demonstrate the relevance of the current promising observations in different disease-relevant in vivo animal models, as well as in human samples.

In general, the ambition of Jan’s lab is to understand the mechanisms by which metabolic rewiring is translated into altered macrophage function, thereby uncovering new treatment options for major diseases.

The role of the mesentery in Crohn's Disease: from bedside to bench and back within 6 months...

Christianne Buskens, Manon Wildenberg, Marte Becker and Eline van der Does de Willebois

Dr Christianne Buskens is a colorectal surgeon, specializing in IBD. Together with prof. Willem Bemelman and the IBD gastroenterologists in the AMC this IBD research group has initiated several innovative RCT's comparing medical treatment to surgical intervention for both Crohn disease (CD) and ulcerative colitis (UC). The trials are generally viewed as cutting edge research leading to changes in daily clinical practice for IBD patients. Examples are the ACCURE trial (role of appendectomy in UC), PISA trial (anti-TNF or surgical closure in CD perianal fistulas) and the LIR!C trial (anti-TNF or surgical resection in CD terminal ileitis). The trials are also characterized by an accompanying translational research line. Ever since the start of her IBD career in 2012, Christianne works closely together with Manon Wildenberg, immunologist at the Tytgat laboratory. The highlight of their collaboration is the surgical IBD biobank. For years they have collected all sorts of tissue from IBD patients undergoing a surgical intervention, leading to a wealth of available research material.

One of the projects where Christianne and Manon are most proud of, is the role of the mesentery in CD. We know already since the original paper describing the condition by Dr. Crohn and colleagues in 1932, that the mesentery is involved in this disease. The hypertrophic adipose tissue surrounding the affected ileum is a hallmark of CD and correlates with locations of severe inflammation. Surprisingly, there are only few studies available regarding its biology showing conflicting results. Moreover, in daily clinical practice this tissue has been largely ignored for decades. Surgical guidelines emphasize the importance of sparing as much tissue as possible (bowel and mesentery), and in daily clinical practice a limited, close bowel resection is performed in Crohn's patients undergoing surgical resection. But there has always been one exception: in case of a rectal resection, an oncological resection with resection of the mesentery (total mesorectal excision, TME) was preferred. This operation in the pelvis is technically more demanding and adhering to anatomical planes was easier and associated with less blood loss. After 2010, with the introduction of better sealing devices and the TAMIS technique (transanal minimally invasive surgery), performing a close rectal dissection (CRD) became much easier and was quickly introduced for Crohn's patients. In CD, performing a rectal resection is frequently associated with a non-healing wound. It was assumed that performing a more limited resection, leaving a smaller defect, would lead to improved results. In contrast. In 2016 a retrospective study of the AMC results demonstrated that patients undergoing CRD had significantly more perineal complications and less wound healing. With these counter-intuitive results Christianne went to Manon: "Is there something in the mesentery that can explain these results?" With the available resection material, Manon and her research group could demonstrate that the phenotype of the macrophages was altered in CD mesentery. Macrophages are key-players in tissue homeostasis, and consist of several subtypes including pro-inflammatory and anti-inflammatory subsets. The numbers of myeloid cells/macrophages were significantly increased in CD mesorectum, and this population was strongly skewed towards a pro-inflammatory phenotype. The results were in sharp contrast with data from UC patients and non-IBD controls, where the majority of macrophages expressed anti-inflammatory / regulatory markers, suggesting a completely different phenotype in these patients. Interestingly, further analysis indicated that these differences were present irrespective of previous bowel resection, suggesting a disease specific rather than a pure inflammation induced phenotype. The finding that CD activity was ongoing in the mesentery even after rectal resection, quickly led to a change in the surgical approach for these patients. Moreover, as there were no good treatment options for CD patients with ongoing perineal sepsis after CRD, Christianne and Willem started to offer patients with non-healing perineal wounds, a mesorectal resection. Within six months after the demonstration of ongoing Crohn's activity in the mesentery in the lab, an operation was planned that was never performed before. And it was a success. A total of eight patients were treated with the new intervention within the next two years, of which six completely healed. The mesorectal excision

Manon Wildenberg, Marte Becker, Eline van der Does de Willebois and Christianne Buskens

improved the quality of life of these young patients tremendously. One example that we would like to mention is the fact that two female patients with severe ongoing wounds and perineal sepsis for years became pregnant. Something they had desired for a long time but was not possible previously.

These data triggered the interest as to whether taking the mesentery in an ileocecal resection could also improve clinical results and reduce recurrences. Manon and Christianne started with some fundamental analyses looking at whether the pro-inflammatory macrophages could also be demonstrated in the mesentery of the terminal ileum. They tried to find a gradient of aberrancies towards a more regulatory phenotype in the central mesenteric area, with the aim to provide a rationale for an extended mesenteric resection in CD patients. Unfortunately, findings so far did not support the hypothesis that there is a clear-cut gradient axis that could be targeted by operative means. In contrast, current data suggest that the creeping fat surrounding the affected bowel is an effort to protect the inflamed bowel. Since the mesentery is important for the vascularization of the intestine, a carefully weighted balance between resection and sparing is of crucial importance. Further investigation is therefore necessary to determine the most optimal balance between more resection with the aim to reduce recurrences versus the need to preserve as much intestine as possible and reduce postoperative complications.

To investigate the outcomes of a more extensive ileocolic resection, an RCT has been initiated comparing the more extensive mesenteric resection to a mesenteric sparing resection in terminal ileitis. Eline van der Does, PhD student at the department of surgery, coordinates the recently started SPICY trial. Results will be most relevant when specific mesenteric aberrancies could be demonstrated directly during surgery.
Fluorescence-guided surgery (FGS) has exhibited great potential for improving the accuracy in oncological resections by in vivo imaging of aberrant tissue. Therefore, Eline together with Marte Becker, PhD student at Tytgat laboratory, are currently in the preparatory phase of in vitro and in vivo studies to demonstrate the aberrant pro-inflammatory macrophages with fluorescence imaging during surgical resection to create a true ‘patient-tailored treatment approach’.

AGEM Best Publication 2020

In 2021 AGEM again organized the Best Publication battle. For this, firstly all AGEM principal investigators (PIs) had the opportunity to nominate publications of their best researcher, PhD student or post doc, that published as first author in a top journal in 2020. Out of these nominees the AGEM Research Board selected a top 5.

These lucky ones were offered a pitch workshop and with the skills learned pitched their publication during the AGEM Retreat of 2021. After this so-called “battle for the AGEM Best Publication 2020 award”, the attendants of the retreat voted for their ultimate favorite. The author of the publication with the most votes was named winner of the AGEM Best Publication 2020.

Best Publication 2020 nominees

Please meet the nominees for the AGEM Best Publication 2020...

Annieke van Baar

Annieke van Baar was nominated by Jacques Bergman for her article published in Gut: "*Endoscopic duodenal mucosal resurfacing for the treatment of type 2 diabetes mellitus: one year results from the first international, open-label, prospective, multicentre study".*
Gut. 2020 Feb;69(2):295-303.

Prof. Bergman's motivation for the nomination was: "Treating diabetes by duodenal ablation: the ultimate crossroad of GI and metabolics. The impact on endoscopy and management of metabolic syndrome will be enormous. The sham-controlled RCT is submitted. An insulin elimination trial showed 70% of patients off insulin. Three new technologies to be tested as First-in-Human studies in 2021. Gamechanger!"

Yama Issa

Yama Issa was nominated by Marc Besselink and Marja Boermeester for his article published in JAMA: *"Effect of Early Surgery vs Endoscopy-First Approach on Pain in Patients With Chronic Pancreatitis: The ESCAPE Randomized Clinical Trial".*
JAMA. 2020 Jan 21;323(3):237-247.

Prof. Besselink's motivation for the nomination was: "This multicenter randomized trial, coordinated by the candidate under the supervision of prof.Marja Boermeester, will change clinical practice and improve patient outcome."

Marte Molenaars

Marte Molenaars was nominated by Riekelt Houtkooper for her article published in Cell Metabolism: "*A Conserved Mito-Cytosolic Translational Balance Links Two Longevity Pathways".*
Cell Metab. 2020 Mar 3;31(3):549-563.e7.

Prof. Houtkooper's motivation for the nomination was: "In a massive effort combining hypothesis-free and hypothesis-based approaches Marte and her co-workers identified new mechanisms that underlie the process of aging, especially involving mitochondria. Published in leading metabolism journal, Cell Metabolism".

Sanne Jolien van der Veen

Sanne van de Veen was nominated by Mirjam Langeveld for her article published in International Journal of Molecular Sciences: *"Predicting the Development of Anti-Drug Antibodies against Recombinant alpha-Galactosidase A in Male Patients with Classical Fabry Disease".*
Int J Mol Sci. 2020 Aug 12;21(16):5784.

Dr. Langeveld's motivation for the nomination was: "This study uses unique data of patients with a rare genetic disorder (Fabry disease) to build a statistical model predicting treatment outcome. By employing complex statistical methods the investigators have managed to build an applicable model that can be used to improve outcome of Fabry disease and can be applied to other disorders in the future."

Sanne Verberk

Sanne Verberk was nominated by Jan Van den Bossche for her article published in Nature Communications: *"Macrophage ATP citrate lyase deficiency stabilizes atherosclerotic plaques".*
Nat Commun. 2020 Dec 8;11(1):6296.

Dr. ir. Van den Bossche's motivation for the nomination was: "Sanne took up this complicated study and made it a great success that resulted in its publication in Nature Communications. We generated a new macrophage-specific KO mouse for Acly and by doing so we were the first to demonstrate that targeting this key enzyme in macrophages results in more favorable atherosclerotic plaques."

And the winner of the AGEM Best Publication 2020 is...

Sanne Jolien van der Veen

My name is Sanne van der Veen, an MD-PhD student in the group of Prof. Carla Hollak, dr. Mirjam Langeveld and dr. Andre Kuilenburg. During my studies in medicine and biomedical science I developed a strong interest in pathophysiological processes, specifically within the field of metabolism, (auto)immunity and endocrinology. In the last few years, while doing my PhD, a strong appreciation for statistics and methodology got added to that list. Our group is organized in SPHINX, a collaboration of the departments of Internal Medicine, Pediatrics, Radiology and the Laboratory of Genetic Metabolic Diseases at the Amsterdam UMC. The aim of our group is to integrate preclinical and clinical research on lysosomal storage disorders, including Fabry disease, in order to improve diagnosis and treatment of our patients.

Predicting the development of anti-drug antibodies against recombinant alpha-galactosidase A in male patients with classical Fabry disease

Fabry disease is a rare hereditary lysosomal storage disorder, caused by a defect in the enzyme alpha-galactosidase A. The resulting accumulation of the glycosphingolipid ceramidetrihexoside (Gb3) causes progressive damage to heart, kidney and brain of patients. Fabry disease can be treated by replacing the missing enzyme through biweekly infusions, so called enzyme replacement therapy (ERT). One of the main issues with this treatment is the development of anti-drug-antibodies (ADAs) targeted against the recombinant enzyme in male patients with little or no native enzyme. Not only are ADAs associated with (severe) allergic reactions, necessitating treatment with corticosteroids and antihistamines before each dose, but they also bind the drug and inhibit its effect, rendering the treatment ineffective. Although the allergic reaction may lessen over time, once immunization has occurred, the inhibiting effect of ADAs on treatment tends to persist. In our paper 'Predicting the development of anti-drug antibodies against recombinant alpha-galactosidase A in male patients with classical Fabry disease' published in the International Journal of Molecular Sciences (IJMS) in 2020, we describe the mathematical models we have developed to identify risk factors for ADAs formation in male Fabry patients with a classical disease phenotype.

We found three factors that were significantly associated with an increased ADA risk. The first was the mutation type; nonsense and frameshift mutations resulted in a higher ADA risk compared to missense mutations ($p=0.05$). The second was a biomarker we can measure in plasma called lysoGb3; the higher the baseline lysoGb3, the higher the ADA risk ($p<0.001$). The third was the treatment type; there are 2 different preparations of recombinant enzyme available that differ in production method as well as in registered dose (namely). Starting treatment with the higher dosed agalsidase beta resulted in a higher ADA risk. The prediction performance of a Random forest model (that can use all known variables) was compared to a logistic regression (LR) model that only used the mentioned significantly associated variables. No differences were found between the performance of the 2 models.

The outcome of the LR model was utilized to build an algorithm to predict individual ADA risk in new Fabry patients. These predictions are currently used at our site to identify patients with a high a-priori ADA risk. These patients receive a customized treatment protocol, aiming to reduce the chance of ADA development. The a-priori calculated risk can be included in future statistical evaluation of the effect of intervention, making it possible assess the effect of the intervention without randomization.

AGEM Grants 2020

In 2020, AGEM awarded eight types of grants. Like previous years AGEM awarded the AGEM talent development grant for exceptionally talented researchers who are in the first 5 years after obtaining a PhD-degree and want to develop their own research line, the AGEM innovation grant for innovative ideas beneficial to the AGEM research institute as a whole, and the AGEM international student fellowship for (bio-)medical students (in their MSc-program or just graduated) to participate in a research internship for a 6-12 months at an international top institute.

Newly introduced grants in 2020 were the AGEM matching grant for newly starting multidisciplinary research projects (PhD-students or post docs), the AGEM clinical research matching grant to support investigator initiated clinical research that can improve care of AGEM diseases, AGEM support for clinical consensus meetings to facilitate (inter)national multicenter clinical research meetings leading to a new consensus, the AGEM PhD-student course project for the group of PhD-students that wrote the best proposal during the AGEM PhD-student course, and the AGEM contribution printing costs of theses of AGEM PhD-students

The AGEM talent development grant 2020 (€75.000)

Ruben Zapata-Perez

Enhancing brown adipose tissue metabolism through supplementation with novel NAD precursors

Ruben Zapata-Perez

I started my research career after obtaining my degree in Biology at the University of Murcia (Spain). In 2015, already as a PhD student in Molecular Biology, I came to the Laboratory of Genetic Metabolic Diseases for a short stay of 3 months at the Translational Metabolism group. I liked it so much that, as soon as I defended my thesis, I came back to the Netherlands to continue with my research, this time as a postdoc. Since 2018, my research has been focused on nicotinamide adenine dinucleotide (NAD+) metabolism, specifically in ways to increase cellular NAD+ with the aim to prevent or cure metabolic diseases.

The AGEM talent development grant allows me…

… to continue developing the research project that I started in 2015 together with Prof. Riekelt Houtkooper. Back then, we identified a new NAD+ enhancing molecule called reduced nicotinamide mononucleotide, or NMNH. We had already demonstrated that NMNH outperforms all the other classical NAD+ enhancers in different cell lines, but it was through this grant that we could hire a technician to assist with the in vivo aspects of this project. This way, we could prove that NMNH is also an outstanding NAD+ enhancer in mice, potently increasing NAD+ levels in tissues. Following up on these findings, we now aim to demonstrate that NMNH is also orally available, and that it protects against the effects of obesity and diabetes in mice. It goes without saying that our ultimate aim is to bring NMNH to the clinic to prevent or even improve the outcomes of metabolic diseases in patients.

Ruben Zapata-Peres

The AGEM innovation grant 2020 (€50.000)

Chun-Xia Yi and Gertjan Kramer

Dissecting microglial insulin signal pathway and insulin resistance by rare cell proteomics.

Chun-Xia Yi

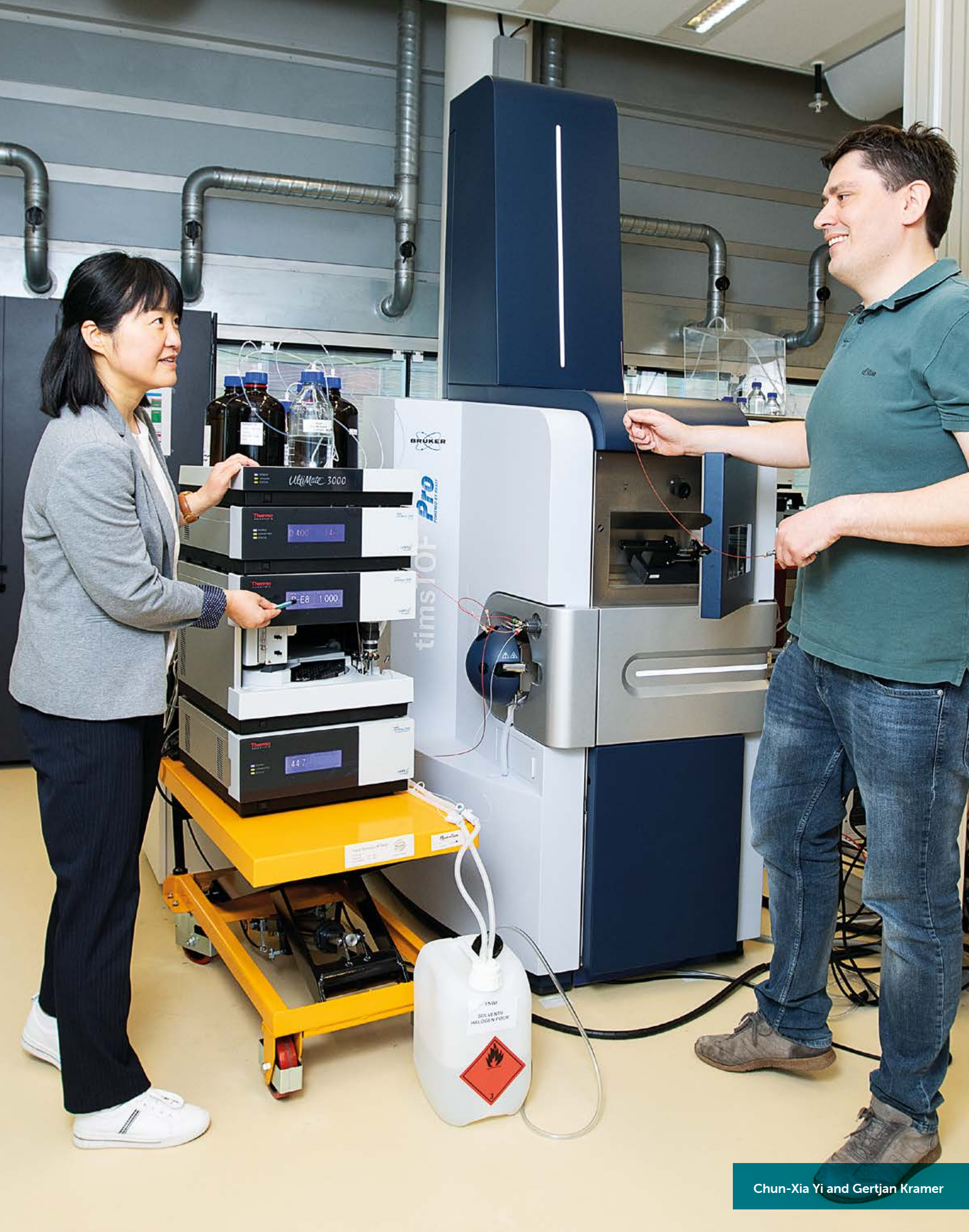
Since I discovered that the brain immune cells microglia are invloved in hypothalamic control of glucose metabolism and energy homeostasis of our body, I am fascinated with dissecting the immunometabolic machinery of microglial cells. In the context of obesity and diabetes, this is essential, for us to understand how the blood-borne factors such as metabolism-regulatory hormones and nutrients affect the microglial function, and how the crosstalk takes place between the microglial cells and neurons in critical brain regions that control energy homeostasis. Eventually, we should find targets not only in neurons but also in brain immune cells to develop therapeutic approaches to combat human metabolic disorders.

Gertjan Kramer

Pushing the boundaries of mass spectrometry technologies has been a passion of mine since the very beginning of working in science. Using the newest technology both in instrument development and sample preparation to solve difficult to access questions in medicine and biology. Currently I focus on combining different high sensitivity approaches in a unique way to obtain better proteomic and metabolomic insights in rare cell populations in order to unlock them for omics wide studies. Through our partnership with driven scientists like Chun-Xia Yi we hope to bring our solutions to bear on questions which will have a large impact in biological understanding and patient welfare.

The AGEM innovation grant allows us…

…to study insulin signalling in microglial cells by dissecting its downstream pathways with differential protein expression. It is technically challenging to profile microglial protein expression, as the total number of microglia isolated from animals or human brain tissues is very limited. This is particularly so for cells isolated from specific brain regions like the hypothalamus. We therefore decided to assemble our unique expertise of microglial pathophysiology and state-of-the-art rare cell proteomics, to take on the challenge of providing deep proteome profiling in small microglial cell populations. We are taking a step-by-step approach. We start with primary cultured microglial cells, before moving to microglia obtained from a genetic-modified mice model lacking the insulin receptor specifically in the microglial cells. Finally we will apply this technique with the microglial samples obtained from postmortem hypothalamic tissues donated by type 2 diabetic patients or non-diabetic control subjects.



Chun-Xia Yi and Gertjan Kramer

Hilde Herrema and Peter Henneman

Nanopore sequencing; conductivity leads to connectivity

Hilde Herrema

Hilde Herrema is a medical biologist with specific molecular and systemic expertise on development of cardiometabolic diseases in obesity, in particular diabetes and fatty liver disease. After her postdoc at Harvard Medical School (Boston, USA), she joined the group of Prof. Nieuwdorp (AMC) to study the role of the gut microbiome in the complex pathophysiology of cardiometabolic disease. She is currently junior group leader and uses a translational and multidisciplinary approach to study cardiometabolic disease development, with a particular focus on gut bacteriophages (viruses of bacteria) and their role in gut microbiome function and human health.

Peter Henneman

Peter Henneman, trained in genetic epidemiology (Leiden University and NIHES, ErasmusMC, Rotterdam), is a molecular epidemiologist with a particular focus on the epigenetics of complex disease and disorders. His current work comprises research projects and studies connected to genome diagnostics. His primary work (group leader) involves the further development of DNA methylation signatures for the molecular diagnosis of patients with mendelian disorders (EpiSign). Similarly, Peter is working on to the development of a epigenetic personalized prognosis tool in the context of therapy response in Crohn's disease patients. In these studies he applies omics profiling ("bulk" and single cell), CRIPR/CAS, third generation sequencing and machine learning techniques.

The AGEM innovation grant allows us…

Next generation sequencing has greatly advanced a broad range of research and diagnostic applications. Most state-of-the-art next generation sequencing technologies are available and integrated in the Amsterdam UMC. We proposed to invest in a novel third generation sequencing methodology, namely Oxford Nanopore Technology (ONT). ONT enables direct sequencing of large single DNA (or RNA) molecules (> 80kb) that are substantially longer reads than obtained by next gen sequencers (<300bp). In addition, these long read sequencers can detect and quantify modifications on DNA molecules without a need for bias-inducing pretreatments such as a bisulfite conversion and PCR. Challenges that can be addressed using ONT involve detection of complex copy number variation, novel genome(s) assembly and the detection of molecular epigenetic modifications (RNA and DNA).

Using the AGEM innovation award, we aim to advance our knowhow on performing and designing Nanopore experiments. Moreover, we aim to improve the availability of this knowledge for both human and microbiota DNA/RNA, the technology (e.g., sequencers) and the infrastructure that is required (e.g., sophisticated ICT solutions for real-time data acquisition) for researchers within AGEM and the Amsterdam UMC as a whole.

Hilde Herrema and Peter Henneman

The AGEM international student fellowship 2020 (€500/month)

Iris Loise Mimpen

Immune Potentiating Effect of the Gut Microbiome on the Non-Small Cell Lung Carcinoma (NSCLC) Tumor Microenvironment

Immunotherapy, a cancer therapy that helps your immune system to fight cancer, has been shown to be an effective new treatment for cancer. However, there are still many patients that do not respond to this therapy. Recently, the microbiome, a complex community of microorganisms in our body, has been shown to have a big impact on the response to immunotherapy. This microbiome plays a key role in many processes that are relevant to human health, including regulating the immune system, which may explain its importance in the response to immunotherapy, as bacteria can produce molecules that are able to boost an anti-cancer immune response. This suggests that if we can boost the 'good' bacteria that are able to help the immune system fight against tumor cells, we could improve the response to immunotherapy. There are currently many different strategies being tested to modify a patient's microbiome. One of these strategies is by the intake of food, specifically prebiotics, which are natural ingredients that aim to stimulate the growth and activity of beneficial bacteria. Recently, we have found a prebiotic compound called Prebio1 (name is changed for intellectual property), which can shift the microbiome to a more beneficial composition, thereby boosting an anti-tumor immune response and increasing the effect of immunotherapy. This study aimed to investigate what the effect of Prebio1 is on immunotherapy, and how Prebio1 can produce this effect. This study ultimately leads to a new combinatorial approach that could dramatically improve the outcome of many cancer patients.

Marene Hardonk

The effects of astrocytes on cognitive flexibility in lean and obese mice

Astrocytes are the most predominant glial cell type in the brain. Implication of this cell type in other processes besides of their known functions, such as supporting the blood-brain barrier and interactions with the vasculature, is recently being investigated. As our first interest, we tested how astrocytes are involved in obesity-induced impairment of cognitive flexibility. Cognitive flexibility is dependent on the interaction between the prefrontal cortex (PFC) and the dorsal striatum (DS). Previous studies show that cognitive flexibility is affected by modulating dopamine receptor 1 (DRD1)-expressing neurons and astrocytes in the PFC, while in the DS same effects were found for DRD2-expressing neurons, but involvement of astrocytes remains to be elucidated. Therefore, I investigated how astrocytes in the DS and nucleus accumbens (NAc) are implicated in several neurological, behavioural and metabolic components in obese mice. Astrocytes were specifically activated in the DS or NAc using the DREADD-Gq system. Viral GCaMP expression allowed for recording astrocyte activity with in vivo fiber photometry or neuron activity with calcium imaging in slice. Moreover, a calorimetry system was used to assess metabolic correlates and several behavioural paradigms were used to test cognitive flexibility, involvement of DRD1- or DRD2-expressing neurons, and changes in food preference. Mice were subjected to a high fat diet to make comparisons between lean and obese groups. The generated results highlight the importance of the interplay between DS astrocytes and MSN dialogue in obesity, and enhance the understanding of DS astrocytes mediating neurobiological, behavioural and metabolic components.

Rick Hogenboom

FGF21 signaling in the brain of UCP1 KO mice

The prevalence of metabolic diseases continues to rise globally, reaching pandemic numbers worldwide. Therefore, approaches to understand mechanisms of body weight regulation and insulin resistance must be intensified to come up with novel or improved therapeutic strategies. Fibroblast growth factor 21 (FGF21) is an interesting target, as exogenous administration of FGF21 improves metabolic profiles in mice and humans. Over the last years, the brain and adipose tissue have emerged as main target tissues for the actions of FGF21. This is supported by the restricted expression of obligate signalling factor beta-klotho in amongst others hypothalamic areas and the ability of FGF21 to cross the blood-brain barrier. Other recent findings suggest central FGF21 signalling is the major mediator of the beneficial effects of FGF21. Yet, obesity is characterized by increased systemic levels of FGF21, suggesting that obesity might be accompanied by an FGF21 resistant state. Very recently it was discovered that brown adipose tissue (BAT)-derived FGF21 is responsible for the lean phenotype of uncoupling protein 1 (UCP1) deficient mice at room temperature, resistant to diet-induced obesity. This is a paradoxical observation given that UCP1 is solely responsible for heat production in BAT, thereby normally facilitating non-shivering thermogenesis, marking FGF21 as anti-obesity factor in absence of UCP1. Thus far, it is unknown how FGF21 signals to adipose tissue and might include central actions. We aimed to unravel whether the brain is included but found limited evidence for this claim, and suggest that it is more likely FGF21 signals directly to adipose tissue.

Megan Engels

Innovative early detection methods for pancreatic cancer and pancreatic cysts with malignant potential

Pancreatic cancer is one of the deadliest forms of cancer, with a 5-year all-stage survival rate of 9%. Screening and surveillance programs have been designed aiming for an increased survival benefit. Those with a family history of pancreatic cancer, pathological genetic mutations and visible precursor lesions are recommended to participate. A combination of clinical characteristics, biomarkers and cross-sectional imaging is the current approach to risk stratification. Our research is focussed on improving current methods of detection and researching new possibilities. The analysis of pancreatic juice, secretions from the lining of the ductal system of the pancreas, is one of the new possibilities. Most pancreatic cancers originate from cells lining these ducts, making pancreatic juice ideal for very specific biomarkers. DNA methylation is a process in which the activity of a gene is changed during a person's lifespan. Earlier discovery work focussed on establishing a panel of three 'methylated DNA markers' that can distinguish pancreatic cancer from a pancreas that is normal or has benign disease with an AUROC value of 0.90. We are validating this panel in the pancreatic juice of our cohort of patients to see if the diagnostic capability demonstrated in the initial study is maintained. Additionally, we are investigating known biomarkers that distinguish between pancreatic cyst types (such as CEA, Glucose and KRAS/GNAS) in pancreatic juice. Our first aim for these biomarkers is to differentiate between pancreatic duct dilatation in chronic pancreatitis and main-duct precursor lesions, two diseases with distinct management strategies but similar imaging features.

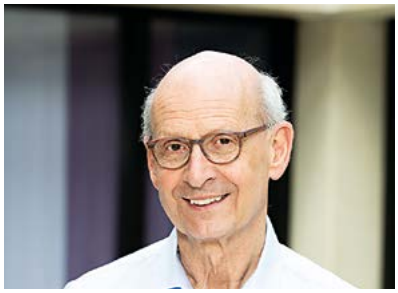
The AGEM matching grant 2020 (€100.000)

Clara van Karnebeek, Ronald Wanders, Marion Brands and Hans Waterham

"Bird's Eye View for Gyrate Atrophy"

Clara van Karnebeek

Clara is professor in pediatrics and head of the metabolic diseases department in Radboud University Medical Center, and affiliated as principal investigator in Amsterdam UMC. She dedicates her work as a pediatrician and biochemical geneticist to early diagnosis and innovative treatments for inherited disorders. Vitamin B6 metabolism with its capacity to boost function of more than 150 enzymes - among which the OAT enzyme responsible for GACR - is one of her areas of research. She believes in interdisciplinary collaboration and crossing boundaries as an avenue towards personalized health care. United for Metabolic Diseases (www.umd.nl) was established in 2019, and with professor Hans Waterham she directs this translational research and care consortium uniting 6 metabolic centers and patient organizations in The Netherlands.



Ronald Wanders

Ronald is Emeritus Professor in Clinical Enzymology and Biochemistry of Metabolic Diseases and was head of the Laboratory Genetic Metabolic Diseases at the Academic Medical Center, Amsterdam University Medical Centers until 2018. From his early days as PhD student, he has always been fascinated by Metabolism and especially its derangements in Metabolic Diseases and has contributed to the field through the identification of many novel Metabolic Diseases and their pathophysiological mechanisms. His main focus has been devoted to Peroxisomal Disorders and mitochondrial Fatty Acid Oxidation deficiencies but more recently his interests have extended to Gyrate Atrophy, and Hyperoxaluria. He continues to work as Senior researcher and contributes to various research projects.

Marion Brands

Marion succeeded Frits Wijburg as a co-researcher on the GACR project. Marion is a pediatrician metabolic diseases working at the Emma's Children's Hospital Amsterdam. She has always been intrigued by the complexity of human metabolism and metabolic diseases. Her research work is mainly focused on lysosomal storage disorders and gyrate atrophy. Together with PhD student Berith Balfoort she is working on treatment guidelines for GACR and establishing a GACR Patient Registry.

Ronald Wanders, Marion Brands and Hans Waterham

Hans Waterham

Hans is Professor Functional Genetics of Metabolic Diseases, Principal Investigator, and Clinical Laboratory Geneticist in the Laboratory Genetic Metabolic Diseases. His general research interest is functional genetics of metabolic disorders in a broad sense but with special focus on inherited defects in peroxisome biogenesis/function and cholesterol/isoprenoid biosynthesis. His research is aimed at understanding the consequences of genetic defects for encoded proteins, metabolism, cellular functions and patients, with the ultimate goal to develop targeted therapeutic approaches.

The AGEM matching grant allows us…

To perform translational research on gyrate atrophy of the choroid and retina (GACR), an autosomal recessive disorder of protein metabolism. The close collaborations between clinicians, laboratory scientists, patients and families catalyzes AGEM funded research to further understand, diagnose and treat this devastating metabolic blindness. To establish the phenotype and natural history, we will establish an (international) patient registry. Biochemically we are unraveling the pathophysiology and potential biomarkers of ornithine δ-aminotransferase (OAT) deficiency, by untargeted metabolomics. Novel therapeutic targets are explored by high-throughput screening of FDA approved drugs, and the development of gene and cell-based therapies in the laboratory of prof Bergen. Our mission is to prevent or delay the devastating vision loss in GACR patients.
https://gyrateatrophy.nl.

Marjolein van Egmond, Jeroen den Dunnen, Manon Wildenberg and Riekelt Houtkooper

C-reactive protein: not only a marker, but also a cause of inflammation in Crohn's Disease through metabolic reprogramming

Marjolein van Egmond

Marjolein van Egmond obtained her PhD at the University Medical Center Utrecht, department of Immunology. The main focus of her research centers around antibody activation of innate myeloid immune cells, with emphasis on understanding the role of immunoglobulin A (IgA) in physiology and IBD pathology. Additionally, it is investigated whether obtained knowledge can be used for novel immunotherapeutic approaches in cancer. The research is highly translational and because of a cross appointment with the Department of Surgery and the Department of MCBI, rapid progression of pre-clinical findings into clinical applications is facilitated.

Jeroen den Dunnen

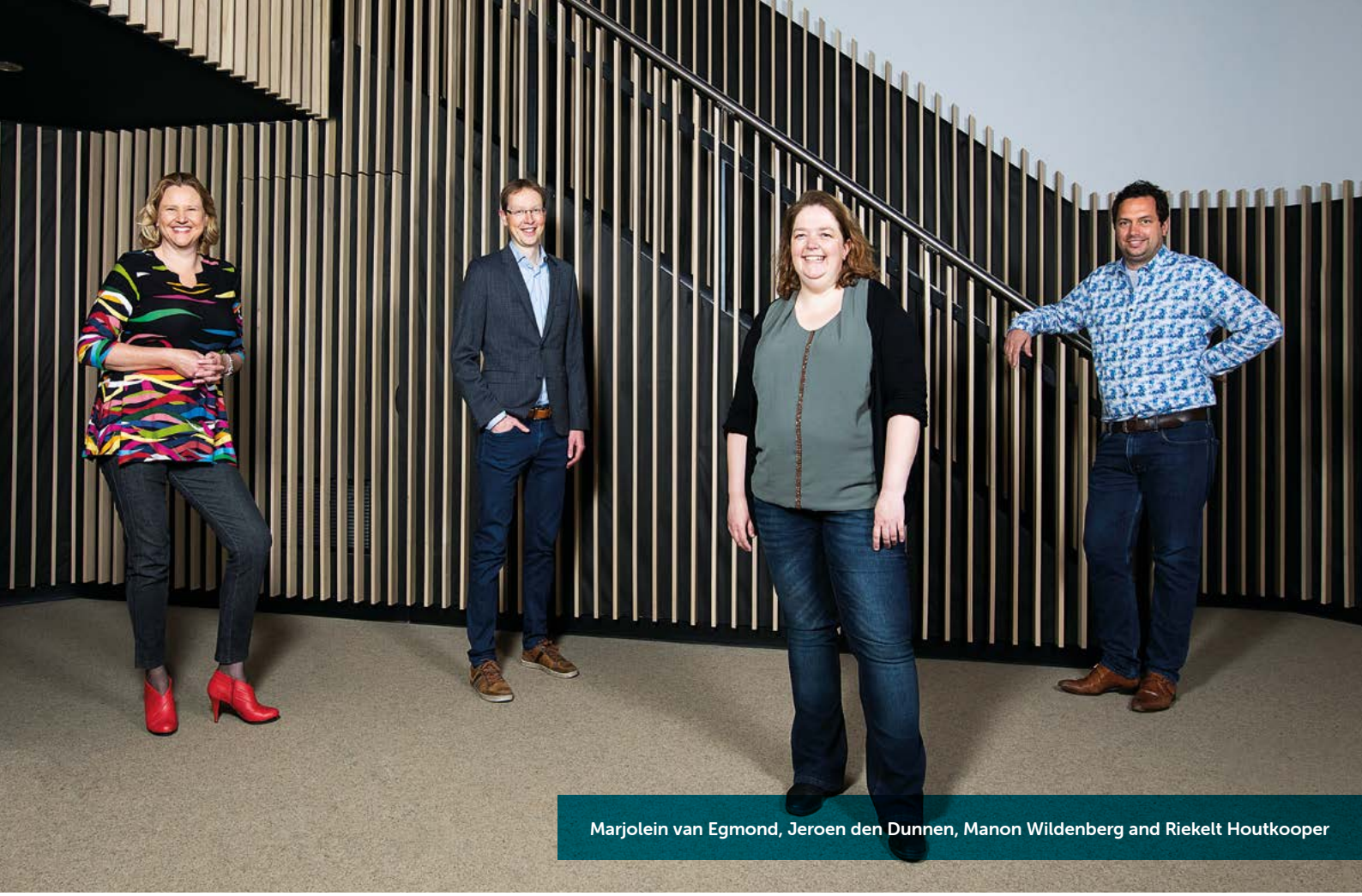
Jeroen den Dunnen obtained his PhD in Immunology at the Free University (VU) of Amsterdam. The main topic of his research group is how antibodies and antibody receptors (Fc receptors) induce inflammation in a large variety of disorders. A hallmark of his research is its multidisciplinary nature, illustrated by his studies on various different topics, including infectious diseases, rheumatology, and (chronic) gastrointestinal inflammation. Currently, a main interest of his research group is the interconnection between immunology and metabolism.

Manon Wildenberg

Manon Wildenberg performed her PhD studies at the Erasmus MC, department of Immunology, focusing on myeloid cells in local tissue immune processes. This interest was further solidified in her postdoctoral project (LUMC) studying specifically the intestinal immune system in inflammatory bowel disease. She has been at the Amsterdam UMC since 2011 as a research fellow and assistant professor, and currently principal investigator. Her research group is strongly focused on translational studies, collaborating with both the clinical gastroenterology and surgical departments. Current topics of investigation include the effector mechanisms of therapy for IBD and wound healing processes in both intestinal inflammation and surgical complications in IBD.

Riekelt Houtkooper

Riekelt Houtkooper received his PhD from the laboratory Genetic Metabolic Diseases of the Amsterdam UMC-AMC. His research centered on cardiolipin metabolism, particularly in relation to the rare mitochondrial disorder Barth syndrome. During a postdoctoral project in Lausanne (CH) geared towards understanding and treating more common metabolic diseases, he became interested in the metabolic aspects of aging. Early 2012 Riekelt moved back to Amsterdam to start his own group, for which he received funding from NWO and the ERC. Current research in the group focuses on molecular and translational metabolism, both in the context of inborn errors of metabolism and aging.



Marjolein van Egmond, Jeroen den Dunnen, Manon Wildenberg and Riekelt Houtkooper

The AGEM matching grant allows us…

… to combine the expertise of four different AGEM laboratories to unravel how C-reactive protein (CRP) contributes to excessive inflammation in patients suffering from Crohn's disease. CRP is produced in abundance by mesenteric fat in Crohn's disease patients. Our preliminary data indicate that this CRP breaks the immune tolerance of intestinal immune cells to the microbiome, thereby promoting chronic inflammation. Moreover, our data indicate that this is induced by the activation of a unique metabolic pathway in intestinal immune cells. By unraveling this metabolic pathway, we not only aim to unravel a novel key process in the pathogenesis of Crohn's disease, but also to identify new therapeutic targets to suppress chronic inflammation in these patients.

The AGEM clinical research matching grant 2020 (€15.000)

Koen Dreijerink

Progesterone for Breast Development in Trans Women; Assessment of effects and safety - a pilot trial

Trans women (male sex assigned at birth, female gender identity) receive hormone therapy in order to induce secondary female sex characteristics. Traditionally, this hormone therapy includes estradiol and anti-androgenic treatment. A potential role for progesterone with regard to breast development in trans women has not been investigated in a controlled experimental set up.

In this randomized controlled pilot trial using a factorial design, we will explore the effects on breast development of addition of progesterone to the treatment with estradiol in 90 trans women after vaginoplasty or orchiectomy. Secondary objectives include safety and patient satisfaction, mood, and sleep. The duration of the study is 12 months. Breast volumes will be determined using 3D imaging.

Sarah Siegelaar

Time-restricted-eating to treat gestational diabetes mellitus

Gestational diabetes mellitus (GDM) is associated with adverse maternal and neonatal outcomes and its incidence is increasing. Risk factors for development of GDM are, amongst others, obesity and non-alcoholic fatty liver disease. Dietary advice is the first treatment step, but the optimal dietary treatment is unknown. Time-restricted-eating (TRE) is a promising approach in the prevention and treatment of diabetes mellitus causing weight loss, reduction of fat mass and improvement of insulin sensitivity in obese subjects and men with prediabetes, probably by resetting clock gene patterns. We hypothesize that TRE will be effective to treat GDM, a group with a disturbed sleep-wake pattern and hypothesized longer eating period. Pilot data from our own clinic show a lower incidence of GDM when eating <11h a day. Therefore, we will perform a randomized controlled trial to study the effect of TRE on glucose regulation, clock gene expression patterns and liver fat in women with GDM.

Kyra van Rijn and Floris de Voogd

Stenosis in Crohn's Disease, is it inflammation or fibrosis?

Crohn's disease (CD) is often complicated by a bowel stricture, resulting in symptoms of obstruction. Whereas inflammatory strictures might benefit from anti-inflammatory therapy, fibrotic strictures often need a surgical approach. However, current biomarkers are unable to adequately determine stricture composition. Ultrasound and MRI are frequently used in the evaluation of CD activity. Previous studies showed that advanced modalities of both techniques are promising in stricture characterization. Four departments within the Amsterdam UMC have initiated the STRICTURE-study to find novel advanced cross-sectional imaging modalities to determine stricture composition and assess the clinical value of these novel imaging techniques.

Charlotte van Veldhuisen

Endoscopic and surgical treatment of Chronic Pancreatitis in Europe (ESCOPA): A Prospective, International Snapshot Study of the Dutch Pancreatitis Study Group (DPSG), European-African Hepato Pancreato Biliary Association (E-AHPBA), and European Society of Gastrointestinal Endoscopists (ESGE).

Some patients with chronic pancreatitis (CP) experience extreme abdominal pain which requires endoscopic- or surgical intervention. Due to the heterogeneity, the optimal treatment is often seen as challenging and also varies widely between pancreatic units. Endoscopic and surgical management is mostly only offered as a 'last resort'. However, the recent ESCAPE-trial reported that early surgery results in lower pain scores when compared with an endoscopy-first approach in some. This raises the question what the current state is of endoscopy and surgery for CP, and Pan-European studies are lacking. Hence, there is a need for an international pragmatic prospective multicenter study to provide an overview. The aim is to evaluate practice variation and outcome of endoscopic and surgical treatment for CP across Europe. We will compare different techniques in indication and peri- and postoperative outcomes with postoperative morbidity and improvement in pain scores as primary endpoint. Primary- and secondary outcomes will be assessed during a follow-up of 12 months.

Mirjam Langeveld

Early treatment, better outcome? Understanding optimal timing of treatment initiation in Fabry disease

Fabry disease (FD) is an X-linked lysosomal storage disorder caused by deficiency of the enzyme alpha galactosidase A (aGAL). Accumulation of Gb3 and its derivatives damages tissues including vascular endothelium, the heart, brain and kidneys. For over 15 years now, enzyme replacement therapy (ERT) is available in Europe to treat Fabry disease. Longitudinal studies have shown that despite ERT, cardiovascular and renal complications occur, especially in those patients that have started treatment later in life. Early treatment may improve outcome, though there currently is no evidence for improvement on clinically relevant endpoints and it is unclear whether 'early' means starting in the first or the second decade of life. In this study we will assess whether initiation of treatment early in childhood improves outcome by comparing sex, age and disease phenotype matched treated patients with untreated patients. The outcome is of particular importance, as it will help to determine whether or not this very expensive, burdensome and lifelong treatment should be initiated in very young patients.

fotografie A. Edridge

Anton Engelsman

A Proof-of-Concept Study of Somatostatin Receptor Subtype-2 Targeted Fluorescence Guided Surgery of Gastroenteropancreatic Neuroendocrine Neoplasms

Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) have a high tendency to metastasize to mesenteric lymph nodes and the liver. Surgical resection shows best results compared to other modalities. However, intra-operative identification of multifocal primary tumours, affected lymph nodes and liver metastases remains challenging. Neuroendocrine neoplasms show overexpression of somatostatin subtype-2 receptors (SSTR-2), which is already targeted for PET tracers. Previous research has established that modification of this with a fluorophore is feasible, and thus can be used as highly specific intra-operative fluorescent tumour targeting. However, none of the previous research translated this advancement to intra-operative real-time identification of tumours and metastases. The aim of this project is to develop, synthesize and implement a SSTR-2 targeted fluorescent tracer in a proof-of-concept study with GEP-NEN patients.

Hans de Vries

Artificial bihormonal pancreas in patients after total pancreatectomy (APPEL 5+)

Inreda Diabetic BV developed the first artificial bihormonal pancreas (AP) to improve treatment of diabetes by automatically controlling glucose concentrations. This system comprises continuous subcutaneous insulin and glucagon infusion with continuous glucose monitoring.

Patients who underwent total pancreatectomy will all develop insulin dependent diabetes and could experience reduced awareness for hypoglycemia. In this randomized, monocenter cross-over study (APPEL 5+) patients who underwent total pancreatectomy will be included. The study will start with a feasibility test including two patients. The main study will be performed in 12 patients and comprises a closed loop (i.e. using the AP) and open loop period (i.e. own treatment). During the closed period patients will perform their normal daily activities. It is hypothesized that the AP provides better glucose control than standard open loop therapy which will ultimately allow patients to optimally participate in society by alleviating their treatment burden and increasing quality of life.

Annet Bosch

Living with Galactosemia

Classical Galactosemia (CG) is an inborn error of galactose metabolism. Infants with CG develop a life-threatening illness after ingestion of galactose. Unfortunately early diagnosis and dietary treatment do not prevent long term complications which include cognitive impairment, movement disorders and primary ovarian insufficiency. In 2004 a negative effect of having CG on the Health Related Quality of Life (HRQoL) of patients was demonstrated. New HRQoL studies in CG are relevant at this time because 1) since 2004 major changes have taken place in treatment and follow up in our Galactosemia Center of Expertise, 2) patients with

a previously unknown milder types of CG are found since the start of newborn screening in 2007, and 3) the evaluation of HRQoL is important for the trial readiness of CG patients as new therapeutic options are expected in the foreseeable future.

Rogier Voermans

UPGRADE trial: Ursodeoxycholic acid for the prevention of symptomatic gallstone disease after bariatric surgery: a multicentre, randomised, placebo-controlled, double-blind trial.

Rapid weight loss is a major risk factor for gallstone development. Approximately 8-15% of patients undergoing bariatric surgery develop symptomatic gallstone disease within 24 months after surgery. Prophylactic administration of ursodeoxycholic acid (UDCA), an oral bile acid, can prevent the formation of gallstones after bariatric surgery by reducing bile lithogenicity. However, little evidence is available regarding the efficacy of UDCA in preventing symptomatic gallstone disease. The UPGRADE-trial is a multicenter, randomised, placebo-controlled, double-blind trial designed to investigate this. All patients (n=985) are randomly assigned to either UDCA 900mg daily for six months or placebo. Endpoints consist of: differences between the two groups in symptomatic gallstone disease within 24 months, number of cholecystectomies, newly formed gallstones on ultrasound at 24 months, side-effects of UDCA, safety outcomes, therapy compliance, quality of life, costs and revenues. The end of follow-up is expected in October in 2020.

Sanne Bootsma

Clinical evaluation of a novel metal binding compound for colorectal peritoneal metastases

Colorectal cancer can disseminate to the abdominal cavity and give rise to peritoneal metastases (PMs). Current treatments for metastatic disease show limited activity against PMs, resulting in poor prognosis in this group of patients. Effective treatment options for patients with PMs are therefore urgently needed. Our analyses revealed that in vitro models of PMs are highly sensitive to a novel compound. The cytotoxic mechanism of this compound depends on its metal ion shuttling action. Divalent ions are delivered to the mitochondria, inducing rapid cell death. We hypothesize that by intra-abdominal administration of this compound with metal salts via a peritoneal access port, PMs can be effectively targeted. Following promising preclinical results we will now prepare a phase I dose escalation trial where we aim to determine the safety and feasibility of the compound as a treatment for patients with PMs.

The AGEM support for clinical consensus meetings 2020 (€7.500)

Lynn Nooijen

The AGEM support for clinical consensus meeting allows us…

… to set up an international consensus meeting with surgeons from over 20 different centers to determine a pre-operative classification system for patients with perihilar cholangiocarcinoma. In the Netherlands, we followed a Delphi like method in order to find clinical consensus. During several online discussions, we came up with a simple classification of resectable, borderline and unresectable patients, in strong analogy with the developments in pancreatic surgery. These criteria are necessary for patient selection and inclusion in new European prospective studies or trials regarding pre-operative treatment. In order to move forward, we would like to do an international Delphi on radiological, clinical and surgical resectability criteria. This Delphi will consist of several online meetings and questionnaires and will finish during an off-line meeting with all participating surgeons.

Marc Besselink

The AGEM support for clinical consensus meeting allows us…

… to organize the Brescia 2021 AGEM International Consensus Meeting: Histopathological Distinction between Ampullary Cancer Types. A meeting of International Study Group of Pancreatic Pathologists (ISGPP). The ISGPP was established by our research group in November 2020.

Ampullary cancer is a rare disease with three histological subtypes (intestinal, pancreatobiliary, mixed). These subtypes could be considered different diseases, with different prognoses ,and different preferred treatment modalities. Therefore, histopathological distinction between subtypes is key for accurate prognostication, and for treatment selection. Currently, however, the histopathological distinction between subtypes is difficult, and there are no international guidelines or consensus on how to classify the subtypes of ampullary cancer.subtyping and substantial inter observer variability among pathologists.

In an attempt to identify, discuss, and overcome the challenges encountered by the pathologist in distinguishing between subtypes, we aim to publish an overview of the considerations, outcomes, and consensus statements that will originate from this meeting.

The AGEM PhD-student course project 2020 (€5.000)

Dion Muller, Jelmer Jukema and Anne Linde Mak

Auto brewery syndrome in the general population and its associated gut microbiota

In January 2020, Jelmer Jukema, Dion Muller, and myself attended the Amsterdam Gastroenterology Endocrinology Metabolism Course. Part of the course was to design a research proposal in a collaboration between PhD candidates from different departments. We had heard an interesting talk from speaker Coen Paulusma on the role of the microbiome in non-alcoholic fatty liver disease (NAFLD). He presented an article showing that certain patients in Asia had alcohol-producing Klebsiella strains leading to auto-brewery syndrome and fatty liver disease. We were intrigued, thinking that maybe NAFLD isn't so 'non-alcoholic' after all and that alcohol production in the gut may also affect liver steatosis in the general population?

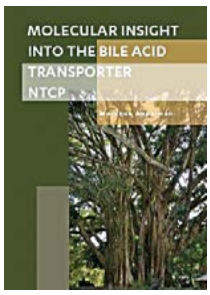
We proposed to find out whether there are also alcohol-producing bacterial strains in the gut of Dutch subjects causing auto-brewery syndrome. For this, we planned to study the HELIUS cohort. A subset of HELIUS participants already provided fecal samples in which their gut microbial composition was determined, and alcohol intake questionnaires were available as well. Here we proposed to measure their blood alcohol levels to find out whether some degree of auto-brewery syndrome might be at play, and to potentially find links to certain gut microbes.

After our proposal received the €5000 grant to fund this project, we decided to use fresh blood samples from the NILE substudy of HELIUS into NAFLD, to measure blood alcohol contents, starting with a pilot of 20 individuals with NAFLD and signs of fibrosis as evaluated by FibroScan during the NILE study visit. Since then, HELIUS has unfortunately been halted due to the pandemic. However, the NILE inclusions have recently been restarted, and we aim to include individuals for our pilot experiment soon!

Anne Linde Mak; also on behalf of Jelmer and Dion

Dion Muller, Jelmer Jukema and Anne Linde Mak

The AGEM contribution printing costs of theses 2020 (€250)



Monique Appelman

Date of thesis defence: 7th May 2020

Molecular insight into the bile acid transporter NTCP

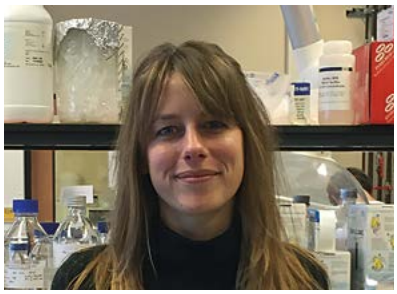
This thesis provides mechanistical insights in the regulation of the bile acid transporter NTCP by newly identified interaction partners, FGF19 and newly identified posttranslational modifications. NTCP is important for a balanced bile acid metabolism and has been identified as the entry receptor for hepatitis type B viral infection. A reduction in NTCP expression can have beneficial effects and due to this NTCP is a fascinating protein to target for therapeutic use in virology and metabolic disorders.

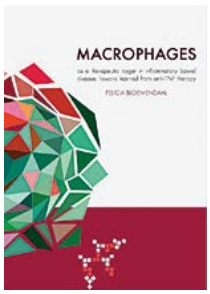
Sandra van de Wiel

Date of thesis defence: 8th May 2020

Intestinal transport and signaling of bile salts, A focus on OSTα-OSTβ

The organic solute transporter alpha-beta (OSTα-OSTβ) facilitates bile acid efflux mainly in ileal enterocytes, liver and kidney, and protects cells from an overload of bile acids. Deficiency of this transporter in humans leads to chronic diarrhea and features of cholestatic liver disease. The goal of this thesis was to gain a better understanding of this transporter and to gain more insight into the differences between OSTα and OSTβ in both mice and humans.



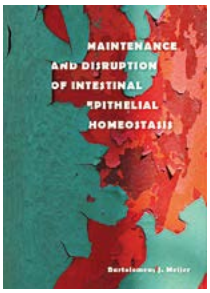


Felicia Bloemendaal

Date of thesis defence: 3rd July 2020

Macrophages as a therapeutic target in inflammatory bowel disease, lessons learned from anti-TNF therapy

This thesis aims to increase our understanding about the effector mechanism of anti-TNF therapy in inflammatory bowel disease (IBD). Although anti-TNF is essential in the treatment of IBD, around 50 percent of patients do not respond. This thesis demonstrates the need for Fcγ-receptor engagement by anti-TNF to decrease intestinal inflammation in vivo and in vitro, furthermore therapeutic efficacy improved when Fc-binding affinity was increased. Mechanistically, we characterize the role of macrophages as Fc binding effector cells.

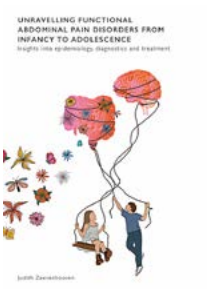


Bart Meijer

Date of thesis defence: 10th September 2020

Maintenance and disruption of intestinal epithelial homeostasis

Renewal of the intestinal inner cell layer, the epithelium, occurs every 4 to 5 days. The intestinal stemcell fuels this renewal by cell division and differentiation to a specific intestinal cell. A differentiated cell is not able to divide and therefore does not contribute directly to cancerous growth. In this thesis we investigate whether cancerous growth could be reduced by forcing a cancerous stem cell to differentiate through activation of a cellular process called ER-stress.



Judith Zeevenhoven

Date of thesis defence: 2nd October 2020

Unravelling functional abdominal pain disorders from infancy to adolescence; insights into epidemiology, diagnostics and treatment

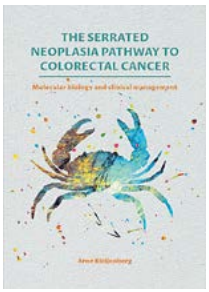
Functional gastrointestinal disorders (FGIDs) are a group of disorders that are characterized by chronic gastrointestinal symptoms. Despite that FGIDs are common in infants and children and have a considerable impact on the daily life of patients and families, they still remain incompletely understood. In this thesis, we particularly focused on one FGID and on a subgroup of FGIDs at different developmental stages: infant colic during infancy and functional abdominal pain disorders (FAPDs) during childhood. Novel insights on definitions, epidemiology, etiology, diagnostic work-up and clinical management were discussed.

Emmeline Peters

Date of thesis defence: 26th October 2020

Implications of Postoperative Ileus, from experimental to clinical studies

Perioperative lipid-enriched enteral nutrition has no effect on the development of complications in patients after colorectal surgery. Furthermore, we describe in this thesis that postoperative ileus has an enormous impact on patient and society. Postoperative ileus is associated with other complications such as anastomotic leakage. We strengthen the evidence that inflammatory processes also in humans play a critical role in the development of postoperative ileus.

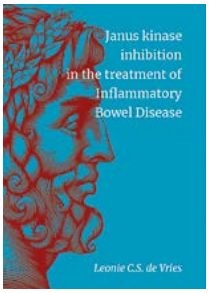


Arne Bleijenberg

Date of thesis defence: 28th October 2020

The serrated neoplasia pathway to colorectal cancer: Molecular biology and clinical management

Colorectal cancer is the second leading cause of cancer-related mortality world-wide. About 15-30% of all colorectal cancer develops from serrated polyps. The studies in this thesis have all aimed to improve care for patients with serrated polyps and serrated polyposis syndrome, and to increase our understanding of how serrated polyps progress into cancer. This will hopefully lead to a reduction in the number of serrated polyps that progress into cancer.

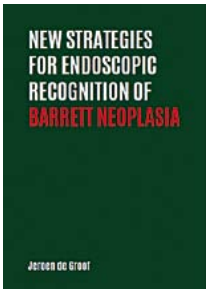


Leonie de Vries

Date of thesis defence: 11th November 2020

Janus kinase inhibition in the treatment of Inflammatory Bowel Disease

We investigated how Janus kinase (JAK) inhibition affects immune responses during intestinal inflammation. We demonstrated that JAK1 selective inhibition is the major contributor in altering the innate immune response in vitro and in vivo, when compared to pan-JAK inhibition by tofacitinib. In addition we found that tyrosine kinase 2 (TYK2) drives pathogenic T cells in experimental colitis models. Lastly, we showed that treatment with tofacitinib and a JAK1 selective inhibitor induced histological response and remission in human IBD.

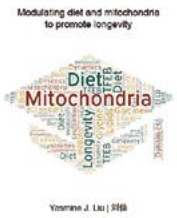


Jeroen de Groof

Date of thesis defence: 18th November 2020

New strategies for endoscopic recognition of Barrett neoplasia

In the thesis “New strategies for endoscopic recognition of Barrett neoplasia”, 3 different approaches are interrogated to increase the endoscopic recognition of Barrett neoplasia. In part 1, the use of optical chromoscopy techniques to increase the visualization of neoplasia is evaluated. In part 2, the development and validation of an online, interactive training module is described. In part 3, the use of machine learning techniques that assist the endoscopist in the recognition of neoplasia is evaluated.

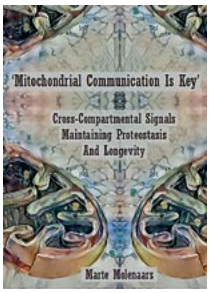


Yasmine Liu

Date of thesis defence: 4th December 2020

Modulating diet and mitochondria to promote longevity

Aging is the major risk factor for various human diseases including cancer, diabetes, cardiovascular disorders, and neurodegenerative diseases. Although life expectancy nearly doubled over 150 years, the age of the onset of most health problems has not been significantly delayed. As such, to increase the length of active longevity free from disease and.disability, known as health span, is an overarching objective of aging research and requires significant scientific endeavor and breakthroughs.

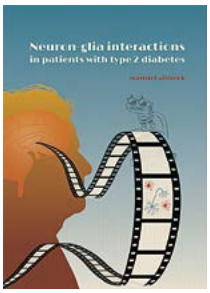


Marte Molenaars

Date of thesis defence: 11th December 2020

Mitochondrial Communication Is Key' Cross-Compartmental Signals Maintaining Proteostasis And Longevity

Aging is a complex biological phenomenon. Better understanding of underlying mechanisms of aging promotes development of preventative therapies for chronic, degenerative age-related diseases such as cancer and Alzheimer's disease. While aging has long been considered a passive process, evidence has accumulated in model organisms that specific cellular pathways strongly affect health and longevity. This thesis presents insights into these age-related processes, with an underlying quest for understanding how metabolism and cellular cross-compartmental signals ensure longevity.



Martin Kalsbeek

Date of thesis defence: 16th December 2020

Neuron-glia interactions in patients with type2 diabetes

In his thesis, Martin Kalsbeek investigated the effects of diabetes and anti-diabetic treatments on neurons and glial cells in different regions of the human brain. Using the unique collection of human brains from the Netherlands Brain Bank (NBB), Kalsbeek et al. showed that diabetes negatively impacts key brain regions controlling energy homeostasis, our sleep/wake-rhythm and memory and cognition. The good news? Anti-diabetic treatment seems to be able to slow down some of these processes.

AGEM Events 2020

AGEM PhD-student course

JANUARY 13th - 22nd

AGEM PhD-student course 2020

Amsterdam UMC, locations AMC and VUmc

In January of 2020, AGEM offered for the first time a course specifically developed for PhD-students that perform research in the field of gastroenterology, endocrinology and/or metabolism. This course aimed to inform (starting) PhD-candidates about gastroenterology, endocrinology and metabolism, including those topics that are not necessarily within the scope of the PhD-candidates own research. The course was coordinated by five AGEM members, Anje te Velde, Dries Kalsbeek, Sarah Siegelaar, Riekelt Houtkooper and Maarten Soeters, and more than 40 teachers gave lectures during the course.

The course runned for a week and a half. In the first week, all participants were given an overview of general insights and methodology applicable to gastroenterology, endocrinology and metabolism in daily lectures with subjects ranging from the pathophysiology of oesophagal diseases from clinic to cell biology, to imaging techniques for insulin resistance, and from epigenetics, to macrophage metabolism.

The following half week consisted of two parallel courses; (1) gastroenterology and (2) endocrinology and metabolism and discussed the matters in more depth.

At the beginning of the course the PhD-students were given an assignment in small groups of three or four students. During the course the PhD students wrote a multidisciplinary grant proposal that was, well-prepared


Lecture Eric Fliers AGEM PhD-student course 2020


Drinks in The Box AGEM PhD-student course 2020


Best pitch AGEM PhD-student course 2020

by the pitch workshop given in the first week, pitched to all participants on the last day of the course.

The course ended with drinks and “bitterballen” in the bar The Box at the AMC.

Judged by the course coordinators, Group E (Dion Muller, Jelmer Jukema and Anne Linde Mak) wrote the best grant proposal and they were given the opportunity to perform the research proposed in their project (See: AGEM Grants 2020 - The AGEM PhD-student course project 2020). Voted by the audience, Group D (Chan, Habibe, de Jong and Pitotti) gave the best pitch and they received a candy bouquet for their great performance.

AGEM annual retreat

OCTOBER 8th

AGEM retreat 2020

Online via ZOOM

AGEM retreat 2020: We adapted and succeeded!

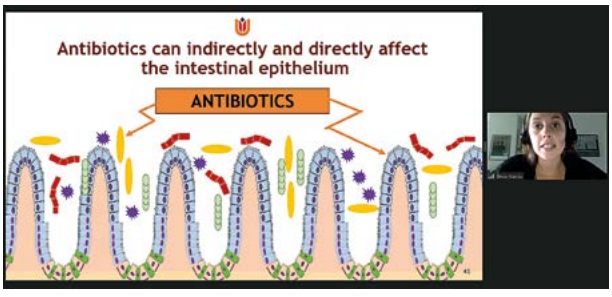
The goal of the AGEM retreat is to discover, share and learn from each other’s research. This year was particularly challenging for the organization of the AGEM retreat. With some delay in the usual calendar due to the situation with COVID-19, we managed to organize a one-day online event to substitute the 2-day presential retreat that normally takes place in Garderen.

With participation of over 80 attendees, among which not only PhD candidates but also several postdocs and PI’s, we can look back on a fantastic AGEM online retreat for the year 2020. At the start of the event three winners of “Best publication of 2019” were announced (Thijs de Rooij, Joanne Donkers and Marjolein van den Boogert).

The program started with a keynote lecture, given from Dr. Giles Yeo (University of Cambridge), that gave us extremely interesting arguments to explain why being obese is not a personal choice and helped us deepen into genetics of obesity.

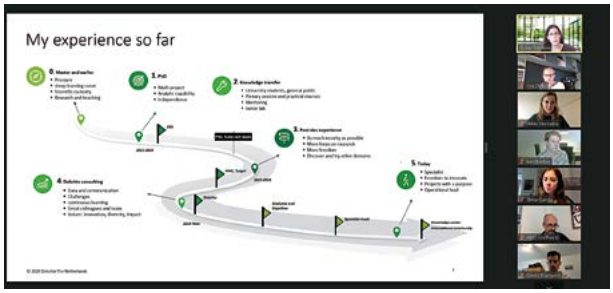
One of the most important parts of the AGEM retreat is to give a space for PhD candidates to share their research and receive input from a diverse audience. Luckily, the online format of the retreat allowed us to organize this. Four different PhD candidates from different AGEM scientific fields gave a 7 minute presentation with time for questions and discussion. The first presentation was given by Karl Harber that presented his work on succinate as an immunoregulatory metabolite in macrophages, then Tânia Garcia introduced the influence of early life use of antibiotics in the intestinal epithelium, Robin Erken continued the session explaining the effect of peginterferon treatment in Chronic Hepatitis B patients and lastly, Fernando Cazarez Marquez closed the session presenting how kisspeptin and not RFRP3 affects energy metabolism in male Wistar rats.

Keynote speaker Dr. Giles Yeo



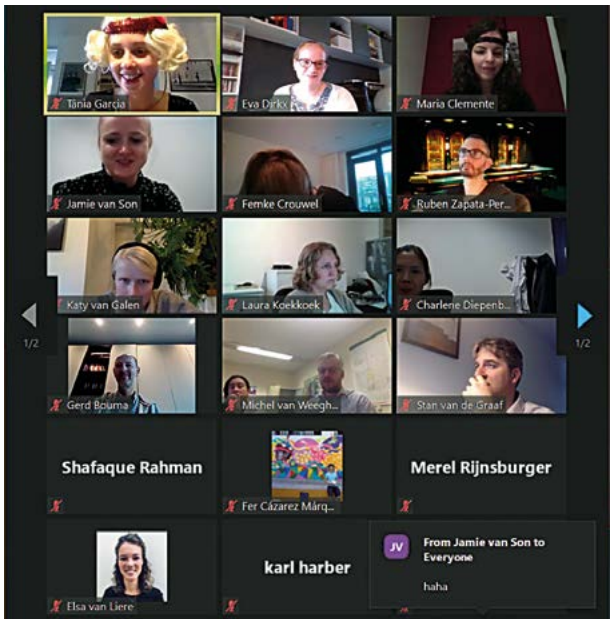
AGEM PhD-student Tânia Garcia

Given the success of the workshops from last years, we could also offer the attendees the opportunity to choose which workshop to attend from an array of relevant topics. The options offered this year were: "Working from home" in these strange times, "Dealing with PhD stress", "Online presentation skills", "Teaching the teacher" and "PhD career development" where we could learn the different career paths and possibilities that a PhD holder can pursue.



Workshop "PhD career development" by Marion Robin and Hilde Herrema

To continue the spirit of previous years, this years' entertainment part at the end of the day was also themed: "The crazy 20's". Participants could join a pub-quiz hosted by professionals (Mr. Bright's Quiz Night) and answer from the comfort of their houses a variety of questions, enjoying a "prohibition era" cocktail, that ended with an overall winner. The winner will receive a prize from the AGEM retreat committee after the event. It was a real pity not being able to interact as much as we normally do in this retreat but given the circumstances, we can affirm that the alternative event was a success.



At the end of the event a poll was made during the Zoom meeting to obtain feedback from participants in order for us to acknowledge the positive and not so positive sides of the online event. The overall rating of the event was positive, specially the keynote speaker. Workshops were also positively evaluated although a considerable proportion of participants did not attend. Most participants are willing to join an online AGEM retreat in the future although the vast majority prefers to have it at location.

Thank you all for making this a great AGEM retreat in 2020. We look forward to see you again (hopefully in person), and to welcome new participants in 2021!

On behalf of the Organizing Committee,
Maria P. Clemente

AGEM symposia

NOVEMBER 5th, 12th, 19th, 26th

AGEM Webinar Series: "Owning Obesity & Negating NASH"

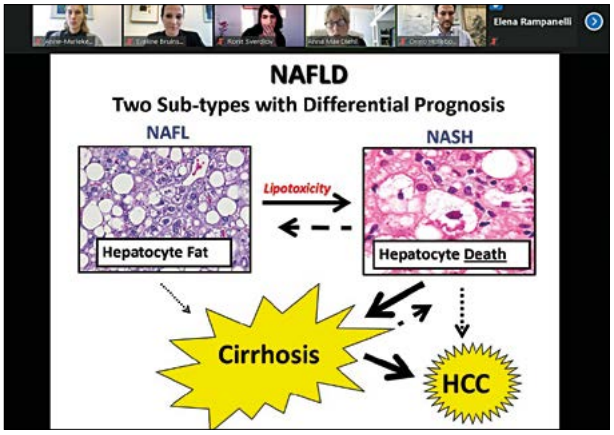
Online via ZOOM

November 2020 gave rise to the birth of "NAFLD November", when the 4-part series of webinars on obesity and Non-Alcoholic Fatty Liver Disease (NAFLD) took place. Originally intended to be a live symposium, the organization was quickly changed, first into a hybrid partly live - partly online version, but then as a result of the COVID crisis into a completely online event consisting of 4 sessions, each Thursday afternoon in November. This change, however, did not dampen the inspirational character of the series, in which 8 (inter) national speakers shared their research and views on NAFLD and obesity, ranging from basic research related talks, to more clinically aimed presentations. The online setting also allowed for many international participants attending the series, with over 100 attendees during the first session! Dr. Onno Holleboom and dr. Eveline Bruinstroop were there each week to chair the sessions and moderate the lively discussions at the end.

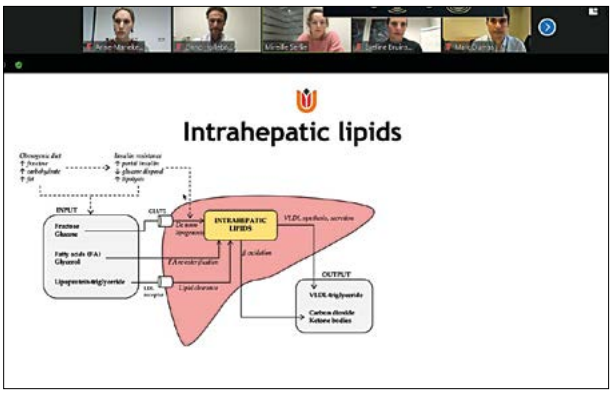
The series was kicked off in Episode 1 with talks by Ronit Shiri-Sverdlov, professor in genetics & cell biology at Maastricht University and Anna Mae Diehl, professor in Hepatology at Duke University, USA. Prof. Sverdlov presented her basic research on the lysosomal proteinase Cathepsin D as a regulator of metabolism and a marker of inflammation in NASH. Professor Diehl presented an intriguing paradigm in which NASH can be regarded as a dysregulated wound healing response. Indeed, pathways involved in fetal development are re-activated during NASH, and repair-related cell types (such as myofibroblasts) are accumulating in the liver, forming fibrosis, cirrhosis, or liver cancer.

In Episode 2, the two speakers were AMC professor of Medicine Mireille Serlie, and professor Marc-Emmanuel Dumas, Chair in Systems Medicine at Imperial College London. Prof. Serlie shared her work on the connection between insulin resistance and NAFLD and presented the paradox of selective insulin resistance, causing reduced suppression of endogenous glucose production but increased hepatic lipid metabolism. Professor Dumas shared his multi-omics approach to understanding NAFLD, and presented a very interesting vision on how NAFLD and NASH research might progress in the coming years.

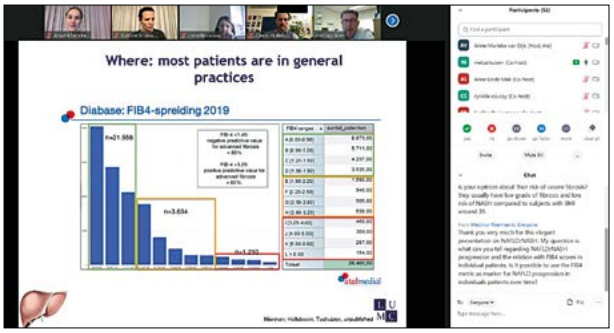
The speakers in Episode 3, focused on the clinical side of NAFLD, were dr. Cyrielle Caussy, endocrinologist from Lyon and dr. Maarten Tushuizen, hepatologist at the LUMC. Both of their talks underlined the importance of screening for NAFLD fibrosis, since this is the strongest predictor for mortality in NAFLD. Especially amongst at-risk patients with cardiovascular disease and/or type 2 diabetes mellitus, it is imperative to identify NAFLD early to ensure preventative measures such as weight loss and strict glucose regulation before end stage liver



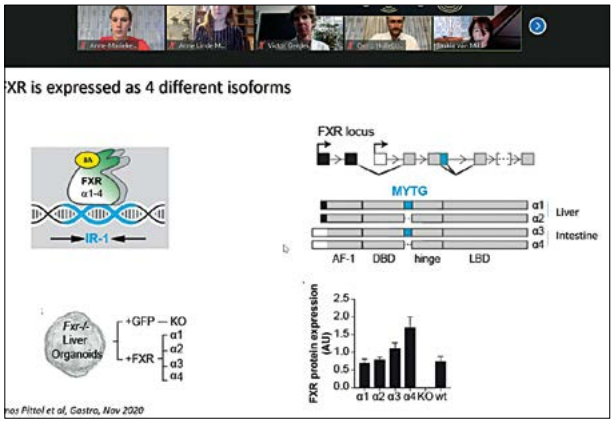
November 5th Prof. Dielh and Prof. Sverdlov



November 12th Prof. Serlie and Prof. Dumas



November 19th Dr. Caussy and Dr. Tushuizen



November 5th Prof. Dielh and Prof. Sverdlov

disease occurs. In this session it was great to see that an endocrinologist from France and a hepatologist from the Netherlands both agreed on the necessity of improving detection and treatment for patients with this (often underestimated) disease!

In the fourth and final episode of the series, prof. Saskia van Mil from the UMC Utrecht and AMC internist dr. Victor Gerdes gave two very different talks. The first was prof. van Mil's presentation on her basic research into the role of the Farnesoid X Receptor (FXR) in NASH, which underlined the importance of distinguishing between the four FXR isoforms α1-α4. Since expression levels of these isoforms in the liver differ, and the genes they regulate differ per isoform, this is an important factor in treatment outcome of medications aimed at the FXR. During the second talk dr. Gerdes took us back to the clinical side of things as he shared his insights on effective weight loss strategies, spanning from lifestyle interventions, weight-loss medication to bariatric surgery.

Thank you to all our participants for tuning in each Thursday in November and for engaging in the interesting discussions at the end of each session. Perhaps we will see you again in 2021 for NAFLD November!

Anne Linde Mak and Anne-Marieke van Dijk

NOVEMBER 13th

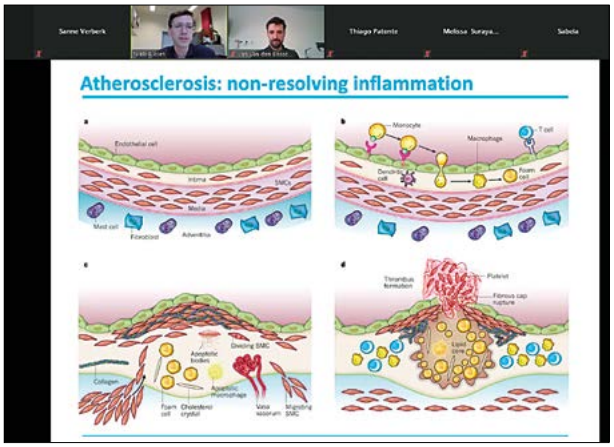
Symposium: "ImmunoMetNet" supported by AGEM

Online via ZOOM

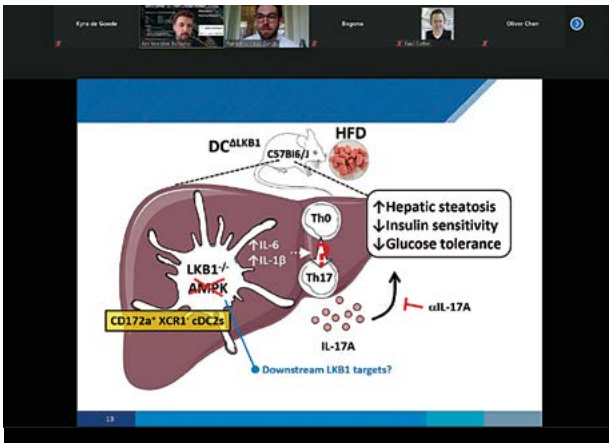
Friday 13th of November was the lucky day for ImmunoMetNet: the Immunometabolism Network of the Netherlands. After replacing the planned physical ImmunoMetNet meeting in May this year by a series of virtual seminars, there was still enthusiasm for a virtual meeting focused on immunometabolic research performed in the Netherlands. The meeting was opened by Jan Van den Bossche after which the first session started, with talks from Niels Riksen, Marianne Boes, Ivan Ramirez Moral and Thiago Patente.

Niels Riksen (Radboud UMC) showed how exposing monocytes to high amounts of oxLDL in early differentiation increases their capacity to mount inflammatory responses. This talk was followed by Marianne Boes (UMC Utrecht), who discussed how CD1d in iNKT cells protect adipocytes from becoming hypertrophic in healthy conditions. The third presentation was given by Ivan Ramirez Moral (Amsterdam UMC, AMC). Ivan talked about bronchial epithelial cell activation by flagellin and how it can be blocked using the mTOR inhibitor rapamycin. After this, Thiago Patente (LUMC) highlighted the role of retinoic acid (Vitamin A) in the tolerogenic response in the gut.

Following this session, we began a virtual coffee break in which everyone could join breakout rooms to ask any remaining questions to the speakers. This was a great way for attendees to have some in depth discussions about research that peaked their interest, which made this symposium very engaging. After this coffee break, the second session started. Here, Geert Wiegertjes



Lecture Niels Riksen



Lecture Patrick van der Zande

(Wageningen University) began with a talk about the conservation of macrophage metabolism in carp fish followed by Paul Coffer (UMC Utrecht) who gave a comprehensive presentation in how the glycolytic switch in activated T cells modulates chromatin remodeling. Begoña Porteiro (Amsterdam UMC, AMC) then showed her results on plasma bile acid signaling and its role in fat droplet buildup in the liver and inflammatory signaling. Patrick van der Zande (LUMC) finalized this session by explaining the role of LKB1 in hepatic steatosis during obesity.

After the lunch break, the interesting day was followed up by a talk from the keynote speaker of the day Maxim Artyomov (Washington University, St Louis). By using paintings of Rembrandt and other Dutch painters he explained the fundamentals of RNAsequencing and metabolomics. His focus was particularly on how these datasets can be combined and integrated to get a more detailed overview of what is happening within your cells of interest. This interesting and vibrant day was closed by talks from the sponsors of this event: Agilent, Biolog, Sartorius and BioSPX. They showed how their methods can contribute to your immunometabolic research and they were available for specific questions in breakout rooms afterwards.

Despite the virtual set-up of the meeting, there were still numerous interesting discussions due to the meet-the-speaker sessions in the small breakout rooms and the possibility to ask questions after each talk. All in all, a very inspiring day for everyone working on immunometabolism. See you next year!
Sanne Verberk, Karl Harber, Kyra de Goede

DECEMBER 3rd

Amsterdam UMC & COVID-19 research event supported by AGEM

Online

On the 3rd of December the research institutes jointly organized the Amsterdam UMC & COVID-19 Research event entitled 'Unorthodox Teams, Accelerating Science'.

With eighteen young researchers, several supporting experts, a brief interview with Anthony Fauci, and nine illustrative videos we showed a brief outline of the COVID-19 research at Amsterdam UMC. In addition, it illustrated how the network of all research institutes combined its scientific expertise and full capacities to contribute to the COVID-19 pandemic, therefor providing a hopeful perspective for the future.

For those interested to catch up with the three conversations on acute COVID-19 research, translational COVID-19 research, and cohorts, rehabilitation & public health please watch watch the event via the link below.
https://www.youtube.com/watch?v=gpxoSjOWiTo

AGEM Tager Lectures

The AGEM research institute has a seminar series in the Amsterdam UMC, location AMC, focused on metabolism; the Tager Lecture, called after Professor Joseph Tager. Joseph Tager made important contributions to Fabry, Pompe and Gaucher disease and had a major impact on our understanding of peroxisomal diseases. He was chairman of the Biochemistry Department at the University of Amsterdam (1980-1991).

The Tager Lecture series is organized by AGEM PI's Riekelt Houtkooper, Susanne La Fleur, Stan van de Graaf and Noam Zelcer. Suggestions for future speakers for the Tager lecture are always welcome.

Amsterdam UMC, location AMC

JANUARY 30th

Prof. dr. Anu Suomalainen

Research Program of Stem Cells and MetabolismFaculty of Medicine, Biomedicum Helsinki, University of Helsinki, Finland

"Metabolic mechanisms of tissue specificity: lessons from mitochondrial disorders"

Online via ZOOM

OCTOBER 29th

Prof. dr. Stephan Herzig

Helmholtz Diabetes Center, Institute for Diabetes and Cancer, Munich, Germany

"Coordination of systemic metabolism by inter-cellular signaling"

DECEMBER 10th

PhD, Associate Prof. Xavier Fioramonti

INRAE, NutriNeuro Institute, Bordeaux, France

"Brain glucose- and insulin-sensing in physiological and diabetic conditions"

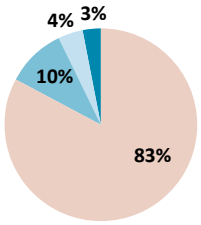
AGEM Numbers and Facts 2020

AGEM finances 2020

For 2020, the AGEM research institute was provided with €558.500,00 (€250.000,00 from board of directors VUmc and €308.500,00 from board of directors AMC). In the table below is shown how this money was budgeted and spend. Most of the 2020 budget was used for the AGEM grants. In 2020 AGEM had an extra call for Clinical Research proposals. Because most meetings were online, less money than previous years was spend on meetings.

Income 2020	
AMC	€ 308.500,00
Vumc	€ 250.000,00
Total	**€ 558.500,00**

Expenditure 2020



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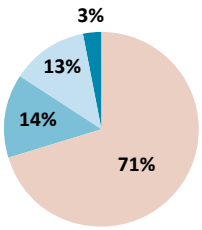
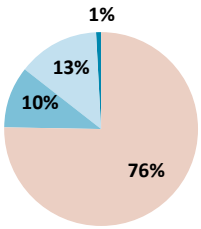


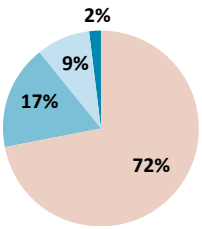
Income 2018	
AMC	€ 308.500,00
Vumc	€ 250.000,00
Total	**€ 558.500,00**

Expenditure 2018



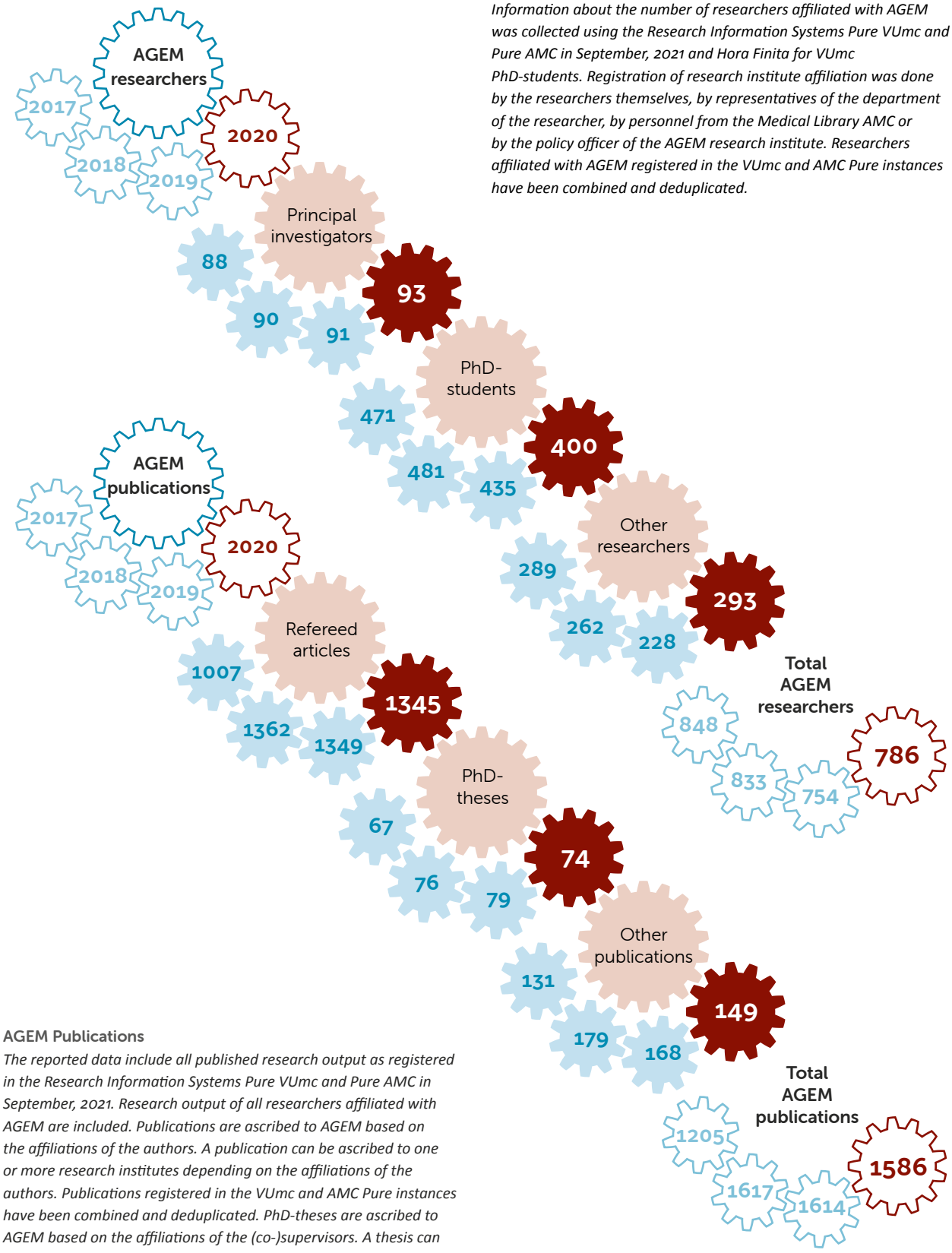
Income 2017	
AMC	€ 250.000,00
Vumc	€ 250.000,00
Total	**€ 500.000,00**

Expenditure 2017



AGEM grants *Personnel* *Meetings* *Miscellaneous*

AGEM numbers 2020



AGEM Researchers

Information about the number of researchers affiliated with AGEM was collected using the Research Information Systems Pure VUmc and Pure AMC in September, 2021 and Hora Finita for VUmc PhD-students. Registration of research institute affiliation was done by the researchers themselves, by representatives of the department of the researcher, by personnel from the Medical Library AMC or by the policy officer of the AGEM research institute. Researchers affiliated with AGEM registered in the VUmc and AMC Pure instances have been combined and deduplicated.

AGEM Publications

The reported data include all published research output as registered in the Research Information Systems Pure VUmc and Pure AMC in September, 2021. Research output of all researchers affiliated with AGEM are included. Publications are ascribed to AGEM based on the affiliations of the authors. A publication can be ascribed to one or more research institutes depending on the affiliations of the authors. Publications registered in the VUmc and AMC Pure instances have been combined and deduplicated. PhD-theses are ascribed to AGEM based on the affiliations of the (co-)supervisors. A thesis can be ascribed to one or more research institutes depending on the affiliations of the (co-)supervisors.

Appointed professors 2020

Prof. dr. Anita Boelen

Thyroid hormone metabolism; in particular molecular and diagnostics aspects

On 31 March 2020, Anita Boelen was appointed professor of Thyroid Hormone Metabolism, in particular Molecular and Diagnostic Aspects, at the Endocrine Laboratory of the Amsterdam University Medical Center, University of Amsterdam.

Anita Boelen is a basic scientist whose research is focused on thyroid hormone metabolism and action in innate immune cells during inflammation. Her PhD project on the role of cytokines on thyroid hormone metabolism during illness was carried out at the Department of Endocrinology. Since 2000, Boelen established her own research group at the Endocrine Laboratory of location AMC to study the mechanisms involved in the illness induced alterations in thyroid hormone metabolism and their effects on cellular and tissue function. To this end, a variety of animal models but also cells derived from patients are used, in close collaboration with clinicians and other (international) research groups.

Anita Boelen is in charge of the regional Dutch Neonatal Screening laboratory, situated in the Endocrine Laboratory. In addition to the studies in innate immune cells, she has a strong research focus on the mechanisms involved in isolated central congenital hypothyroidism, one of the diseases included in the Dutch Neonatal Screening program. Gastroenterology, with a special focus on Neurogastroenterology and Motility

Prof. dr. Els Nieveen van Dijkum

Surgery, with a special focus on endocrine surgery

In June 2020 Els Nieveen van Dijkum was appointed professor in Surgery, especially in Endocrine Surgery.

Els started her career as a PhD student under supervision of Prof Dr D. Gouma at the department of Surgery in the Academic Medical Center (AMC) of Amsterdam. The subject was laparoscopic staging of gastroenterological malignancies, with special interest in pancreatic malignancies. After a residency program in Rotterdam and a Fellowship in Endocrine Surgery supported by the Dutch Cancer Fund, she was appointed staff surgeon in the AMC again, the department she had once started her research. She is dedicated in clinical studies improving patient care for patients with endocrine and neuroendocrine tumors, specifically neuroendocrine pancreatic tumors. She continuously expands her research concerning these rare endocrine and neuroendocrine tumors, expanding to more translational research as well as more internationally driven studies. The Amsterdam UMC gives an enormous opportunity to expand the research group. All research is organized in ACcENT, the Amsterdam Center for Endocrine and Neuroendocrine Tumors, a center which includes all associated specialists and researchers.

Prof. dr. Annemieke Heijboer

Endocrine Laboratory Medicine

September 1, 2020, Annemieke Heijboer was appointed professor of Endocrine Laboratory Medicine at the VU University.

After a PhD at the department of Endocrinology in the Leiden University Medical Center titled 'Insulin sensitivity, modulation by the gut-brain axis', and a training as clinical chemist at the department of Clinical Chemistry in the VU University Medical, Annemieke combined these two interests and specialized in endocrinology. Since 2010 she is heading the Endocrine Laboratory of the VU University medical center which she merged with the Laboratory of Laboratory of Endocrinology of the Amsterdam Medical Center, being the Endocrine Laboratory of the Amsterdam UMC since 2018. Her research focusses on physiology and pathophysiology within the field of endocrinology and the translation to endocrine laboratory medicine in particular the development and the use of high quality biomarkers. Surgery, with a special focus on colorectal surgery.

Did you know that...

... as of April 2020, Amsterdam Gastroenterology & Metabolism (AG&M) continued as Amsterdam Gastroenterology Endocrinology Metabolism (AGEM). For more information visit the AGEM website.

... the article of one of the AGEM international student fellowship 2019 laureates Samantha Wolff' called "*The Effect of Rev-erbα Agonist SR9011 on the Immune Response and Cell Metabolism of Microglia*" was published in Frontiers in Immunology (Front Immunol. 2020 Sep 25).

... AGEM researcher Dr. F.A. Vieira Braga was awarded an NWO VENI grant.

... Dr. Hilde Herrema, Dr. Onno Holleboom, Dr. Wieger Voskuijl, Dr. Roos Pouw, Dr. Nanne de Boer, Dr. Peter Henneman, Dr. Marleen Kemper, Prof. dr. Paul van Trotsenberg, Dr. Fred Vaz and Dr. Johan van Limbergen were appointed as (AGEM) PI.

... the Pancreatitis Werkgroep Nederland created five international guidelines:

- International consensus guidelines for surgery and the timing of intervention in chronic pancreatitis.
- International consensus guidelines for pancreatic cancer in chronic pancreatitis.
- The role of total pancreatectomy with islet autotransplantation in the treatment of chronic pancreatitis: A report from the International Consensus Guidelines in chronic pancreatitis.
- International consensus guidelines on the role of diagnostic endoscopic ultrasound in the management of chronic pancreatitis.
- Standards for reporting on surgery for chronic pancreatitis: a report from the International Study Group for Pancreatic Surgery (ISGPS).

Future perspectives for the AGEM research institute

As 2021 proceeds, with all AGEM researchers/clinicians vaccinated and the number of Covid patients in the hospital wanes, what will be the new normal for the AGEM? How do co-directors Professors Gerd Bouma and Stan van de Graaf intend to move forward? First, for them, will be to re-establish the importance of direct interaction between scientists, clinicians, students. Professor Bouma: "As a clinician, I still go to work and see my colleagues but I do know scientists who are forced to work from home a great deal and have really had to re-think their science. As soon as possible we need to return to a normal where people meet real-life to discuss science. Education too, students need to return to normal classes, how education has been affected really hurts."

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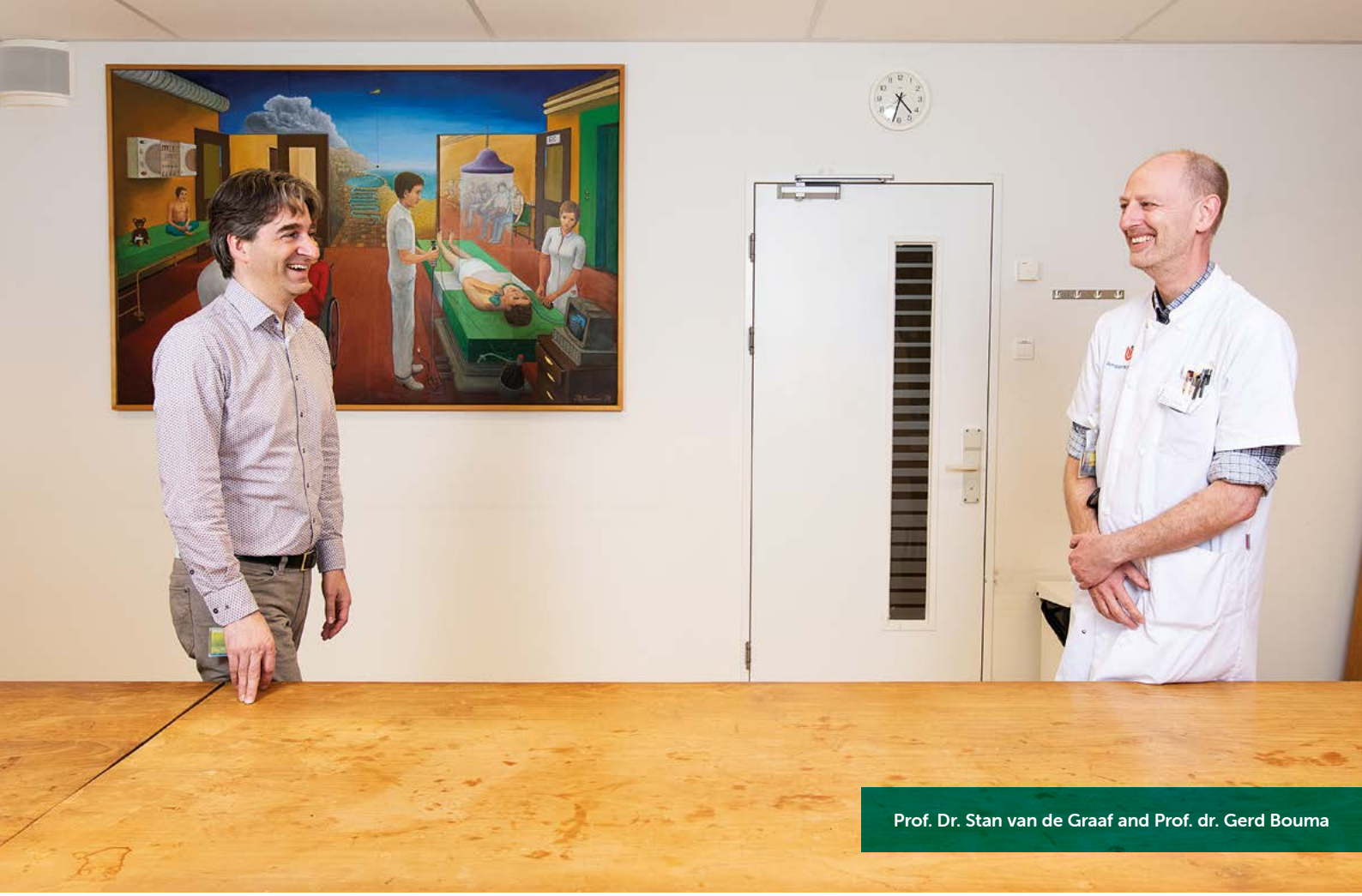
Professor Van de Graaf adds that it is not just direct interaction itself, some contacts and plans have continued to flourish, but "what you really miss is the non-planned chance meetings, people who are not aware of each other's expertise. I feel this has again become a barrier which interferes with collaboration." The Institute has striven in the past to organize events so that people who did not even know each other suddenly saw an opportunity to collaborate. Re-establishing that is now the real challenge for Professor Van de Graaf.

Professor Bouma agrees that, typically, things that have been missed are going to a meeting and squeezing in a lecture about something not entirely in your field. "You listen and you think, heh, this is something I can use for my research. This simple interaction even at the coffee machine, you chat, your work comes up, new ideas, this is what I hope will return when we get back to normal." For the future the AGEM's tools will mostly be the same, the annual retreat, symposia, and funds to try to boost original cross-discipline solutions and increase the chance of external funding of talented individuals, consortia and public-private collaborations.

Another priority for the future is to look at the areas where the work of the AGEM overlaps with the other seven Research Institutes in the new single hospital. To date the AGEM has loosely defined its boundaries as anything relating to the three disciplines: gastroenterology, endocrinology, and metabolism. Typically divisions come about because people in a particular Institute are working on a particular



Prof. Dr. Stan van de Graaf and Prof. dr. Gerd Bouma

disease or group of diseases. However, Professor Bouma explains, there is overlap as a disease is not entirely specific to a single Institute. “Rheumatology, for example, is closely related to inflammatory bowel disease (IBD) they are both inflammatory disorders and people with intestinal inflammation can also have joint problems.”

So now the AGEM is more or less settled on what it is, he feels it is time to broaden its horizons and look at where it can find others. “We are starting to look over the boundaries at the other Institutes. Once the Covid restrictions are over, we plan a meeting with the Amsterdam Infection and Immunity (AII) Institute because there is a lot of research being carried out which is of interest to us and vice versa. We are going to talk with their Principal Investigators to tell them about our science and to hear about theirs, for the purpose of serendipity, to look for where we overlap, what are the commonalities within the other institutes. It is good to look over your boundaries, to see what you can learn and how you can collaborate with people who, maybe, work in the same corridor.”

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Looking forward Professors Bouma and Van de Graaf also want to ensure the work of their Institute has a relevance to society. It needs to question which diseases it should study and how it should organize in the field. Only then can it facilitate research not just for its own patients but also for patients treated in other hospitals.

Hereto, collaboration with other, regional hospitals will be required. The government has mandated that university hospitals such as the Amsterdam UMC should concentrate of specialized tertiary care. As a result many of the most common disorders from which


Gerd Bouma


Stan van de Graaf

Dutch people suffer, diabetes, irritable bowel disease, much of inflammatory bowel disease are being treated elsewhere. Professor Bouma: “We don’t generally see these patients in a university hospital any more, but the science to address these problems is urgently needed. So we need to collaborate more closely in future, not just taking referrals, but viewing regional hospitals more and more as partners in a bigger network, sharing our knowledge and our patients.”

How best to collaborate in future with the pharmaceutical industry through public’/private partnerships has also been under consideration by the AGEM over the past year. Professor Bouma stresses that investigator initiated clinical research is very important to academic science as this is from where the new ideas emerge and have to be tested. Researchers at the AGEM can build the patient groups and lay down networks so that studies can be carried out. Equally he does not believe this excludes other parties and stresses that industry-driven research can connect with academia. Collaborations with industry can benefit patient research, it can lead to new therapies, new treatment options for instance.

Despite the Covid-19 lockdown measures of 2020, the two co-directors share confidence in the progress AGEM has made the last year and will continue to make in 2021. Professor Van de Graaf: “We have not lost a year. We have slowed down but certainly not gone back in time. We can now catch up where we left off.” In particular, he stresses the importance of the way clinical research and care are now organized has already shown benefits in recent months. “People come together in one location with the basic science also in the same place. If people are in the same area for a large part of the day that will help us a lot.”

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Professor Bouma agrees: “We have not been set back in time. Several aspects have slowed but this has also created opportunities to re-think about how we do and can work.”

And the AGEM is no longer its infancy but growing. “We definitely are not beginners any more. We are a research institute. We have a solid place in the organization for which research is imbedded and facilitated and that place becomes more and more relevant.”
Gerd Bouma, AGEM director
Stan van de Graaf, AGEM director
Eva Dirkx-Beuling, AGEM policy officer
Linda van den Noord, AGEM secretary


Gerd Bouma
Eva Dirkx
Stan van de Graaf
Linda van den Noord

Amsterdam UMC
University Medical Centers

Amsterdam Gastroenterology Endocrinology Metabolism