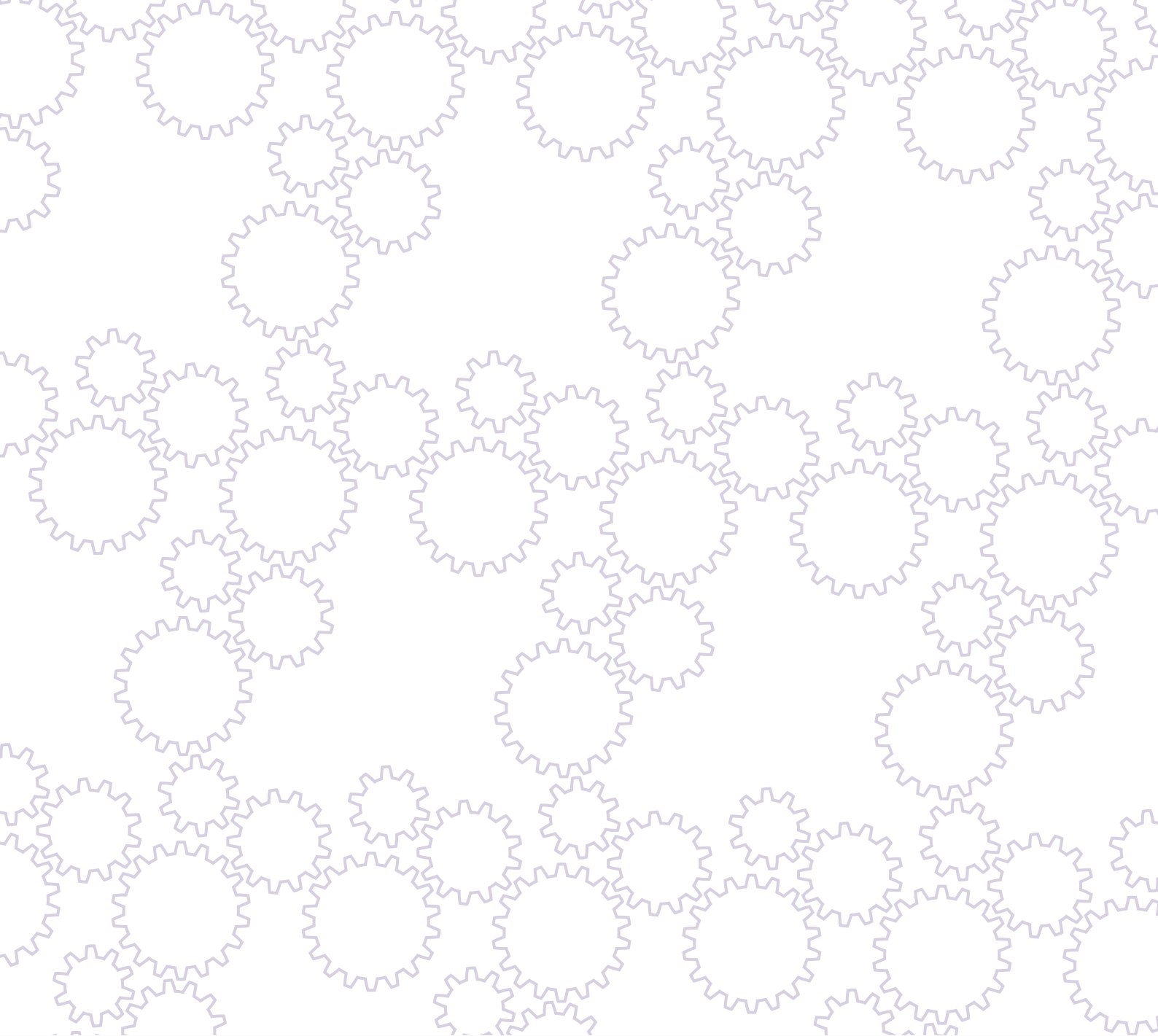


Amsterdam Gastroenterology Endocrinology Metabolism

# AGEM Annual report 2019





## Colophon

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# AGEM directors looking back



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

Three years into the project, and co-director Professor Gerd Bouma sees a momentum building, an evolution and waves of relocation, as the physical merging of whole departments gets underway. It is no longer just about bringing people together, he says, as they are “already there”, it is about helping people in a research institute do what they do best – research.

Amsterdam Gastroenterology & Metabolism, one of eight research institutes forged from the merger of Amsterdam’s Academic Medical Center (AMC) and the VU medical center (VUmc) became, in 2019, less theory and more reality. The Gastroenterology & Hepatology department prepared to move its Upper-GI group to the Boelelaan early in 2020, while Endocrinology had already gone the other way to the Meibergdreef. It was even decided to adopt a new ‘married’ name reflecting, more accurately, the research undertaken by the Institute. It will now be known as Amsterdam Gastroenterology Endocrinology Metabolism (AGEM).

Professor Bouma explains that at the start we were “two entirely different worlds” and so they began from scratch, “from the bottom up”, by facilitating young professionals, PhD students, working together through the retreat, the symposia and the lectures.

“There is a realization that we are getting more mature, we know what we want, to facilitate the research. It is more about deciding how we want to distribute resources with input from people for whom we are doing this.”

Co-director Dr Stan van de Graaf stresses: “We facilitate research, but not just for the sake of the Institute. The idea that has become clearer over the last two years is that the Institute is a means to an end – supporting research- but not an end in itself.” And, as such, relations with other research institutes have changed too. “I get the feeling with the other directors that the competition has vanished. If people see an opportunity to collaborate with other institutes that’s fine.” They are no longer building walls but acknowledging that their research is frequently overlapping and that everyone benefits from inter-institutional collaboration.

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**“We facilitate research, but not just for the sake of the Institute. The idea that has become clearer over the last two years is that the Institute is a means to an end – supporting research- but not an end in itself.”**

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Driving this momentum for change, and the first 2019 highlight cited by Professor Bouma and Dr Van de Graaf, was the two-day annual PhD retreat in April. Here more than 100 PhD students, postdocs and Principal Investigators got to share, discuss, and learn from each other’s research. Everyone also enjoyed a chance to present their own work, with all PhD students giving brief, elevator pitches, of their research in just three minutes. This included dual presentations, combined data, with a direct colleague from their research group or a collaborator. This year postdocs also got to play a bigger role and will do so in future.

There were keynote speakers too, and some illustrated the power of storytelling, even with minimal visual aids such as PowerPoint. For example, Professor dr. Aart Jan van der Lely presented a “cool story” with a key message on the adverse effects of sugar, and ‘out of the box speaker’ Gerko Tempelman challenged notions of belief. Meanwhile workshop subjects ranged from, ‘Scientific outreach and how to use it for public awareness’, to ‘Commercializing technology’.

But the secret of its success- and one which is now been discovered by other research institutes- is the added value of being together for two days, having a good time, in a different environment. Social events, for example, were themed on the idea of, ‘the year you were born’, to help people get to know each other better and to stimulate teambuilding.



Professor Bouma goes as far as to say: “It is the most focused moment in the year when all the scientists come together and we are really a multi-disciplinary institute. Putting all the people together for two days who, on an everyday basis, are spread across many different departments, connected only loosely, is very special. It creates a separate, a great, environment, physically merged in one place where we can all tell each other what we are doing and what we want to achieve. This creates an enormous amount of energy and enthusiasm, people want to learn from each other, to create collaboration during the scientific programs, and to continue to want to talk about their interests during the social ones.” With research constantly changing, new ideas move in which scientists have to follow and the PhD retreat is, therefore, “a perfect moment to all be together”.

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**Putting all the people together for two days who, on an everyday basis, are spread across many different departments, connected only loosely, is very special.**

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Dr Van de Graaf admits it is difficult to prove just what’s going on but the theory is simple. If you work in the same department for years, you may create a wall around yourselves, an academic bubble. The retreat bursts it. “If you force people to be together for a couple of days and they like it, it opens them up a little bit. We believe it is possible for completely different disciplines, like laboratory research with clinicians, to collaborate. We want to reinforce that whenever we can.

One of the significant developments in 2019, linked to the retreat, and to the aim of breaking down walls between disciplines, was the preparatory work for launching a two-week teaching program. This aims at “broadening the horizons” of PhD students by allowing them to gain a general background in the many different disciplines taught in a such a diverse Institute, many of which relate, in a greater or lesser degree, to their own research.

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**One of the significant developments in 2019, linked to the retreat, and to the aim of breaking down walls between disciplines, was the preparatory work for launching a two-week teaching program.**

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Professor Bouma argues: “PhD students often focus on a very minute piece of health care or science. Here they will get a broader view of the context of their research and how their specific topic is incorporated into the bigger picture.” In a practical sense, this will enable students to understand better the short presentations given at the PhD retreat where there is little time to give a lot of background. But, in a broader sense, Professor Bouma also sees this evolving in future years. “We want to see what are the questions and the needs from the PhD students, for example whether they relate to more general scientific matters such as biostatistics or bioinformatics.”

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This broader view of the work of the Institute, bringing together different disciplines in order to create new ideas, was an approach which was reflected too in the three successful symposia hosted in 2019: Complex genetics of metabolic disease; Hormones & Digestion, and; Imagine the Image.

2019 has also seen the awarding of grants for talent, innovation, and international study, and, in doing so, the distribution of resources to facilitate young careers and collaboration.

A source of pride for the two directors was being able to send students to study abroad, through internships at top foreign universities, funded through the AGEM international student fellowship. Professor Bouma believes building the Institute from the bottom up means identifying ambitious young talent and facilitating their careers. AGEM sends them to Boston, Massachusetts in the US, to London in the UK and, for first time in 2019, to a university in China. Samantha Wolff travelled to China's Nanjing Medical University to research microglial immunometabolism for her master's thesis. Other examples include Remco Kersten who studied in the US, and Elsa van Liere who returned from studying in London and is now looking into setting up a multi-center study evaluating the safety and efficacy of thioguanine in the management of inflammatory bowel disease (IBD).

Dr Van de Graaf: "Students, both clinicians and laboratory researchers, are all very enthusiastic about this. They say it helps them develop as a person and, afterwards, improves their chances of returning to a PhD position."

Talent development grants, meanwhile, are aimed at postdoctoral students. One example in 2019 was Joep Grootjans, a clinician-scientist working on IBD. After receiving an AGEM talent grant, he then went on to receive a further Veni grant from the Dutch Organisation for Scientific Research (NWO). Professor Bouma: "We can't claim credit for this, these are competitive programs, but, in general, if we award research grants it shows to the outside world that we have confidence in them." Talent grants went too to Jung-Chin Chang and Eveline Bruinstroop, mentioned later in the annual report.

The Institute also awarded an innovation grant last year to Eduard Struys and Clara van Karnebeek for

their work on a form of inherited neonatal epilepsy. What impressed Dr Van de Graaf is that they combined different backgrounds. Clara is a clinician and Eduard a laboratory scientist. "They want to combine metabolomics, using an advanced laboratory technique, with clinical expertise to try to figure what exactly is the mechanism, the action, why do these children get sick, and which could, maybe, point to future therapy. Here, we bring together disciplines, one laboratory diagnostics, he is an expert in measuring metabolites, and the other is seeing patients. Clara has a special talent for setting up consortia and facilitating people working together."

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**Here, we bring together disciplines,  
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expert in measuring metabolites,  
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2019 saw other changes. Six new professors were appointed, and two people, Annet Bosch and Marc Besselink, were appointed to fill vacancies in the eight-person research board, which represents the various research programs of the institute and advises the two directors on its direction. Here, Professor Bouma believes in the added value of also including PhD students and postdocs in the board, to bring in fresh ideas and different perspectives.

However, what has not changed is the overall size of the Institute. At approximately 400 PhD students and 90 Principal Investigators it is already sufficiently large to achieve our goals, argues Professor Bouma: "It is not our aim, eventually, to be the biggest institute. It is about quality not quantity."





# AGEM Research Programs

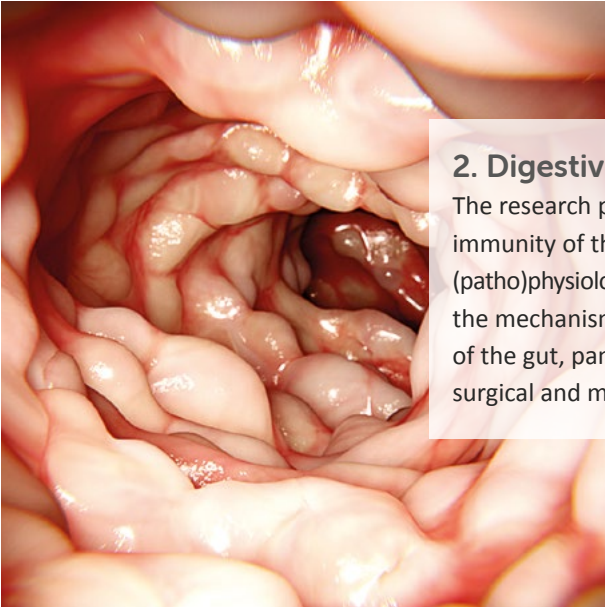
Based on an inventory of the strengths of the research in gastroenterology, endocrinology and metabolism conducted at the Amsterdam UMC, the following four research programs have been specified. Our aim is to stimulate research in these 4 themes, and also multidisciplinary research that bridges them.



## **1. Re-generation and cancer of the digestive system**

The groups embedded in the research program “Re-generation and cancer of the digestive system” focus on the postnatal development, repair and carcinogenesis, and functionality and motility of the digestive tract. The physiological homeostasis of the digestive tract, the deregulation thereof in the oncogenic state, and the development of novel treatment strategies are important areas of study.



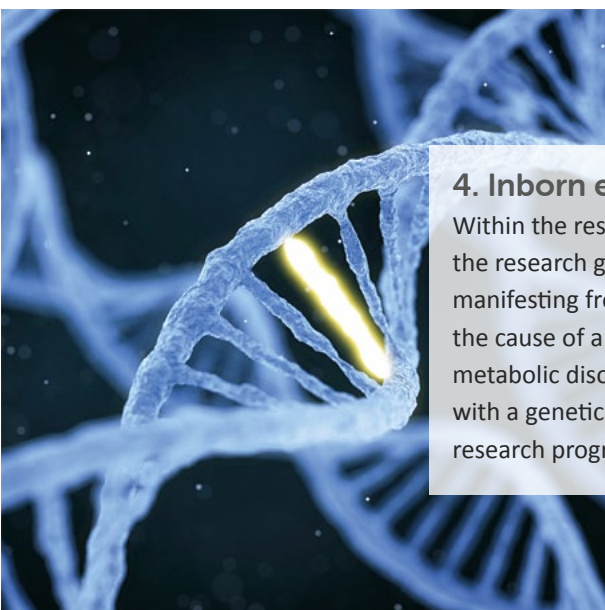


## 2. Digestive immunity

The research program “Digestive immunity” focusses on the mucosal immunity of the human digestive system in health and disease. The (patho)physiology of the digestive immunity, the relation to the microbiome, the mechanism of action of therapies of immune mediated diseases of the gut, pancreas and liver, nutrition and the development of novel surgical and medical treatment strategies are the main research areas.

## 3. Endocrinology, metabolism and nutrition

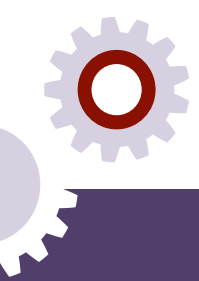
In the research program “Endocrinology, metabolism and nutrition”, the effect of lifestyle, diet and malnutrition on metabolism and hormonal regulation plays a central role. The ultimate aim of this research program is to improve metabolic health of patients with metabolic and endocrine pathologies.



## 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.





# AGEM Research Board 2019

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



The AGEM research board 2019

## New to the AGEM Research Board



### Annet Bosch

Since October 2019 Annet Bosch, joined the AGEM research board. Annet is a Pediatrician for Metabolic Diseases. She is the coordinator of the NFU recognized Metabolic Diseases Center of Expertise and AMC representative at the European Metabolic Reference Network (Metab ERN). As Amsterdam UMC Principal Investigator she performs clinical and translational research, with specific focus on the metabolic diseases Galactosemia, Phenylketonuria and Riboflavin Transporter Deficiencies.

#### *What I want to achieve with the AGEM research institute...*

As a clinician I am happy to participate in the AGEM research board aiming to build bridges between the different preclinical and clinical research fields within the AGEM. Awareness of all the expertise that is available in the research groups of our institute will increase cooperation and excellence.





**Marc Besselink**

Since April 2019, Marc Besselink, joined the AGEM research board. Marc is the professor of Pancreatic and Hepatobiliary (HPB) surgery at Amsterdam UMC. As principal investigator he studies novel and existing clinical treatment strategies for pancreatic and hepatobiliary diseases, which includes acute pancreatitis, chronic pancreatitis, and pancreatic cancer. He has initiated numerous clinical studies and multicenter randomized trials in the Dutch Pancreatitis Study Group, Dutch Pancreatic Cancer Group and the European Consortium on Minimally Invasive Pancreatic Surgery.

***What I want to achieve with the AGEM research institute...***

As a surgeon-scientist I would like to bridge the gap between basic and clinical research and make sure the unmet needs of our patients are being addressed in good translational research. In the other direction I would like to bring developments within AGEM under the attention of clinical-scientists in AGEM. AGEM is a very large and active research institute which can facilitate the work that is being done by a large group of young researchers in the field of gastroenterology and surgery.

## AGEM directors



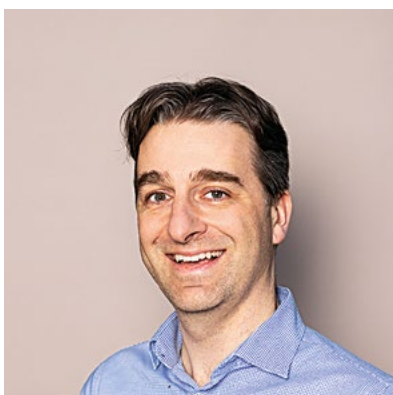
### Prof. dr. Gerd Bouma

*Department of Gastroenterology and Hepatology*

Professor of Gastroenterology and Hepatology  
AGEM Co-Director VUmc

**Specialization:** Gastroenterology

**Research subject:** Mucosal immunology



### Dr. Stan van de Graaf

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

Associate professor  
Principal investigator at Tytgat Institute for Liver and Intestinal Research  
AGEM Co-Director AMC

**Specialization:** Biochemistry/Physiology

**Research subject:** Targeting metabolite dynamics to treat metabolic and liver diseases

## AGEM Research Board members



### Prof. dr. Max Nieuwdorp

*AMC and VUmc Internal Medicine*

Professor of Internal Medicine, with a special focus on diabetes mellitus  
Head of the department of Experimental Vascular Medicine  
AGEM Research Board member

**Specialization:** Internal medicine: Endocrinology

**Research subject:** The role of gut microbiota in development of human obesity, insulin resistance and dyslipidemia.





**Prof. dr. Riekelt Houtkooper**

*Laboratory Genetic Metabolic Diseases*

Professor of Translational Metabolism  
 Principal investigator at Laboratory Genetic Metabolic Diseases  
 AGEM Research Board member

**Specialization:** Biochemistry/Physiology

**Research subject:** Mitochondrial metabolism in health and disease.  
 Metabolic aging



**Prof. dr. Louis Vermeulen**

*Center of Experimental and Molecular Medicine*

Professor of Molecular Oncology  
 Principal investigator at Center of Experimental and Molecular Medicine  
 AGEM Research Board member

**Specialization:** Molecular oncology; colorectal cancer

**Research subject:** Molecular subtype specific stem cell dynamics in  
 developing and established colorectal cancers.



**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  
 AGEM Research Board member

**Specialization:** Immunology

**Research subject:** Study of chronic intestinal inflammation (inflammatory  
 bowel disease, IBD); pathophysiology and therapeutic interventions.



**Dr. Annemieke Heijboer**

*Endocrine Laboratory & Department of Clinical Chemistry*

Associate professor  
 Principal investigator at Endocrine Laboratory  
 AGEM Research Board member

**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

AGEM Research Board member

**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



**Dr. Annet Bosch**

*Department of Pediatric Metabolic Diseases*

Principal investigator at AMC

AGEM Research Board Member

**Specialization:** Metabolic Diseases

**Research subject:** Diagnosis and Treatment of Galactosemia, Phenylketonuria, Riboflavin Transporter Deficiencies

**AGEM office**



**Dr. Eva Dirkx-Beuling**

*Amsterdam Gastroenterology Endocrinology Metabolism (AGEM)*

Policy officer AGEM

Secretary AGEM Research Board

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





# AGEM Science Impressions 2019

To give an impression of the research conducted in the AGEM research institute, six couples of young investigators and their supervisors were invited to present the research projects they worked on in 2019.

## Monitoring diseases activity and therapy responsiveness in IBD patients

*Reina Mebius and Estefany Burniol Ruiz*

Secondary lymphoid organs, such as lymph nodes, greatly enhance the odds by which rare antigen-specific lymphocytes encounter dendritic cells that present antigen to T cells. It is therefore within lymph nodes that adaptive immune reactions are started. We study the cellular and molecular mechanisms that are necessary to form these highly organized lymphoid organs. Special attention is paid to the differentiation requirements of stromal precursor cells to the different stromal subsets that are present within adult lymphoid organs. For this differentiation process, stromal cells need to interact with immune cells. Within adult lymph nodes, stromal cells are able to convey location specific as well as survival signals to immune cells. Additionally, lymph node stromal cells are involved in controlling autoreactive T cells, a function that is similar and potentially complementary to the process of T cell selection in the thymus. We study how this process of T cell selection within lymph nodes is controlled and regulated.

The formation of lymphoid compartments is not restricted to ontogeny, since ectopic lymphoid structures are formed during chronic inflammatory diseases as well in solid tumours, where they can either contribute to the inflammatory response or mount an anti-tumour response, respectively. Within these organized structures various different stromal subsets are present, each with their own function. Further characterization of these functions reveal more specifics by which the immune system is controlled by its environment.

Immune activation within lymph nodes occurs in response to inflammation within the tissues. Soon after the start of an inflammatory response, innate cells will travel to the draining lymph nodes, to start the adaptive immune response that is tailored to the inflammatory response within the tissue. Not only adaptive lymphocytes, but also innate lymphoid cells





Reina Mebius and Estefany Burniol Ruiz

are activated within the draining lymph nodes and both activated innate and adaptive lymphocytes will leave the lymph nodes and appear in the blood in order to travel to the inflamed tissue. In collaboration with Prof. dr. Gerd Bouma, we are using this knowledge to further study this mechanism in patients with inflammatory bowel disease (IBD). With the use of extensive flow cytometry panels for both fluorescence as well as mass cytometry, we aim to monitor the presence of activated subsets of (innate) lymphoid cells within peripheral

blood of patients as an indicator of disease-activity and therapy responsiveness. For this, we are working to establish a cohort of 100 patients which we will analyse over time.

We additionally monitor whether therapy responsiveness can be predicted from in situ analyses of tissue biopsies from diseased areas within the intestines in a retrospective study.



## The Yin and Yang of cyclic AMP

*Ronald Oude Elferink and Simei Go*

The liver group within the Tytgat Institute has historically concentrated on the pathophysiology of bile formation. In more recent years there has been a gradually increasing interest in hepatic and intestinal metabolism. Our research into the role of soluble adenylyl cyclase was started because of its potential role in liver disease, but now concentrates for a large part on metabolism. The reason for this is a long story. In the early '90s of the last century, the group of prof. Jesus Prieto in Pamplona (Spain) discovered that the chloride/bicarbonate exchanger AE2 is downregulated in bile duct epithelial cells (cholangiocytes) of patients with primary biliary cholangitis (PBC). These patients (mostly middle-aged women) suffer from progressive cholestasis due to the loss of bile ducts. This loss of cholangiocytes is associated with striking infiltration of immune cells around the bile ducts and the presence of anti-mitochondrial antibodies in the circulation. Because of these observations, it has been thought for many decades that this disease is an autoimmune-type like disease with unknown trigger. However, over the years no definite proof could be found to support that hypothesis; e.g. immunosuppression has no effect on the patient. Hence, it is possible that the disease has a different etiology and that the immune response is secondary to cholangiocyte damage.

The finding of the Spanish group made us wonder whether downregulation of AE2 might be a secondary consequence of an unknown insult that triggers cholangiocyte damage. Therefore, in collaboration with this group, we made a knockout mouse for this gene (*SLC4A2*) and searched for potential effects on cholangiocytes. This was a hazardous undertaking because AE2 is expressed in many cell types and fulfills a crucial role in maintaining the intracellular pH. Once the mouse strain was finally established (after a lot of difficulties) it kept us busy for many years. As expected this animal was full of phenotypes. It suffered from achlorhydria because AE2, as a basolateral chloride/ bicarbonate exchanger, turned out to be necessary for

the intracellular pH correction during proton secretion in gastric parietal cells. It also suffered from severe osteopetrosis because AE2 corrects the intracellular pH in osteoclasts during acidification of the extracellular lacuna during bone resorption. Furthermore, the animals completely lacked enamel on their teeth. It turned out that AE2 is necessary for the correction of intracellular pH of ameloblasts during the acidification cycle that ensures the replacement of amorphous hydroxyapatite by enamel during the growth of the teeth. Finally, the homozygous male knockouts were infertile. While the elucidation of all these phenotypes provided us with a number of nice papers, it did not solve the problem of PBC, because the mice had only very weak signs of bile duct damage. The reason for this was probably the fact that mice can compensate for the absence of AE2 by overexpression of another chloride/ bicarbonate exchanger.

Meanwhile, our mouse model was also lost: for some unknown reason (probably a subtle environmental change in the animal institute) the (heterozygous) AE2 knockout mice could not breed anymore and the strain was lost. Fortunately, we still had fibroblasts from the animals, so we could study the role of AE2 at the cellular level (modern and rapid knockdown or knockout procedures were not yet available). Using these cells we found that the absence of bicarbonate secretion by AE2 had profound effects on the cellular homeostasis of cyclic AMP (cAMP). Since cAMP is an extremely versatile second messenger molecule, this triggered our interest and we dug into this deeper. To make a long story short, we found that a non-canonical adenylyl cyclase (soluble adenylyl cyclase, sAC encoded by the *Adcy10* gene) is overexpressed in these fibroblasts, which turned out to be caused by the increased intracellular bicarbonate concentration due to the absence of AE2. In hindsight this is not a strange finding as the main trigger of sAC expression and activity is the prevailing intracellular bicarbonate concentration.



Simei Go and Ronald Oude Elferink

Jung-Chin Chang and Simei Go found that inhibition of sAC protects cells from apoptosis by oxidative stress. This means, conversely, that signaling through sAC is required for apoptosis. This brings us back to the liver disease PBC. As mentioned before these patients have a problem with biliary bicarbonate secretion, leading to increased sAC expression and activity. In turn, this may sensitize cholangiocytes to oxidative insults that induces apoptosis (more than in healthy persons), which may explain the basis of this disease. The latter part is still speculation and remains to be proven in new animal models.

However, sAC has brought us more interesting findings. It turns out that inhibition of sAC has profound metabolic consequences. It induces a shift from oxidative phosphorylation to aerobic glycolysis, a phenomenon called the Warburg effect, which is a crucial condition for many tumor types. Hence, sAC may turn out to be a tumor suppressor gene.

We also have indications that sAC may play a role in the maturation of cilia-associated proteins and may regulate the proper function of the primary cilium on

cholangiocytes. This is very important for yet another liver disease, namely polycystic liver disease. Although these experiments look very promising, they are still in a very early phase and are actually also part of the work of Simei Go.

An overarching aspect of our studies into the role of soluble adenylyl cyclase is that in all of the mentioned regulatory roles (apoptosis, glucose metabolism and cilium function) it turns out that cAMP generated by the non-canonical sAC (ADCY10) has the opposite effect of cAMP generated by the canonical adenylyl cyclases (ADCY1 to ADCY9). Hence, it makes all the difference WHERE the cAMP is generated; whereas sAC generates cAMP at intracellular sites, the canonical adenylyl cyclases generate cAMP at the plasma membrane. Apparently, depending on the intracellular site of generation, cAMP can have opposite functions. This could be called the Yin and Yang of cAMP.

This work is supported by a grant of the KWF to Ronald Oude Elferink and Simei Go is recipient of an AMC PhD scholarship. Jung-Chin Chang received an AGEM talent development grant this year (see later in this report).



## Personalized treatment selecting and response predicting in IBD using epigenetics

*Geert D'Haens, Vincent Joustra and Ishtu Hageman*

Geert D'Haens was appointed as head of the AMC-IBD Unit in December, 2010 and Professor of Inflammatory Bowel Diseases at the University of Amsterdam. He specialized in inflammatory bowel disease already early in his career and presented his doctoral thesis in 1996 on 'early postoperative recurrence of Crohn's disease'. From 1999 till 2011 Geert D'Haens created and led the Imelda GI Clinical Research Centre at the Imelda general hospital in Bonheiden, Belgium, where many new medications for inflammatory bowel disease and colorectal cancer have been investigated. D'Haens was the president of the Flemish Society of Gastroenterology from 2007 to 2011 and co-founder and now honorary member of the European Crohn's and Colitis Organization ECCO in 1999. Until 2019 he was chairman of the International Organization for Inflammatory Bowel disease IOIBD and director of Robarts Europe, an academic clinical research organization with headquarters in Canada devoted to the study of IBD.

During more than 2 decades, D'Haens' research has focused on improving treatment of patients with IBD. He currently supervises over 10 PhD students and a research office of 16 staff, while being head of the IBD outpatient clinic. Under the supervision of Geert D'Haens the IBD Research Unit has grown to be the largest of our country.

He has come to realize that development and testing new drugs is not the only way forward in improving long-term outcomes in IBD patients. Therefore a new focus on the more translational side, considering biomarker research using a multi-omics approach and big data machine learning analysis to predict treatment choice and/or response has become increasingly important in the research of Prof. Dr. D'Haens.

### **Development and validation of epigenetic biomarkers to predict treatment response in Crohn's Disease: EPIC-CD project**

Vincent Joustra and Ishtu Hageman are two PhD students in the group of Geert D'Haens, working closely together with Andrew Li Yim under supervision of

Prof. Dr. W. de Jonge and Dr. P. Henneman on the discovery and validation of epigenetic biomarkers to predict treatment response in Crohn's disease using state of the art machine learning statistics.

Although the use of biologicals dramatically improved the care of CD patients over the past two decades approximately 40-75% still fail to respond to either one or more biologicals thus highlighting the need for adequate prediction of therapeutic response prior to starting therapy.

An increasing body of evidence suggests that epigenetic alterations, such as aberrant DNA methylation, are involved in the pathogenesis of CD. DNA methylation is the binding of a methyl to 5'-cytosine-phosphate-guanosine-3' (CpG) dinucleotides near gene promoters and is generally associated with altered gene expression, which is thought to occur through the inhibition of transcription factor binding. Multiple studies show that differentially methylated loci across different cell types are relevant for chronic inflammatory disease states and are therefore capable of differentiating between IBD phenotypes underscoring their potential as putative biomarkers.

Our group has recently shown that specific genome-wide DNA methylation patterns prior to treatment using an unbiased approach can accurately discriminate patients responding to biological treatment with Infliximab, Adalimumab or Vedolizumab in a PILOT fashion.

The EPIC-CD project aims to further expand the discovery of epigenetic marks using 15 responders (R) and 15 non-responders (NR) for each of the four main biologicals (Infliximab, Adalimumab, Vedolizumab and Ustekinumab) and validate these marks in an external cohort at the Radcliffe Infirmary in Oxford (also 15R and NR per biological treatment). A third separate validation cohort collected at the AMC will also investigate the functionality of found markers using RNA expression analysis and the association of epigenetics and the gut microbiome. A total of 360 patients (45 R and 45NR/ drug) will be included in this project.



Over the course of 26-52 weeks both endoscopic-, clinical- (Harvey Bradshaw Index) and biochemical (CRP, F. Calprotectin, TDM) parameters are tightly monitored using our established biological care path. Both baseline and follow-up DNA, RNA, serum, plasma, stool and biopsy samples are collected through our established Future IBD biobank.

We recently expanded and analyzed the first discovery cohort using methylation data from bisulfite converted DNA in 16R and 14NR to Vedolizumab treatment. Data were split in two sets, 70% training and 30% testing. Stability selected gradient boosting with a 10-fold cross-validation, a supervised tree-based machine learning approach identified 40 predictor CpGs capable of distinguishing response from non-response to Vedolizumab (AUC 0.82,  $p = 0.01$ ) prior to treatment.

Notably, the degree of methylation for the response-associated DMPs did not change after 14 weeks of treatment ( $n=30$ ), or even after 79 weeks ( $n=10$ ). Our observations provide evidence towards the

establishment of epigenetic marks with predictive biomarker capabilities, paving the road towards personalized treatment selection in CD.

### Studying DNA methylation using CRISPR-Cas9 based technology

The EPIC-CD project is a collaboration between the clinical department and the Tytgat Institute for Liver and Intestinal Research. Isthu Hageman, PhD-student under supervision of prof.dr. Wouter de Jonge is setting DNA methylation editing technique in collaboration with dr.P.Henneman, dr.C.Paulusma and dr.T.Hakvoort. CRISPR-Cas9 technology is an upcoming technology used worldwide for genomic engineering. One type of the CRISPR tool box is a modified version of dCas9 ("dead Cas9"), fused to enzymes involved in the methylation process, methyltransferases (DNMT or TET) for specifically editing DNA methylation. Using this technique we aim to establish effect of methylated or unmethylated genes that are involved in the pathogenesis of Crohn's disease.



## The brain as link between obesity and diabetes

*Susanne la Fleur and Laura Koekkoek*

The way the brain responds to consuming excess amounts of fat and sugar, and how this, in turn, influences food intake and glucose metabolism is the focus of the research group of Susanne la Fleur.

The prevalence of obesity and type 2 diabetes has grown to epidemiological proportions in recent years. An important cause of these metabolic disturbances is the daily abundant intake of high palatable food items such as fat and sugar. Energy obtained via nutrients is important for brain function as nutrients are used by the cell for energy and building blocks. The brain, however, is limited in its capacity to store energy and thus depends on what circulates in the bloodstream. By stimulating feeding, the brain can meet these energy needs. And when no food is available, the brain can free energy from metabolic tissues, such as liver and adipose tissue. Because of this important role of the brain in regulating eating behavior and metabolism, disruption of brain function can contribute to the development of obesity and type 2 diabetes.

To study the response of the brain to fat and sugar and the consequences for behavior and metabolism, the group developed an animal model. For this, animals are provided with a dish of saturated fat and a bottle of sugar water in addition to nutritionally-balanced pelleted food and tap water to mimic the variety of healthy and unhealthy foods, humans consume on a regular basis. Animals like to consume the extra fat and sugar and are doing so by showing snacking-like behavior. They rapidly become obese due to overconsumption, develop insulin resistance and beta cell insufficiency. Interestingly these changes are accompanied by changes in the brain. The animal work has also been translated to a human experimental setting in close collaboration with Prof Mireille Serlie. We showed that, similar to data from our rodent model, snacking fat-sugary drinks alters metabolism and brain centers involved in regulating energy balance. The next step is to determine the causal relation between diet-induced brain changes and alterations in behavior and metabolism.

Two regions in the brain of interest in relation to energy metabolism are the hypothalamus and striatum. The hypothalamus is important for regulating glucose metabolism, and signals to eat when hungry and to stop eating when being satiated, and is thus important for regulating our homeostatic energy balance. When providing animals with the additional choice to consume fat and sugar, we observed marked changes in the hypothalamic arcuate nucleus, and specifically in Neuropeptide Y (NPY), a peptide that stimulates feeding and reduces insulin sensitivity. Instead of an expected reduction in NPY in response to overeating to counter the increased adiposity by reducing feeding, we observed that this diet increased NPY. This increase was specific to the combination of fat and sugar, as just consuming extra fat or extra sugar did not increase NPY. Next we showed that the arcuate nucleus is connected to the striatum. This area is well known for its involvement in the rewarding-aspects of feeding behavior, and we showed that NPY when infused in the striatum increases food-motivation. Interestingly, together with Prof Mireille Serlie, we discovered that in both humans and rodents the striatum can also regulate glucose metabolism. This recent finding initiated new research into the role of the striatum in regulating glucose metabolism and how it links to consuming palatable food.

To further unravel the effects of the fat-sugar interaction on the brain, PhD student Laura Koekkoek investigates, in rodents, the effect of high fat diet exposure on the response of the brain to a repeated bolus of sugar solution. By providing a small amount of sugar every day during 7 days, she is able to determine how the brain handles the sugar when animals are either consuming a regular diet, or a high-fat diet. She investigated the expression of genes involved in glucose sensing and glucose utilization in both hypothalamus and striatum, and showed, for example, a synergistic effect of high-fat diet consumption and the sugar bolus in the striatum on a marker of cell excitability. To further understand the fat-sugar interaction at cellular level in a *in vivo* setting, Laura together with



Laura Koekkoek and Susanne la Fleur

PhD student Margo Slomp, used *in vivo* two-photon fluorescence microscopy, to analyse the activity of excitatory and inhibitory neuronal population while animals were drinking sugar with prior excess to regular or high-fat diet. This was performed in the lateral hypothalamus, an area involved in integrating hypothalamic hunger and satiety signals with striatal reward information and regulates palatable food preference. They showed interacting effects of fat and sugar consumption on excitatory output of this area. In a new project, she will focus on the striatal opioid system, and how its sensitivity is altered when drinking sugar. Furthermore, she aims to investigate how the striatal opioid system is involved in the control of systemic glucose homeostasis.

The la Fleur group is part of the Department of Endocrinology and Metabolism and the Endocrine Laboratory of the Department of Clinical Chemistry. Mid 2018 the Endocrine Laboratories of VUMC and AMC were the first to join forces and moved into the new laboratory at the AMC location. A couple of months later, the AMC clinicians from the Department of Endocrinology and Metabolism joined as well, now sharing offices between research, diagnostics and clinic which strengthened the already intensive collaborations enabling translational research.



## Functional Genetics of Metabolic Diseases

*Hans Waterham and Frouwkje Politiek*

### Combining Research and Diagnostics of inherited Metabolic Diseases

Prof. dr. Hans R. Waterham is Professor Functional Genetics of Metabolic Diseases, Principal Investigator, and certified Netherlands and European Clinical Laboratory Geneticist (VKGL and EBMG) in the Laboratory Genetic Metabolic Diseases of the Amsterdam UMC, location AMC. He gained his MSc and PhD degree in Biological Sciences at the University of Groningen, and is broadly trained in microbiology, molecular & cell biology, genetics and biochemistry (yeast and mammalian cells). After obtaining his PhD degree, he performed 3 years postdoctoral research in Portland, Oregon, USA, and 0.5 year in Nijmegen, after which he was recruited in 1997 by Prof. dr. Ronald Wanders to join the Laboratory Genetic Metabolic Diseases with the challenging task to introduce and integrate molecular biology and genetics in the laboratory. Since then the laboratory has steadily grown to become a world renowned expertise centre for translational research and diagnosis of human inborn errors of metabolism. In addition to research, Hans established and supervises the laboratory's CCKL/RvA-accredited DNA diagnostic unit which offers clinical genetic testing of inborn errors of metabolism (>70 different disorders).

Hans Waterham's 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. Research of his group is characterized by multidisciplinary and translational approaches using different model systems (mammalian and human cells, mice, yeast) and combining contemporary genetic, biochemical, metabolomic and cell biological methodologies. Among others, his research group has been involved or leading in the biochemical and genetic elucidation of the underlying defect of a large number of inherited metabolic diseases. More recently, research focus has shifted more towards studies aimed at understanding the consequences of genetic defects for metabolism, cellular functions and the patient, with the ultimate goal to develop therapeutic approaches.

### The United for Metabolic Diseases consortium

Together with Prof. dr. Clara van Karnebeek, former pediatrician at the Amsterdam UMC and currently Professor Metabolic Diseases at the Radboud UMC, Hans is co-founder and co-director of the *United for Metabolic Diseases (UMD) consortium* ([www.umd.nl](http://www.umd.nl)), which was initiated end 2017 and officially launched in 2019. UMD is a unique collaboration between medical doctors, researchers and laboratory specialists of the different metabolic centers of expertise in the Netherlands and has the mission to apply and translate innovative research and technology into improved diagnosis, prevention, treatment and care for patients and families suffering with an inherited metabolic disease. Thus UMD unites research, diagnostics and clinical care of the six Netherlands Academic Metabolic Expertise Centers and closely collaborates with patient organizations. Main incentives for founding the UMD are the great diversity, complexity and rarity of inherited metabolic diseases, of which currently more than 1000 different conditions are known, which require a more focused and integrated approach, increased awareness, and dedicated funding for research.

### Metabolic Fever in the autoinflammatory metabolic disorder Hyper-IgD syndrome

One main research program in the group of Hans Waterham involves the identification, elucidation and characterization of pathophysiological consequences of genetic defects in human peroxisome biogenesis and function, and the development of therapeutic approaches for patients with relatively mild peroxisomal disease. In this program also baker's yeast is used as translational model organism to study peroxisomal functions (both yeast and human proteins), including the identification and characterization of yeast and human peroxisomal metabolite transporter proteins.





Hans Waterham and Frouwkje Politiek

A second main research program involves the identification, elucidation and characterization of pathophysiological consequences of genetic defects in human cholesterol/isoprenoid biosynthesis. In this program, Frouwkje Politiek started her PhD study in the spring of 2019 in a collaborative research project with the group of Prof. dr. Mihai Netea of the Radboud UMC entitled 'The role of innate immune reprogramming in Hyper-IgD syndrome' (HIDS). HIDS is an intriguing autosomal recessive autoinflammatory disease in which the regulation of the innate immune response is disturbed due to a metabolic defect, i.e. a deficiency of mevalonate kinase (MK), an essential enzyme of the isoprenoid/cholesterol biosynthesis pathway. Patients with HIDS typically suffer from lifelong recurrent attacks of sterile inflammation characterized by fever, rash, abdominal pain, joint pain. Although the group of Hans Waterham already elucidated the genetic defect underlying HIDS in 1999, and since then gained considerable insight in the pathogenic consequences of the mutations and MK deficiency at the cellular level, still little is known regarding the precise molecular mechanisms responsible for these

recurrent inflammatory symptoms, and no effective therapy is available for the patients, despite several anti-inflammatory approaches being targeted and tried. The project combines complementary expertise on metabolism, molecular biology, inflammation, innate immunity and patient treatment with the overall aim to decipher the metabolic, epigenetic and immunological mechanisms that characterize immune cells of patients with HIDS.

The innate immune system forms an essential defense system against pathogens, and inflammation can be an important complicating factor in inherited and acquired (metabolic) disorders. These studies will provide crucial insight in the role of the isoprenoid/cholesterol biosynthesis pathway in the regulation of innate immunity and inflammation, which will be instrumental for the development of specific interventions to prevent, alleviate or suppress inflammation in HIDS patients. The project has the ambition to provide a couple of novel therapeutic leads that eventually can be tested in clinical trials in HIDS patients and, potentially, other pro- and hyperinflammatory diseases.



## Immunoglobulin A: a Trojan horse or magic bullet?

*Marjolein van Egmond and Amélie Bos*

Prof.dr. Marjolein van Egmond is professor in Oncology and Inflammation at the department of Surgery. Her research has a strong bench to bedside (and back) approach and to ensure optimal translation of experimental findings into clinical applications, she also has PI appointment at the department of Molecular Cell Biology & Immunology. Her research centers around the role of antibodies in health and disease with a focus on immunoglobulin A (IgA). This is the most prevalent antibody at mucosal sites, and has important roles in defence by preventing invasion of pathogens. In general, IgA has been considered as a non-inflammatory regulator of mucosal homeostasis. However, our studies show that IgA is a very potent stimulus to activate myeloid immune cells through interaction with the IgA Fc receptor (Fc $\alpha$ RI). Previously, we established an important role for Fc $\alpha$ RI on the interface of mucosal and systemic immunity by demonstrating that liver macrophages eliminate serum IgA-coated bacteria from the blood stream. More recently, research has expanded to neutrophil function, when we discovered that Fc $\alpha$ RI has the unique ability to induce neutrophil recruitment. As such, we proposed an important function for Fc $\alpha$ RI in (mucosal) immunology, as recruited neutrophils can control infectious threats by phagocytosing IgA-coated invading bacteria.

### **IgA in chronic inflammation and autoimmunity**

Normally, IgA-induced neutrophil migration and activation is a self-limiting process. Once the pathogens have been cleared, the absence of IgA complexes (i.e. IgA-coated bacteria) will end inflammatory reactions as newly recruited neutrophils will no longer be activated and will die through apoptosis. However, we have now demonstrated that excessive IgA complexes or autoimmune IgA trigger perpetual inflammation as every newly recruited neutrophil will respond by recruiting even more neutrophils. This results in a continuous neutrophil activation and migration loop that ultimately leads to massive tissue destruction, which is most noticeable in patients with the rare autoimmune disease 'linear IgA bullous disease'. For

unknown reasons these patients develop IgA auto-antibodies that are directed against the skin, which excessively triggers neutrophil activation resulting in severe blistering. Similar aberrant responses have now been observed in rheumatoid arthritis when IgA autoantibodies are present and in inflammatory bowel disease. Importantly, we also demonstrated that blocking Fc $\alpha$ RI with monoclonal antibodies or peptides diminishes neutrophil recruitment and tissue damage, and we are currently developing novel drugs for clinical applications to dampen IgA- induced inflammation.

### **IgA in inflammatory bowel disease**

In her PhD research Amélie Bos focusses on two aspects of IgA biology. Firstly, in collaboration with Prof. dr. Reina Mebius she is investigating the regulation of IgA production by B cells. Vitamin A is metabolized into its active form retinoic acid in the gut. Retinoic acid is a key player in inducing the IgA isotype switch, but the mechanisms have not yet been fully elucidated. Induction of IgA class switching by retinoic acid is important in regulating a balanced microbiota. As microbial dysbiosis is observed in patients with inflammatory bowel disease, we hypothesize that retinoic acid-induced IgA isotype switching may be disturbed. We are studying the effect of retinoic acid metabolism in B lymphocytes and found that human B cells do not have the enzymes needed to produce retinoic acid themselves. Nevertheless, exogenous retinoic acid induces IgA class switching in B cells. As such, B cells require help of other (immune) cells as a source of retinoic acid. We are currently investigating the role of intestinal dendritic cells in this process. Secondly, Amelie is studying the role of IgA-induced neutrophil activation in inflammatory bowel disease in more detail. This project is conducted in collaboration with Prof.dr. Gerd Bouma. We show that patients with ulcerative colitis have increased infiltration of intestinal neutrophils that closely interact with the epithelial lining. Furthermore, IgA antibodies are potent in activating neutrophils of patients, triggering the formation of neutrophil extracellular traps. In an experimental model we demonstrated that the



Marjolein van Egmond and Amélie Bos

interaction of human IgA and Fc $\alpha$ RI leads to excessive neutrophil recruitment, tissue damage and exacerbates pathogenesis of colitis. Altogether, these results support that continuous stimulation of Fc $\alpha$ RI-expressing neutrophils by IgA induces sustained inflammation and significant tissue damage in ulcerative colitis.

### **IgA as novel therapeutic drug to treatment cancer.**

Since IgA has the ability to induce disproportionate neutrophil recruitment and activation, unleashing the destructive capacity of neutrophils in tumours may represent an attractive opportunity for cancer therapy. Therapeutic anti-cancer monoclonal antibodies are currently of the IgG isotype, which can eliminate tumour cells through natural killer cell-

mediated antibody-dependent cellular cytotoxicity and macrophage-mediated antibody-mediated phagocytosis. However, IgG ineffectively recruits neutrophils as effector cells. We already showed that IgA anti-tumour antibodies very effectively induced tumour cell killing by neutrophils. Nonetheless, using IgA also has disadvantages, as it is unable to activate natural killer cells and has a shorter half-life. Together with Dr. Gestur Vidarsson (Sanquin), we are therefore developing novel antibody formats that incorporate both the agonistic activity of IgG monoclonal antibodies as well as Fc $\alpha$ RI targeting. We anticipate that these molecules can activate macrophages, natural killer and neutrophils as effector cells for the killing of tumour cells, which may greatly enhance the therapeutic efficacy of monoclonal antibodies.



# AGEM Best Publication 2019

In 2019 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 2019. Out of these nominees the AGEM Research Board selected a top 3.

The nominees are offered a pitch workshop and with the skills learned will pitch their publication during the AGEM Retreat of 2020. After this so-called “battle for the AGEM Best Publication 2019 award”, the attendants of the retreat can vote for their ultimate favorite. The author of the publication with the most votes will be named winner of the AGEM Best Publication 2019.

## Please meet the nominees for the AGEM Best Publication 2019...



### Marjolein van den Boogert

Marjolein van den Boogert was nominated by Onno Holleboom for her article published in *Circulation*: “N-Glycosylation Defects in Humans Lower Low-Sensity Lipoprotein Cholesterol Through Increased Low-Density Lipoprotein Receptor Expression”.

Dr. Holleboom’s motivation for her nomination was that Marjolein has designed and carried out this insightful translational study from beginning to end in a thoroughly scientific manner, generating and testing hypothesis upon hypothesis. It combines a rare clinical cohort of congenital glycosylation defects and their family members, with intracellular insights from three intricate cell model systems for which she went the University of Pennsylvania in Philadelphia. These model systems all point to an important role for N-glycosylation in regulating LDL-receptor and plasma cholesterol.



### Thijs de Rooij

The publication of Thijs de Rooij: “Minimally Invasive Versus Open Distal Panceatectomy (LEOPARD) – A Multicenter Patient-blinded Randomized Controlled Trial” published in *Annals of Surgery* is also a contender for the title AGEM Best Publication 2019.

Prof. dr. Marc Besselink gave the following explanation for why he nominated Thijs: Minimally invasive pancreatic surgery is complex surgery, aimed to minimize the initial negative impact of surgery on the patients wellbeing. Laparoscopic distal pancreatectomy was rarely performed until recently in the Netherlands and randomized trials and training programs were lacking. Thijs coordinated a nationwide training program which reduced conversion to open from 38% to 8% and increased the use of this procedure with 700% in the Netherlands. Immediately hereafter, he initiated and coordinated the world’s first multicenter randomized, patient-blinded, randomized controlled trial of minimally invasive.

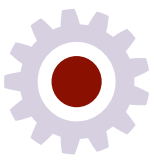
### Joanne Donkers

Last but not least Joanne Donkers was selected to pitch her article: “NTCP deficiency in mice protects against obesity and hepatosteatosis” which was published in *JCI insight*.



Dr. Stan van de Graaf nominated Joanne and says the following about this: Bile acids play a major role in the regulation of lipid and energy metabolism. In this papers Donkers et al propose the hepatic bile acid uptake transporter Na<sup>+</sup> taurocholate co-transporting polypeptide (NTCP) as a target to prolong postprandial bile acid elevations in plasma. Reducing hepatic clearance of bile acids from plasma by genetic deletion of NTCP moderately increased plasma bile acid levels, reduced diet-induced obesity, attenuated hepatic steatosis, and lowered plasma cholesterol levels. This is a great achievement as she effectively identified a novel liver-specific target to exploit the endocrine function of endogenous bile salts to induce metabolic improvement, which is very fitting in the scope of AGEM.





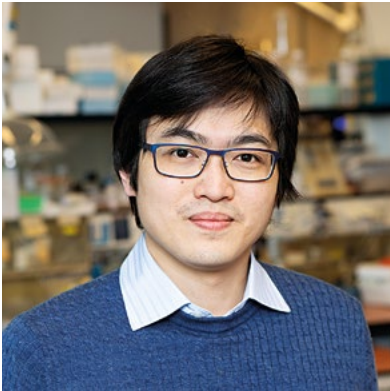
# AGEM Grants 2019

In 2019, AGEM awarded 3 types of grants: The AGEM talent development grant (75kEuro) 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 (50 kEuro) for innovative ideas beneficial to the AGEM research institute as a whole, and the AGEM international student fellowship (€500/month) 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.



AGEM talent development and innovation grant laureates 2019

## The AGEM talent development grant

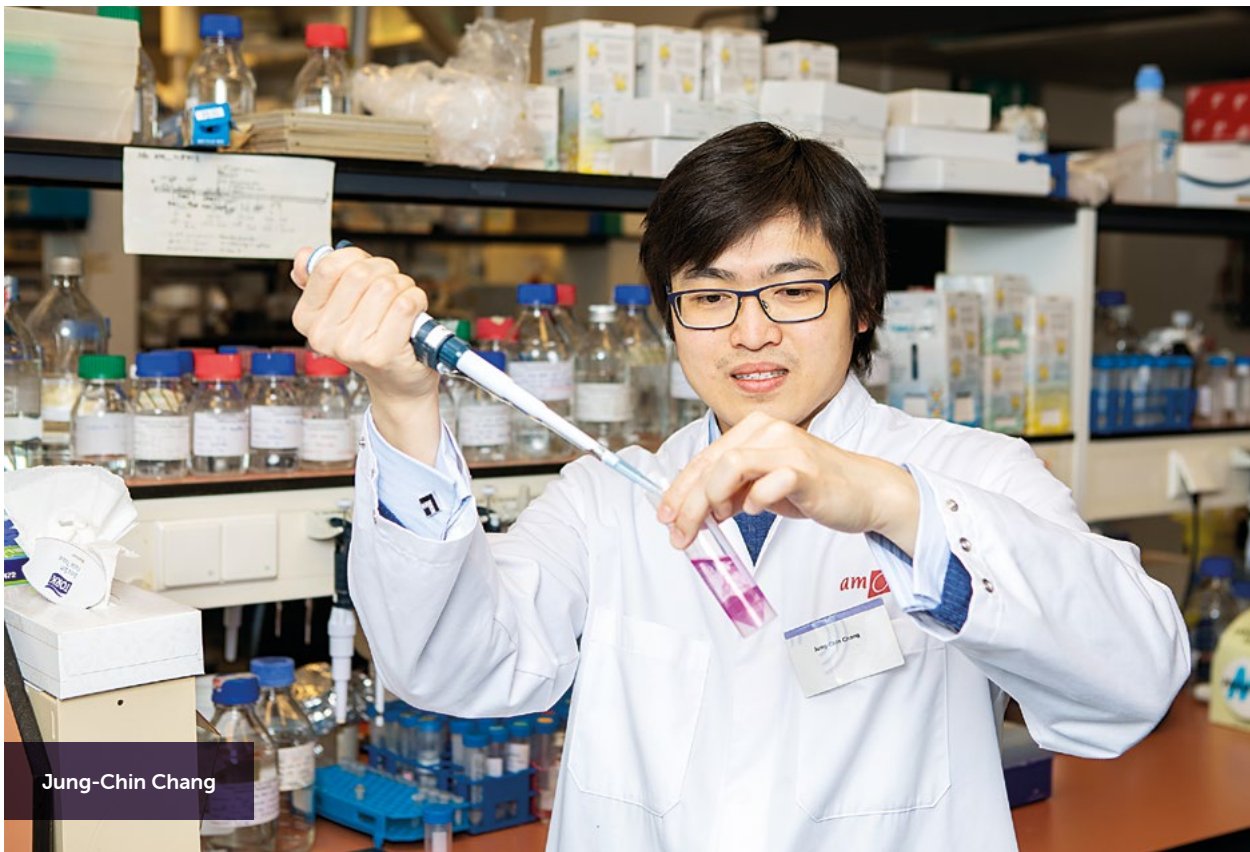


### Jung-Chin Chang

Born and raised in Taiwan, an elective internship at the then AMC Liver Center in 2009 marked the beginning of his adventure into scientific research. He graduated from Medical School of National Taiwan University in 2010 and continued immediately with his internal medical residency training. In May 2012, he moved with his wife to the Netherlands for his PhD research on “soluble adenylyl cyclase”. He was promoted in 2018 and continued to explore the therapeutic applications of soluble adenylyl cyclase. He and his supportive wife are blessed with a lovely daughter and a sportive son. He loves cooking, baking, gardening, and makes music on his violin.

#### *The AGEM talent development grant allows me...*

Macrophages are important players in the pathogenesis of various inflammatory diseases. Targeting cellular metabolism has emerged as a new way to modulate the immune functions of macrophages. During my PhD study, I found that soluble adenylyl cyclase (sAC) is a conserved metabolic regulator of glycolysis and oxidative phosphorylation. The AGEM grant allows me to set up a collaboration with the immunometabolism group of Dr. Jan Van den Bossche from the VUmc campus and to jointly explore how targeting sAC can modulate macrophage functions in different contexts. Using both genetic model and pharmacological approach, we will comprehensively characterize how sAC regulates the metabolism and functions of primary macrophages by an established macrophage workflow at the Van den Bossche lab and multi-layer omics. We aim to translate the result by exploring its therapeutic value in animal models of inflammatory diseases, such as inflammatory bowel disease.



Jung-Chin Chang





### Joep Grootjans

After obtaining his MD degree and Ph.D (both Cum Laude) at the University of Maastricht, Joep Grootjans started his specialization in Gastroenterology & Hepatology at the Amsterdam University Medical Center (location AMC). Devoted to pursue an academic career, he interrupted his clinical training for three years to do postdoctoral research in Mucosal Immunology at Harvard Medical School (Boston, USA). At Harvard, he discovered a protective role of peritoneal immune cells in mouse models of chronic intestinal inflammation. After his return to the AUMC, Joep Grootjans was awarded a Veni grant and is now building his research group, while at the same time he is completing his clinical training.

***The AGEM talent development grant allows me...***

... to explore an exciting new research line in which I aim to decipher the composition of the human peritoneal immune system. Although it is well known that many immune cells reside in the human peritoneal cavity, the composition of this immune system is incompletely understood. Using state-of-the-art techniques such as single cell RNA-Seq and CyTOF, we aim to understand the immune landscape in the human peritoneal cavity in diseases with peritoneal involvement such as peritoneal metastasized cancer and infections of the peritoneal cavity. Combined with mouse studies to functionally understand the role of these immune cells, these studies should ultimately lead to the development of new treatment strategies.



Joep Grootjans





### Eveline Bruinstroop

My research focuses on the neuroendocrine regulation of hepatic metabolism and inflammation. As a graduate student I performed research in the laboratories of Clifford Saper (Harvard Medical School, USA), Andries Kalsbeek and Eric Fliers (Amsterdam UMC, The Netherlands) on neural control of lipid metabolism. Recently, I returned from post-doctoral research on neuroendocrine control of non-alcoholic fatty liver disease (NAFLD) with Paul Yen (Duke-NUS, Singapore). During my clinical training in Internal Medicine I can acknowledge the rise in patients with metabolic disease, such as diabetes, obesity and NAFLD. In my future research, I am hoping to combine my clinical and basic research experience to develop new treatments for metabolic disease.

***The AGEM talent development grant allows me...***

... to develop my research line in the department of Endocrinology & Metabolism in close collaboration with Jan Van den Bossche and Anita Boelen. We are investigating how macrophages within the liver respond to increased flux of glucose in patients with the metabolic syndrome. To this end, we are using siRNAs to knockdown specific metabolic pathways within macrophages. The aim of this research is to develop macrophage specific targets to treat NAFLD in patients with type 2 diabetes mellitus.



Eveline Bruinstroop



## The AGEM innovation grant

### Joris Erdmann and Stan van de Graaf



#### Joris Erdmann

As a young doctor I was mainly interested in becoming a surgeon because of pure technical interest. As a kid I was always opening up all kinds of devices to see how they work and would try to leave an “improved version” of it. And no surprise, with varying results. Luckily I underwent a serious professional training before I got to operate on patients, and nowadays my results are slightly more predictable. Interestingly, during my surgical training and becoming a serious doctor I discovered that helping people, sometimes with a cure, sometimes relief, but always with compassion is actually much more rewarding than the technical success of a procedure.



#### Stan van de Graaf

During my Chemistry training I had the opportunity to work for a year in a Physiology laboratory and there I got hooked on transport processes and organ communication. The liver is a fascinating organ from that perspective, as it integrates signals from the intestine and determines what goes through to the rest of the body’s circulation, while at the same time producing essential compounds such as glucose and eliminating toxic metabolites. My ambition is to come to a detailed understanding how the liver is doing all this and to find novel therapeutic options to restore these functions in diseased conditions.

#### *The AGEM innovation grant allows us...*

With the help of the AGEM grant we are setting up an ex-vivo liver perfusion model. In this model we can try to understand a bit better how the liver works and interacts with other parts of the human body. We hope to improve surgical outcomes (i.e. during ablation of tumors), or perhaps even better to offer non-surgical alternatives in the treatment of cancer, metabolic and bile duct disease. Ex-vivo normothermic perfusion could be helpful in translational studies to investigate (human) liver function and to potentially reduce the requirement of animals in ex-vivo experiments.



Joris Erdmann and Stan van de Graaf

## Eduard Struys and Clara van Karnebeek



### Eduard Struys

For more than 25 years, Eduard Struys has been involved in studying metabolic diseases, the development of analytical biomarker assays and their applications, and mass spectrometry based studies on metabolic pathways. In a multicenter collaborative study in 2005, the genetic basis of a severe neonatal epileptic condition i.e. pyridoxine-dependent epilepsy (PDE) was uncovered, and he has developed a simple urine assay to test for this potential lethal condition, and this test has been implemented in many metabolic laboratories around the world.

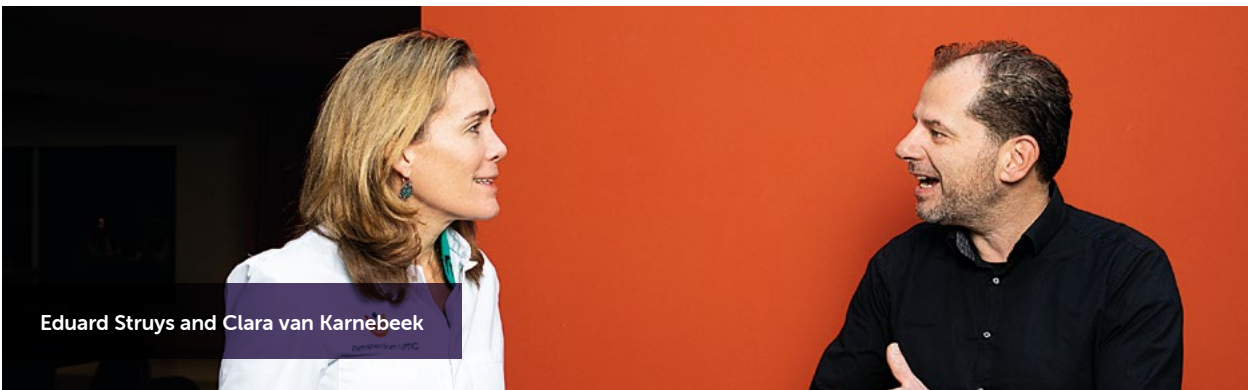


### Clara van Karnebeek

Professor Clara van Karnebeek dedicates her research and clinical work as pediatrician and biochemical geneticist to improving early diagnosis and treatment of neurometabolic diseases. Her international team applies big data technologies to discover their genetic etiology and novel therapeutic targets. Since 2011, Clara chairs the International PDE Consortium, spearheading the PDE patient registry and observational studies which showed that lysine reduction therapy as adjunct strategy is effective for some individuals with this debilitating metabolic epilepsy.

### *The AGEM innovation grant allows us...*

...to investigate the constellation of reactive aldehyde species in a PDE  $-/-$  mouse model in collaboration with a PDE research group at the University of British Columbia, Vancouver Canada. Although we know the genetic basis of PDE since 2005, pinpointing lysine degradation as the affected metabolic pathway with strong increases of the lysine metabolite alpha-amino adipic semialdehyde in body fluids, current therapies do not prevent neurological deficits in affected children. Our hypothesis is that the defective enzyme in PDE (alpha-amino adipic semialdehyde dehydrogenase) has moonlighting functions and is able to convert also other aldehydes in their corresponding acids. With the AGEM innovation grant, we are able to conduct a novel double labelling untargeted metabolomics study to selectively capture only the aldehyde species in the examined body fluids and tissue of the PDE  $-/-$  mouse model. This will potentially lead to new insights in the pathophysiology of PDE, enabling us to further improve treatments of this neurometabolic disease.



## The AGEM international student fellowship

### Samantha Wolff

*The effect of synthetic REV-ERB agonist SR9011 on cell metabolism in primary microglial cells*

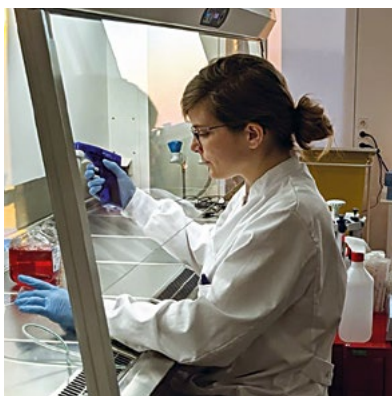


Thanks to the AGEM international student fellowship, I was able to go to Nanjing Medical University in China to conduct research on microglial immunometabolism for my Master thesis. Microglia are the immune cells of the brain and recent research has shown that a high fat, high sugar diet or diet-induced obesity causes hyperactivation of microglia, which can contribute to the pathology of metabolic and neuroinflammatory diseases. Additionally, microglia activity shows a day-night rhythm, but this is disrupted in diet-induced obesity. Rev-erb $\alpha$  nuclear receptors are known to regulate the circadian clock, metabolism and also play a role in neuroinflammation. In this research, we looked at the role of Rev-erb $\alpha$  in primary microglia obtained from rat pups by stimulating Rev-erb $\alpha$  activity

with agonist SR9011. We found that SR9011 disrupts clock gene rhythm and phagocytosis in microglia. Interestingly, pro-inflammatory cytokine expression was attenuated by SR9011, while the expression of anti-inflammatory cytokine Il10 was stimulated. Furthermore, SR9011 decreased mitochondrial respiration, ATP production and metabolic gene expression. These results show that Rev-erb $\alpha$  regulates metabolic and neuroinflammatory responses in microglia and that SR9011 diminishes hyperactivation of microglia during an immune challenge, which can have important implications in treating metabolic and neuroinflammatory diseases. During my research project, I gained considerable knowledge, lab skills and experience in doing research, which will certainly help me advance my career in the future. Simultaneously, living in China has made me experience a different culture and environment, and I had an unforgettable time there with my new friends and colleagues!

### Nienke Willemsen

*Alternative activation of brown adipocytes through a novel G-protein-coupled receptor*



I studied Biomedical Sciences at Leiden University and performed my first (master's) research project in the group of Prof. dr. Riekelt Houtkooper at the genetic metabolic diseases (GMZ) lab (Amsterdam UMC). In this project, we designed a high-fat diet for *C. elegans* as a model for ageing research. *C. elegans* is a very good model for studying ageing and basic metabolic pathways. This internship sparked my interest in metabolic research. As I wished to perform my second internship abroad, Riekelt contacted Dr. Gerhart Hines (University of Copenhagen) who kindly invited me to his lab. In this second project, we looked at the functional consequences of human mutations in a G-coupled protein receptor on brown adipocytes. Brown adipose tissue is the main tissue responsible for

non-shivering thermogenesis and is a remarkable adaptive organ that has been associated with metabolic fitness and health. The AGEM International Student Fellowship allowed me to move to Denmark and perform my second research project there. Through this second research internship, I had the opportunity to apply for a PhD-position in the group of Prof. dr. Bartelt (LMU) on proteasome activity in brown adipocytes. I am very thankful for the people who mentored me during my studies and for the financial support of AGEM, which has ultimately lead me to start a career as a scientist-in-training in the metabolic field.

## Remco Kersten

### *The inositoltriphosphate receptor type 3 and visualization of the biliary bicarbonate*



In 2019, the AGEM international student fellowship enabled me to work abroad in an incredibly inspiring environment at the Liver Center of Yale University. In Prof. Nathanson's laboratory, my research project was focused on the visualization of the 'Biliary Bicarbonate Umbrella'. As the originator of the 'Biliary HCO<sub>3</sub><sup>-</sup> Umbrella' Prof. Dr. Beuers hypothesized that cholangiocytes create a protective apical environment by secreting HCO<sub>3</sub><sup>-</sup> and that this 'biliary HCO<sub>3</sub><sup>-</sup> umbrella' is stabilized by an apical cholangiocyte glycocalyx. This apical cholangiocyte glycocalyx is a 20- to 40-nm membrane-bound barrier which is composed of glycoproteins that (1) could possibly form a trap for secreted HCO<sub>3</sub><sup>-</sup> and (2) repulse bile acids away from the cholangiocyte cell surface. The resulting alkaline

apical environment created by HCO<sub>3</sub><sup>-</sup> secretion and its retention in the glycocalyx would be able to keep toxic glycine-conjugated bile salts in their deprotonated, polar and membrane-impermeant state. It was reasoned that impairment of the HCO<sub>3</sub><sup>-</sup> secretion machinery or disruption of the stabilizing glycocalyx would result in protonation of glycine-conjugated bile salts, rendering them apolar and capable of crossing the membrane where they could lead to detrimental damage in cholangiocytes and lead to chronic fibrosing cholangiopathies.

The excellent confocal microscopy facilities and expertise at Yale University made it possible to visualize components of the biliary HCO<sub>3</sub><sup>-</sup> umbrella such as the AE2 and TMEM16A, which are transporters involved in HCO<sub>3</sub><sup>-</sup> secretion. Furthermore, we were also able to visualize the apical glycocalyx in different cell models ranging from H69 cholangiocytes and polarized primary mouse cholangiocytes to polarity reversed cholangioids.

Importantly, we also tested a new tool called pHuji. pHuji is a construct that upon transfection/transduction of cells inserts itself into the cell membrane, where it has a small hook extended extracellularly of the cell membrane. This extracellular hook allows for the measurement of extracellular pH as pHuji changes its fluorescence intensity based on the extracellular pH. We plan to further build on this technique at the Tytgat Institute for Liver and Intestinal Research.

## Elsa van Liere

### *Efficacy and safety of thioguanine in the management of inflammatory bowel disease.*



I have lived in London for six months to perform research at the gastroenterology department. One of the projects I have been working on was a multicenter study evaluating the safety and efficacy of thioguanine (TG) as a maintenance treatment for inflammatory bowel diseases. I really enjoyed both living in such a big city which offers a lot and working in different large, well-known centers. During my period in the UK, I attended multidisciplinary meetings weekly, read a substantial amount of previously published papers, wrote three papers myself (including the thioguanine study) and gave several presentations about my results. All this contributed to a significant improvement of my (academic) English writing, reading, listening and speaking. I also gained insight in (treatment options for)

inflammatory bowel diseases and ways to perform a study. Besides, this internship convinced me to start a PhD and eventually (hopefully) become a gastroenterologist. As the results of our thioguanine study are promising, we are writing a research proposal for a large randomised, controlled trial evaluating the safety and efficacy of first-line thioguanine (compared with azathioprine) for IBD.

## Nina Frerichs

*Preclinical detection of late-onset sepsis in prematurely born infants: a multicenter case-control study*



I have received the AGEM international student fellowship for the research project which is part of my double master's degree Biomedical Sciences and Medicine. Receiving this grant gave me the opportunity to perform this project at two top universities in the United Kingdom. I have visited the University of Warwick and the University of Birmingham, which both have a research collaboration with Amsterdam UMC. My research project has focused on late-onset sepsis in prematurely born infants. Late-onset sepsis is a main cause of death in premature infants and causes many morbidities. The objective of this research was to investigate whether early detection of late-onset sepsis in premature infants is possible to allow early intervention. We did this by searching for possible disease-specific

components or patterns in the gut microbiome. We have found that it is possible to discriminate the premature infants with late-onset sepsis from the matched control infants up to three days prior to clinical signs of disease. Next to that, we have found changes in the gut microbial composition prior to sepsis onset and a decreased microbial diversity. Hopefully, these findings will contribute to the creation of a novel noninvasive diagnostic tool for detection of sepsis before onset and thus eventually to the improvement of the outcome of premature infants with late-onset sepsis.

## Desiree Baaleman

*3D high-resolution anorectal manometry: a novel technique to study children with constipation.*



In 2019 I was one of the lucky students to receive the AGEM international student fellowship to do research at Nationwide Children's Hospital in Columbus, Ohio, United States of America. I am so grateful to have been able to do research under supervision of one of the leaders in the field of pediatric functional gastrointestinal disorders, dr. Carlo Di Lorenzo. Next to him being an amazing scientist, he is an amazing physician and teacher. During my time in the USA I learned everything I could about motility of the GI tract, and I coordinated research studies focused on motility of the lower GI tract. We studied the possibility of the use of hypnosis during anorectal manometry as an intervention to help children relax during the investigation, and we studied if the use of a three-dimensional high-

resolution anorectal manometry was valuable in evaluating children with constipation. Next to learning how to set-up a research study, how to coordinate it, and eventually how to write a manuscript, this experience has given me a lot of insight in the United States and their health care. Moving forward I've been given the opportunity to continue doing research as a PhD-student, which I am very excited about. I want to expand my knowledge and focus my time on solving the puzzle of why many children struggle with constipation.

## Robin Haring

### *Personalized medicine via patient derived organoids*



The AGEM international student fellowship allows me to realise an abroad internship in a city known for its world-renowned specialised hospitals, high-tech innovations and outstanding research, namely Boston. The fellowship allows me to enrich my curriculum vitae with an abroad internship at the Boston Children’s Hospital, an Harvard affiliated hospitals where patients from all over the world seek medical care. The fellowship gives me the opportunity to work with top-notch researchers and doctors, specialised in gastro-intestinal tract disorders like inflammatory bowel disease (IBD), who continue to inspire and educate me every day. During my internship, I have improved and perfected skills I encountered before but also got the opportunity to learn many new skills like human

pluripotent stem cell derived intestinal organoid culture, single cell culture, conducting mice experiments, performing luciferase assays, transfecting cell lines, scoring disease activity index (DAI), scoring histology slides of DSS mice on disease severity and much more. Without the AGEM international student fellowship, I would not have been able to blossom my professional career as much as I did and still am doing now. Also, I cannot be more thankful to my supervisor Dr. Jodie Ouahed (MDCM, MMSc), assessor Dr. Scott B Snapper (MD, PhD, Chief of Gastroenterology, Hepatology and Nutrition at Boston Children’s Hospital) and the entire Snapper lab for their daily support and education, providing me the opportunity to exponentially increase my scientific knowledge and experience in scientific research.

## Milou van Driel

### *Mutation-directed clonal interactions in colorectal cancer*



Ever since I started performing research in the field of oncology, the specific field of cell dynamics caught my attention. Therefore, as part of my master’s program Oncology, I started an internship in the lab of Dr. Simon Buczacki, whose lab is located in the Cambridge Stem Cell Institute. I am very grateful that receiving the AGEM International Student Fellowship provided me with the opportunity to broaden my international connections in the field of CRC research. During this internship, I focus on cell co-operation. Colorectal cancer (CRC) development is characterised by the accumulation of mutations over time. As not all mutations arise in the same cell during development of CRC, genetically distinct subclones can be identified within a tumour. These subclones can co-exist neutrally within a

tumour, however, as mutations can confer a growth or survival advantage to specific clones and subclones are in constant competition for space and nutrients, the tumours’ clonal composition is continuously changing. Recently, it has become clear that besides clonal competition also co-operation between subclones can be observed. During my time in Cambridge, I will aim to unravel whether there is clonal competition or co-operation between clones that contain a combination of driver mutations often identified in CRCs. This study will provide a more comprehensive insight in tumour heterogeneity and will unravel yet undiscovered clonal interactions and how these can be influenced by therapeutic interference. Ultimately, this knowledge will contribute to the development of better treatment strategies for CRC patients.





# AGEM Events 2019

## AGEM annual retreat

APRIL



### AGEM annual retreat

*Bilderberg Hotel 't Speulderbos, Garderen*

#### We keep on growing!

The goal of the AGEM retreat is to discuss, share and learn from each other's research. Mixing AGEM retreat customs with new ideas, definitely resulted in successfully obtaining this AGEM vision. We can look back on a fantastic AGEM retreat for the year 2019.

This year, not only PhD students and PIs but also postdocs could participate, resulting in over 100 attendees. As a new addition to classical presentations and elevator pitches, participants could give dual presentations e.g. to combine data with a direct colleague from their research group or a collaborator.







Prof. dr. Aart Jan van der Lely



Combined, this resulted in the 100+ participants sharing and discussing their recent findings on a variety of interesting and diverse topics within the fields of gastroenterology, endocrinology & metabolism.

Adding to the above, our keynote speakers invited us to engage in discussing their research experiences and views. Prof. dr. Lisbeth Mathus-Vliegen shared with us the experience she gained of over 30 years of working with patients with obesity, as well as her perspective of how research & treatment should be continued. Prof. dr. Aart Jan van der Lely talked about the adverse effects of sugar consumption. On Friday, our 'out of

the box speaker' Gerko Tempelman challenged us to become aware of what we believe in, during his talk about religion and whether it can be cured.

To continue the spirit of last year, this year's retreat was also themed: "The year you were born". Participants could enjoy a very nice dinner, combined with some small facts about their birth year, which was provided with their seating arrangement. Ideal to break the ice, if need be. After dinner, laughing and relaxing was stimulated by a hilarious stand-up comedian show by BOOM Chicago. To get to know each other even better, and stimulate teambuilding, the evening entertainment



Marit Navis



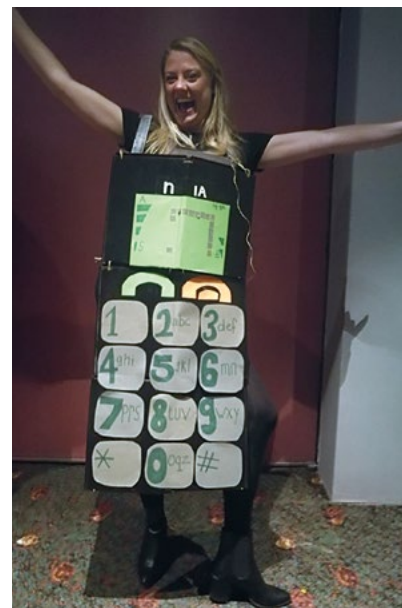
Job Saris



Koen Wortelboer



Marte Becker



continued with a music quiz, supported with and followed by live music, where everybody excelled in their outfits and dance moves. It was incredible to see the great effort participants had made to match their outfits to the retreat's theme.

Another novelty this year was the opportunity for participants to follow workshops. Thursday included workshops to develop skills important during a PhD: 'Scientific outreach and how to use it for public awareness', 'Grant writing for PhDs,' and 'Leading in different situations' i.e. to provide constructive feedback. On Friday, workshops were provided to help participants (to think about the time) after their PhD: 'Uncovering your professional value as a PhD graduate', from 'PhD to consultancy, 'Inside vs outside academia: careers of PhDs' and 'Commercializing technology'. According to the positive feedback, the workshops were a great success.

As in previous years, Friday morning started with a revitalizing bootcamp, and could later be further energized by a coffee tasting workshop. Furthermore, time was scheduled for participants to fill out a digital questionnaire, by which the first perception of attendees could directly be presented at the end of the meeting. Together with more detailed, open questions participants filled out on paper questioners, this will help us to improve the AGEM retreat for next year.

Last but not least we would like to congratulate those who won an award: Marit Navis for best classical presentation, Koen Wortelboer for best pitch, Job Saris for most contributing participant and Marte Becker for best party outfit.

Thank you all for making this a great AGEM retreat 2019. We look forward to seeing you again, and welcoming new participants in 2020!



**AGEM symposia**



**AGEM symposium:  
"Complex genetics of metabolic disease"**  
*Pakhuis de Zwijger, Amsterdam*

On March 15, the first AGEM symposium of 2019 was held in the Pakhuis de Zwijger, Amsterdam. "Complex genetics of metabolic disease" successfully captured the interest of the audience, stimulating in depth discussions following each talk and along the coffee and lunch breaks. Dr. Agata van der Klaauw, invited speaker from Cambridge Neuroscience, University of Cambridge, introduced us to the complex genetics of human obesity – how gene problems lead to mixed signals in the brain. Lisa Willemsen, PhD student at Amsterdam UMC, location AMC, talked about how, in diet – induced obesity, the impaired immune response of the peritoneal macrophages can be reversed by

subsequent weight loss. Professor Ronald Wanders from Amsterdam UMC, location AMC, underlined the importance of the biochemical testing (including enzymology), and the need of awareness of their role in the (diagnostic of) genetic metabolic diseases, especially in the context of the current "omics era". Professor Johan Auwerx, invited speaker from École Polytechnique Fédérale in Lausanne, shared his groups data on system genetics approaches in exploring mitochondria and aging. PhD student Marte Molenaars from Amsterdam UMC, location AMC, talked about how mitochondrial and cytoplasmic ribosomes stoichiometric balance links two longevity

**COMPLEX GENETICS OF METABOLIC DISEASE**

**March 15, 2019**  
**9.00-17.30**

Pakhuis de Zwijger IJ zaal, 5th floor  
Piet Heinkade, Amsterdam

**PROGRAM**

**Amsterdam UMC**  
University Medical Centers

**Complex Genetics of Metabolic Disease**

**PROGRAM**

09:00 – 09:30 Coffee and arrival

09:30 – 11:00 Session 1  
*Dr. Agatha van der Klaauw*  
*Genetics of human obesity - mixed signals in the brain*  
**Selected speaker: Lisa Willemsen**  
*Peritoneal Macrophages Have an Impaired Immune Response in Diet-Induced Obesity Which Can Be Reversed by Subsequent Weight Loss*  
**Prof. dr. Ronald Wanders**  
*Genetic metabolic diseases and the continued importance of biochemical testing including enzymology in the -omics era*

11:00 – 11:30 Coffee/tea break

11:30 – 13:00 Session 2  
**Prof. dr. Johan Auwerx**  
*Systems genetics approaches to explore mitochondria and aging*  
**Selected speaker: Marte Molenaars**  
*Complex genetics reveals stoichiometric balance of mitochondrial and cytoplasmic ribosomes linking two longevity pathways*  
**Prof. dr. Cisca Wijmenga**  
*Men, microbes and mini-guts*

13:00 – 14:00 Lunch

14:00 – 15:30 Session 3  
**Prof. dr. Anne Tybjaerg-Hansen**  
*Liver, lipids, and cardiovascular disease*  
**Selected speaker: Antoine Rimbart**  
*From genetic association to molecular mechanism: focus on the locus 2q14*  
**Prof. dr. Koos Zwinderman**  
*TBD*

15:30 – 16:15 Battle: Best AG&M publication 2018

16:15 – 17:15 Drinks

**Amsterdam UMC**  
University Medical Centers



pathways. “Men, microbes and mini-guts” presented by professor Cisca Wijmenga, invited speaker from University of Groningen, opened up the fascinating and complex world of the gut microbiome, the complex correlations with the human genome, and took the audience to the next research level: mini-guts on a chip. Professor Anne Tybjaerg-Hansen, invited speaker from University of Copenhagen, talked about liver, lipids and cardiovascular disease, highlighting the importance of genetics in illness and the great informative value

of biobanks. Antoine Rimbart, postdoctoral research scientist at University of Groningen, presented the path from genetic association studies to molecular mechanisms, with a focus on the locus 2q14. The scientific program was completed by Professor Koos Zwinderman, from Amsterdam UMC, location AMC, who talked about omics and big data: Multi omics-statistics in systems medicine.

**Ana Pop**

JUNE



## AGEM symposium: "Hormones & Digestion"

ACTA-building, Amsterdam

On June 6th, 2019, the AGEM symposium "Hormones & Digestion" was held in the ACTA-building in Amsterdam. With a wide range of relevant topics covered, both fundamental and clinical scientific researchers were present. This resulted in interesting and thorough discussions after all given talks. The elaborate interaction between the speakers and the audience resulted in new fruitful ideas for future research and possibly even new collaborations.

The first session kicked off with an interesting talk by Daniel van Raalte on the metabolic effects of sodium-glucose cotransporter-2 inhibitors. After a thorough discussion, Stan van de Graaf enlightened us on a more fundamental topic: the dynamic signaling of bile acids.



Dr. Annegreet Veldhuis-Vlug

After the break, the focus changed to bone and digestion. Annegreet Veldhuis-Vlug told about the exciting and growing field of bone marrow adipocytes

# AG&M SYMPOSIUM

## HORMONES & DIGESTION

**Thursday, June 6, 2019**  
 10:00h - 16:30h  
 Venue: ACTA-building, Grote  
 Collegezaal, Gustav Mahlerlaan  
 3004 Amsterdam

### PROGRAM

### Hormones & Digestion PROGRAM

- 09:45 – 10:15** Arrival and Coffee/tea
- 10:15 – 11:15** Session 1 – Bile acids, metabolism and digestion  
Stan van de Graaf - Bile salts: Dynamic signalling by fat-solubilizing hormones  
Daniel van Raalte - Inhibition of sodium-glucose cotransporter-2 inhibitors: metabolic effects and beyond
- 11:15 – 11:30** Coffee/tea break
- 11:30 – 12:15** Session 2 – Bone metabolism and digestion  
Annegreet Veldhuis - Bone marrow fat and food, from anorexia to bariatric surgery  
Stan Ursem - The interplay between FGF23, glucose metabolism and obesity
- 12:15 – 13:15** Lunch
- 13:15 – 14:00** Session 3 – Gender differences in (digestive) disease  
Annemieke Heijboer - Gender sensitivity in medical research  
Daan van Velzen - Gender affirming hormone therapy: changes in metabolism and body composition
- 14:00 – 14:30** AG&M Grant Award Ceremony
- 14:30 – 15:00** Coffee/tea break
- 15:00 – 16:30** Session 4 – Intestinal hormones  
Inge Depoortere - Role of gastrointestinal hormones in the regulation of food intake  
Lotie van Ruiten - GLP-1 and the neuroendocrine control of feeding  
Katy van Galen - Striatal activity decreases following the intragastric infusion of glucose and lipids in lean humans
- 16:30 - 17:30** Drinks





and how this related to disorders such as obesity and anorexia. Next, Stan Ursem presented on the interrelation between the bone-derived FGF23 and glucose metabolism.

In the subsequent section on gender differences in (digestive) disease, Annemieke Heijboer stressed with her presentation the importance of research in both genders in the whole medical research field. Daan van Velzen then showed us the changes in metabolism and body composition after gender affirming hormone therapy.

After the festive AGEM grant award ceremony, the symposium was concluded by the last session on



intestinal hormones. First, professor Inge Depoortere gave an excellent key note lecture on the role of gastrointestinal hormones in the regulation of food intake. This was followed by Lotje van Ruiten, who presented her work on GLP-1 and the neuroendocrine control of feeding. Last, but not least, Katy van Galen gave us exciting preliminary results on striatal activity following the intragastric infusion of glucose and lipids. After, everyone had a toast on the successful symposium.

*Stan Ursem*

NOVEMBER 20<sup>st</sup>

**AGEM symposium: "Imagine the Image"**  
*De Nieuwe Liefde, Amsterdam*

On a brand new location in the heart of Amsterdam at De Nieuwe Liefde, the AGEM Symposium "Imagine the Image" was held on November 20th, 2019. Enlightening its attendees on the wide array of possibilities of imaging in gastroenterology and metabolism. The symposium was kicked off by Dr Karin Horsthuis (Abdominal radiologist, Department of Radiology, Amsterdam UMC, Amsterdam) who gave us a brief history of the development of radiology from the laborious beginnings to the state of the art specialism it has become today. Dr. Ir. Bram Coolen (Assistant professor, Preclinical & Translational MRI, Department of Biomedical Engineerings & Physics, Amsterdam UMC, Amsterdam) took over and told us more about the mechanism of magnetic resonance imaging (MRI), and about his preclinical studies on the cardiovascular system in mice using MRI. The third presentation was given by dr. Anouk Schrantee (Assistant professor, Department of Radiology and Nuclear Medicine, Amsterdam UMC, Amsterdam), who has shown the attendees the multiple ways of using functional MRI in metabolic studies. The best studies stand or fall with a good study protocol; if you are interested in the effects of high caloric food on the reward system, should you use placebo or low caloric food as a control? She also demonstrated the multiple MRI facilities available, and the door is always open for researchers that would like to collaborate.

After the lunchbreak there was no time for an after-dinner dip to kick in as the enthusiastic dr. Luca Marciani, Assistant professor in Gastrointestinal MRI, Nottingham Digestive Diseases Centre took us on a trip to the University of Nottingham campus. As an authority in fMRI studies on fluids, food and gastrointestinal functions he taught us that aeriated drinks can increase gastric distension and decrease the hunger feeling, that patients about to undergo surgery should have a meal two hours before surgery to ensure optimal patient health and a stomach that is emptied sufficiently and that two kiwis a day might keep constipation away (since they are high in fibres as well as fluid), all demonstrated using MRI. Dr. Marciani

also elaborated on a new technique to study bowel motility with MRI using small pills that patients have to swallow whole and which are easily visible because of their water and lipid properties. Prof. dr. Ivana Isgum (Professor AI and Medical Imaging, Department of Radiology and Nuclear Medicine Amsterdam UMC, Amsterdam) led us into the world of artificial intelligence (AI), machine learning and deep learning. In last technique the classifier is trained to learn and create meaningful representations from raw pixels of MRI, using each voxel. So far these techniques have made it possible to perform high quality CT-scans while reducing radiation dose and performing high quality MRIs while reducing the scan time. In endoscopy AI is already able to recognize small non obvious polyps better than endoscopists. Prof. dr. Jan Booij (Nuclear Medicine Physician, Department of Radiology and Nuclear Medicine, Amsterdam UMC, Amsterdam) talked about the research he and his team performed



on Parkinson's disease, using SPECT and PET to visualize the synaptic transmission and post-synaptic receptors of dopaminergic cells in the striatum and substantia nigra. In a trial investigating deep brain stimulation (DBS) in patients with obsessive compulsive disorder a peculiar discovery was made; A patient with OCD and concomitant type 2 diabetes significantly improved after DBS with regards to the diabetes with a significant reduction of daily insulin intake. Following this discovery a new study proposal was set up with GLP-1 receptor agonist therapy in Parkinson's disease, and it was demonstrated that GLP-1 receptor agonist may slow down disease progression.

Dr. Maarten Jacobs (gastroenterologist and head of the gastroenterology training program at the Department of Gastroenterology and Hepatology Amsterdam UMC, Amsterdam) taught us about current and new techniques in endoscopy. With a broad spectrum of pathology in the intestine, colour is used to enhance abnormalities on camera. In the Netherlands, optic filters are used in daily practice with narrow band imaging and flexible spectral imaging colour enhancement, although chromendoscopy (dye based coloring) is also a possibility. Confocal laser endomicroscopy and endocytoscopy are techniques that permit high resolution assessment of the mucosa.



Prof. dr. Frits de Koning (Professor Immunology, principle investigator, Immunohematology and Blood Transfusion LUMC, Leiden) proceeded to imaging the immunological character of intestinal cells. In the last six years, Frits and his group took flow cytometry to the next level with the utilization of mass cytometry by time of flight (CyTOF). The use of metal conjugated antibodies enables the utilization of over 40 different markers. Hierarchical Stochastic Neighbour Embedding is used illustrate the tremendous amount of data obtained with CyTOF. Dr. Marko Popovic (Scientist for Microscopy and Image Analysis, Molecular Cell Biology and Immunology (MCBI), Amsterdam UMC, Amsterdam) closed the day with a presentation on cutting edge new microscopy techniques offered at the MCBI, which has recently become a Nikon centre of excellence. These new techniques allow for light sheet microscopy and high resolution microscopy with whole slide scanning and scanning of live cells among other things.

In conclusion, the symposium on innovative imaging techniques was interesting and inspiring and will definitely serve as a base for new research ideas and collaborations.

*Maxine Rouvroye*



## 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.

<p><b>MAY</b>  <b>9<sup>th</sup></b></p>	<p><b>Prof. Dr. Paul Dawson</b>  <i>Division of Pediatric Gastroenterology, Hepatology &amp; Nutrition, Emory University School of Medicine, Atlanta, Georgia, USA</i></p>	<p>"Molecular Mechanisms of Intestinal Bile Acid Transport and Signaling"</p>
<p><b>SEPTEMBER</b>  <b>12<sup>th</sup></b></p>	<p><b>Prof. Dr. Christian Wolfrum</b>  <i>Department of Health Science and Technology, Federal Institute of Technology (ETH Zurich), Zurich, Switzerland</i></p>	<p>"Brown fat composition and function regulating systemic metabolism"</p>
<p><b>OCTOBER</b>  <b>31<sup>st</sup></b></p>	<p><b>Dr. Katrien de Bock</b>  <i>Department of Health Science and Technology, Federal Institute of Technology (ETH Zurich), Zurich, Switzerland</i></p>	<p>"Metabolic crosstalk between the endothelium and macrophages during recovery from hindlimb ischemia"</p>
<p><b>DECEMBER</b>  <b>12<sup>th</sup></b></p>	<p><b>Dr. Jan Van den Bossche</b>  <i>Department of Molecular Cell Biology and Immunology, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands</i></p>	<p>"Metabolic control of macrophage activation"</p>

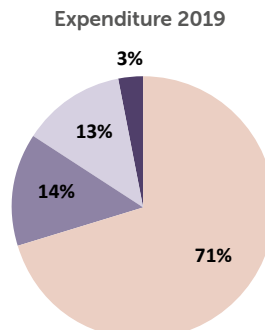


# AGEM Numbers and Facts 2019

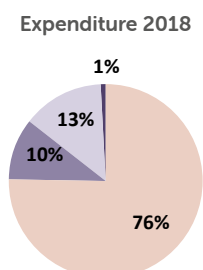
## AGEM finances 2019

For 2019, 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 spend. Most of the 2019 budget was used for the AGEM grants (The AGEM talent development grant, the AGEM innovation grant and the AGEM international student fellowship). In 2020, AGEM will have an extra call for Clinical Research proposals, allowed for by the conservative spending in the start-up phase of the institute.

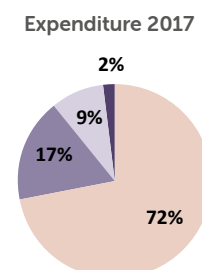
Income 2019	
AMC	€ 308.500,00
Vumc	€ 250.000,00
<b>Total</b>	<b>€ 558.500,00</b>



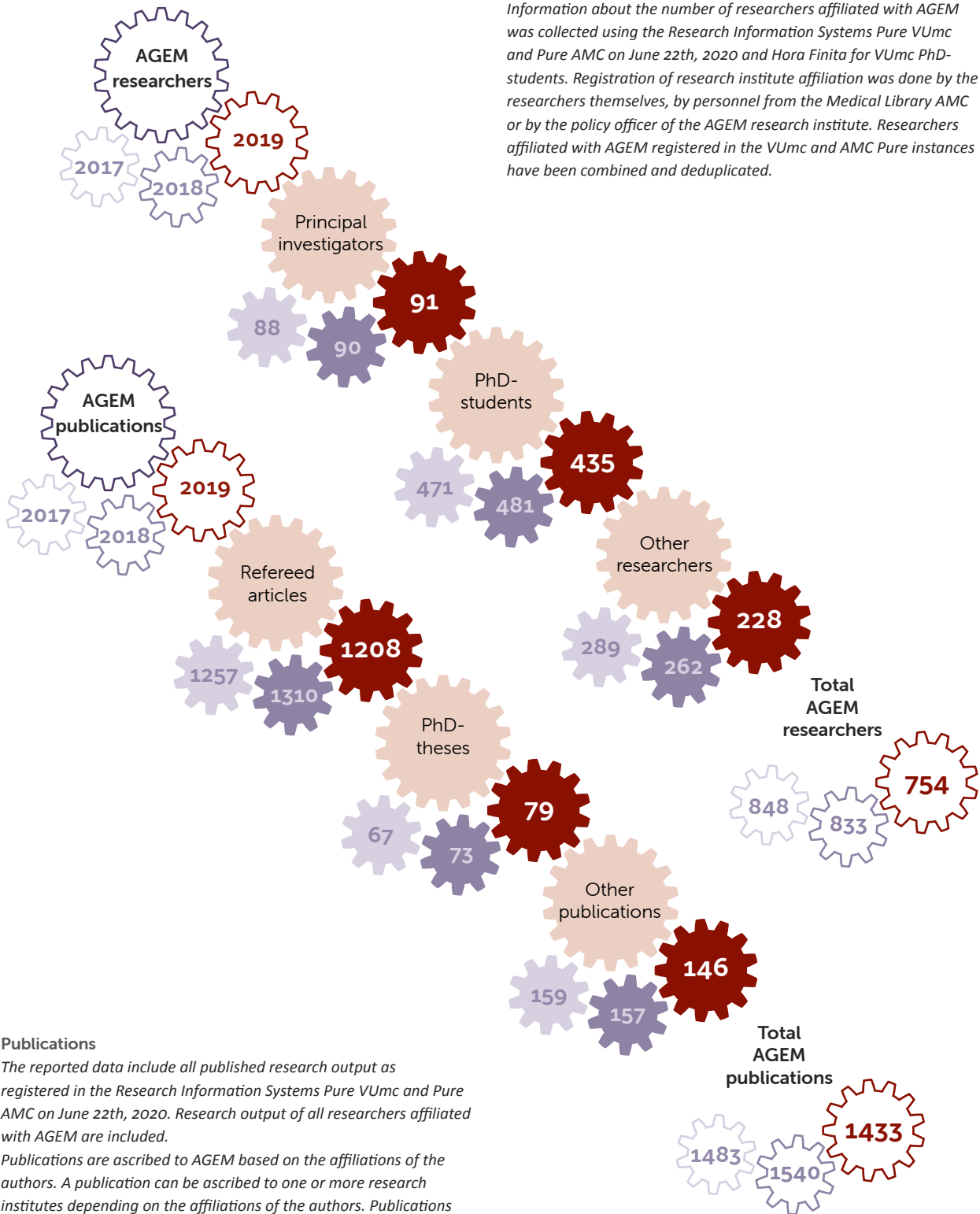
Income 2018	
AMC	€ 308.500,00
Vumc	€ 250.000,00
<b>Total</b>	<b>€ 558.500,00</b>



Income 2017	
AMC	€ 250.000,00
Vumc	€ 250.000,00
<b>Total</b>	<b>€ 500.000,00</b>



## AGEM numbers 2019



### Researchers

Information about the number of researchers affiliated with AGEM was collected using the Research Information Systems Pure VUmc and Pure AMC on June 22th, 2020 and Hora Finita for VUmc PhD-students. Registration of research institute affiliation was done by the researchers themselves, 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.

### Publications

The reported data include all published research output as registered in the Research Information Systems Pure VUmc and Pure AMC on June 22th, 2020. 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 2019



### **Prof. dr. A.J. Bredenoord**

*Gastroenterology, with a special focus on Neurogastroenterology and Motility*

At February 1st 2019 Arjan Bredenoord was appointed professor of Gastroenterology, with a special focus on Neurogastroenterology and Motility.

Arjan's first research project, 20 years ago at Antwerp University, was on the effect of oxidative stress on gastrointestinal motility in mice and he always remained active in the field of Neurogastroenterology and Motility. His PhD was on gastroesophageal reflux disease and in the years following he also worked on other benign esophageal disorders with inflammatory and motility components such as eosinophilic esophagitis and achalasia. The Neurogastroenterology and Motility group now hosts the largest benign esophageal clinic in the Netherlands and clinical care is closely integrated into research projects. Besides the studies on pathophysiology, diagnosis and treatment of these benign esophageal disorders, there is a particular focus on the role of visceral hypersensitivity and stress on symptom generation. Arjan's research projects are financially supported by grants from NWO-TTW, ZONMW Vidi and TKI.



### **Prof. dr. R.H.L. Houtkooper**

*Translational Metabolism*

In February 2019 Riekelt Houtkooper was appointed professor of Translational Metabolism at the University of Amsterdam.

After a PhD on Barth syndrome in the laboratory Genetic Metabolic Diseases (location AMC), under supervision of Prof. Ronald Wanders and Dr. Fred Vaz, and a postdoctoral project in the laboratory of prof. Johan Auwerx at EPFL Lausanne (Switzerland), Houtkooper established his group at the laboratory Genetic Metabolic Diseases of location AMC. The work in his group covers a range of metabolic diseases from rare inherited metabolic diseases to age-related metabolic diseases such as diabetes and cardiovascular disease. Moreover, they work on fundamental mechanisms regulating aging and lifespan. Houtkooper's group uses a variety of model systems including *C. elegans* and mice, but also works in close collaboration with clinical departments (e.g. pediatrics, internal medicine, clinical genetics) to identify new biomarkers and treatment options for patients with acquired or inborn metabolic diseases. To achieve these goals, his group together with the Core Facility Metabolomics develops and uses state-of-the-art technology to measure metabolic changes in detail, including Seahorse respirometry, lipidomics, metabolomics, and stable-isotope tracing through fluxomics.



**Prof. dr. P.J. Tanis**

*Surgery, with a special focus on colorectal surgery*

In May 2019, Pieter Tanis was appointed full professor of surgery, with a special focus on colorectal surgery at the University of Amsterdam.

Pieter Tanis is gastrointestinal and oncological surgeon at the Amsterdam UMC since 2010. Ten years ago, he started a research line on peritoneal metastases of colorectal cancer origin, thereby focusing on risk factors, prevention and early detection. He also leads a research line on perineal wound complications after abdominoperineal resection for rectal cancer. Furthermore, he is involved in technical developments regarding minimally invasive rectal cancer surgery.

Since 2017, Tanis is chairing the national colorectal cancer guideline committee, which he guides through the new process of modular update. Besides, he has been secretary and chair of the Dutch Colorectal Cancer Group and is board member of the Dutch Colorectal Audit since 2010. Further integration of research, auditing and guideline development is one of his goals.



**Prof. dr. M.J.M. Serlie**

*Medicine, with a special focus on Nutrition and Energy Metabolism*

In 2019 Mireille Serlie was appointed full professor of Medicine with a special focus on Nutrition and Energy Metabolism.

After her clinical training in internal medicine and endocrinology, she obtained her PhD cum laude on the subject of free fatty acids and insulin resistance in 2007. In 2008, she started her own lab. Since then, her fascination for the interaction between nutrients, energy metabolism and the regulation of food intake has shaped her research and clinical activities. Currently, Mireille Serlie's research focusses on obesity, insulin resistance and the role of the brain in body weight and glucose regulation in humans. Her lab seeks to understand the underlying pathophysiology of obesity induced insulin resistance in humans as well as the control of energy metabolism and body weight by the brain. Given her interest in the effect of nutrition on human health, she also chairs the Dutch Nutrition Team (NVO) as well the Dutch Society for Clinical Nutrition and Metabolism (NESPEN) and she is a council member of the European Society for Clinical Nutrition and Metabolism (ESPEN). Her clinical work focusses on endocrinology as well as on nutrition and intestinal failure. She leads the Total Parenteral Nutrition and Intestinal Failure Clinic at the Amsterdam University Medical Center, location AMC. The clinical exposure to humans with over- as well as undernutrition motivates her further to unravel the effects of nutrition on human health.





**Prof. dr. J. Verheij**

*Hepatopancreatobiliary Pathology*

In December 2019 Joanne Verheij was appointed professor of Hepatopancreatobiliary Pathology at the University of Amsterdam.

Her research focusses on both oncologic and non-oncologic Hepatopancreatobiliary (HPB) pathology. Research activities include the quest and validation for non-invasive biomarkers for diseases such as non-alcoholic fatty liver disease and steatohepatitis, as well as the molecular subtyping of liver, bile duct and pancreatic malignancies. Of special interest is the search for biomarkers for the differential diagnosis between inflammatory diseases and malignancy in the hepatopancreatobiliary tract: of all patients undergoing surgical resection for a presumed perihilar or (peri)pancreatic malignancy, 10-15% turn out to have benign disease during final pathological examination. Finally, she works on improving the reporting of the essential HPB-specific pathology parameters, including validation of their prognostic and/or therapeutic consequences in patient care.

Joanne Verheij is chair of the Dutch Liver Pathology Panel (<https://dlpp.nl/>) and she is involved in different national and international multidisciplinary research and study groups.



**Prof. dr. P.H.L.T. Bisschop**

*Internal medicine, with special focus on clinical endocrinology*

In December 2019 Peter Bisschop was appointed professor of internal medicine with special focus on clinical endocrinology at the University of Amsterdam.

The research of Peter Bisschop focuses on the neuro-endocrine regulation of energy and bone metabolism.

His research group studies the mechanisms by which sex steroids regulate bone metabolism and bone marrow adiposity. Using a translational approach, his group aims to identify new treatment options for skeletal fragility to prevent fractures.

Peter Bisschop is also lead/co-investigator in several ongoing randomized clinical trials in the field of thyroid and pituitary disease.

## Did you know that...

... the Amsterdam UMC was awarded €5m of lottery funding to help develop its plans to supply its own cost price version of the orphan drug chenodeoxycholic acid (CDCA), an initiative lead by AGEM PI Carla Hollak.

... during the farewell symposium of AGEM PI Ronald Wanders organized on January 31st, 2019 we looked back at the different “walks” of scientific research performed by the department of Genetic Metabolic Diseases.

... AGEM Research Board member Louis Vermeulen, joined the Oncode Institute to further expand his impact in the field of gastrointestinal malignancies.

... Dr. Onno Holleboom was awarded The Amsterdam UMC Fellowship (€750.000) for a research proposal about an understudied patho-process in NAFLD: lipophagy, or the turnover of lipid droplets through fusion with lysosomes.

... AGEM PI’s André van Kuilenburg and Clara van Karnebeek devised a new method to unravel an exceptional genetic mechanism driving a debilitating movement disorder in children.

... AGEM PI Joep Derikx received an NWO VIDI funding for his project: Heal the anastomosis.

... AGEM researchers Joep Grootjans and Georges Janssens were both awarded an NWO VENI grant.

... AGEM PI Carla Hollak won the Huibregtseprijs 2019.

... During the Digestive Disease Days 2019 of the NVGE Coen Paulusma won a Gastrostart grant and Sem Aronson won the Young Hepatologists Award 2019 of the NASL/NVH.

... Dr. Suzanne Gisbertz, Dr. Chun-Xia Yi, Dr. Rutger-Jan Swijnenburg, Dr. Jan Van den Bossche and Dr. Mirjam Langeveld were appointed as (AGEM) PI.





# AGEM future perspectives

In 2021, it will be a decade since the idea of a merger between the Dutch capital's hospital giants, the former Academic Medical Center (AMC) and the VU medical center, was first mooted.

The Amsterdam Gastroenterology Endocrinology Metabolism (AGEM), one of eight joint research institutes forged from the merger, is already three years old. It is no longer just an idea or a brand new project. So what, so far, do directors, Professor Bouma and Dr Van de Graaf believe has been achieved – and where will it go to now? Both are keen on the term “facilitating research”. Dr Van de Graaf explains: “By helping others we mean, firstly, bringing together the different institutions, the VUmc and the AMC, so that people talk. We got to know each other, and became collaborators instead of potential competitors. Then, we advanced to collaborating between the different disciplines and between the different departments. Now, we continue to lower the barriers to help people to do their research and so crossing the Amstel is less of an issue.”

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**“We got to know each other, and became collaborators instead of potential competitors .”**

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And both are adamant it really matters where you are, that researchers are, from time to time, physically in

the same place. Dr Van de Graaf: “For today’s super specialists, who may know everything about a certain topic, but not what their colleagues are doing, it is far easier to collaborate if you are in one department. You are with more people, so you know one is focusing on one part, another the other part. It is easier, if people are joined together, to create better research, which is so important, for example, to address rare diseases.

Professor Bouma explained the two hospitals used to be competitors in tackling conditions such as IBD but they now both work together in one gastroenterology department. Similarly, with nutrition, there were two groups doing different aspects of nutritional care and research, but are now one. Professor Bouma specifically cites the former VUmc’s research into short bowel syndrome combining with the former AMC’s expertise with parenteral nutrition. “Now that we are no longer two hospitals, it becomes much more natural to set up these programs jointly. When we come together, we see that it is a good merger. Now that these groups collaborate on a much more concrete level - and it is for the benefit of the patients.”

Dr Van de Graaf appreciates collaboration may not always be easy. “Most people think that what they do is best. That is human nature. But people need to open up to the concept that others might do things differently, not necessarily worse or better. But we need to figure out how to do it together.” And Professor Bouma acknowledges that clinicians, treating their own group of patients, may come from a less collaborative



culture than many scientists, who often have to share scarce resources. But, he says: “now that I see it has all started, it soon becomes natural and people see the benefits of working together, not the threats or the fears.”

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One of the big things for the two directors is a realization, over the last year, that it is not for them as directors to be deciding the course of research into the future. That is for the researchers themselves. Dr Van de Graaf: “At first it was very unclear who would do what in a research institute. Should the directors decide on a particular research focus? Now it is clear, this is not how it works. You can highlight certain work, stimulate it with some money, but in the end we are the facilitators and are not directing the research. We are not the ones deciding what these 93 principal investigators should do. That is now clear.” Professor Bouma agrees: “Now, as we evolve, we are gaining a good insight into what is actually happening, groups are very productive, there may be major breakthroughs, we can’t name names yet, but we can be proud of what is happening.”

And facilitating research in future years will include putting resources into investigator initiated clinical trials. Professor Bouma: “So far, with our innovation grants, we have predominantly supported basic/translational science, what we want to do this year, and in the near future, is to provide more resources for investigator initiated clinical research.” These clinical trials, not sponsored by pharmaceutical companies but developed by clinicians, and frequently carried out together with surrounding hospitals, struggle to find funding. Therefore, the Institute will be there to help out.”

Links with surrounding hospitals will be important, in future, argues Professor Bouma, as he sees a

university hospital’s research institute acting more like a networking organization. “To do science you need patients and clinical scientists will, in future, not necessarily see all their patients in their hospital”. Instead, he sees them establishing the outlines of care while collaborating with local or national hospitals to conduct research of value to society as a whole. Dr Van de Graaf: “We can’t see all the patients, but we would like to play a crucial function in facilitating this networking, broadcasting what we have to offer, and this network would obviously include basic/translational research.”

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This has, to an extent, already begun through strong clinical collaborations with patients receiving complex care at the Amsterdam UMC, while the rest of their treatment is at one of the surrounding hospitals. Professor Bouma: “Our role as a research institute will be to facilitate the research connected with these groups of patients.”

Another means by which the Institute can facilitate future research is through “seed money”. These are relatively small amounts such as innovation grants, given to help an idea which may then later attract greater funding from the pharmaceutical industry or the European Union. Professor Bouma: “Our strength is that we can be early money to develop an idea not yet supported by a lot of pilot data, we can help with the next step.” He gives the example of the work of Sofieke de Jonge who worked on a novel technique using a dynamic MRI scan to visualize the movement of the bowel in a very sophisticated way. This was used in the clinical observations of a group of patients who, for unknown reasons, do not tolerate food. Dr Van de Graaf: “What I liked was that it answered the question why does the food not go from A to B? Ingested food should be propelled by the intestine in a coordinated



pulsed manner. This MRI-based film made clear what was going on, the movement was uncoordinated.”

Professor Bouma: “So these patients would tell me it’s not going well and before I had no way to diagnose the problem. This is a typical example of a clinical observation and a new technique merging together, a concrete example of how we try to facilitate expertise in different disciplines.”

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**“This is a typical example of a clinical observation and a new technique merging together, a concrete example of how we try to facilitate expertise in different disciplines.”**

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Now that the first years are over, where do Bouma and Van de Graaf see this Institute in 10 years. In truth no one can tell, except that AGEM will need to change constantly to meet tomorrow’s reality. Professor Bouma: “This is a living organization, it is moving with the waves of the hospitals’ mergers, There will be new dynamics, challenges, so we should not say in 10 years, we will be this. We need to be flexible to move with development in the Institute and in society.”

Van de Graaf: “This flexibility was built into to us at the start, so we don’t need to change our vision in

order to be able to change.” They give, for example, hepatitis C virus which used to be a great problem, but is now largely solved. Professor Bouma: “That has consequences for research. There will be breakthroughs in the coming years which solve problems, but also, as you now see with the Corona virus and Covid-19, new challenges to society and as a research institute we have to be able to respond.”

So what would they like to achieve? Professor Bouma: “I still feel very strongly that I want to create an environment that is very competitive but not a competition, to teach to young scientists, yes, you have to be very ambitious, you have to try to be the best you can, and we try to facilitate that, but it is not a competition like a football match where you have to beat the opposition, we are talking in the end about the health and welfare of human beings. Dr Van de Graaf: “I have few doubts that in ten years’ time we can look back at examples such as understanding intestinal motility, and say, we played a role, a minor step in the larger trajectory, at the beginning of these projects.”

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**“I still feel very strongly that I want to create an environment that is very competitive but not a competition”**

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*Gerd Bouma, AGEM director*

*Stan van de Graaf, AGEM director*

*Eva Dirckx-Beuling, AGEM policy officer*



Stan van de Graaf, Eva Dirckx-Beuling and Gerd Bouma



# Amsterdam Gastroenterology Endocrinology Metabolism

