Amsterdam UMC
University Medical Centers

Amsterdam Gastroenterology Endocrinology Metabolism

AGEM
Annual report 2021

Colophon

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Contents

AGEM directors looking back

Undoubtedly, 2021 was a turbulent year in view of the continuously changing COVID-19 situation in the Netherlands. From the roll-out of the national COVID-19 vaccine campaign and relaxation of COVID-19 restrictive measures in summer, to the outbreak of the Omicron strain and a nationwide complete lockdown in winter: the unpredictability of COVID-19 made it difficult for the Amsterdam Gastroenterology Endocrinology Metabolism research institute (hereafter: AGEM) to organize events or to plan ahead.

"Of course we had already mastered valuable lessons in 2020", says prof. dr. Stan van de Graaf, co-director of AGEM, "that allowed us to organize several valuable and well-attended events online in 2021". Next to its own online seminars, the Tager lecture series, AGEM joined forces with others to help organize online lectures such as the ImmonoMetNet series and the Grand Rounds in Digestive diseases. "What I appreciate about these events, is their intrinsic interdisciplinary approach", says Van de Graaf, "which makes these initiatives a valuable addition to the lectures and seminars AGEM was already organizing before".

"that allowed us to organize several valuable and well-attended events online in 2021"

This also has bearings with the directors' goal to increase the institute's collaboration with external partners in 2021. "Several research groups already have a very strong position in the national and international field", Van de Graaf explains, "for instance prof. dr. Marc Besselink and more recently also dr. Rogier Voermans managed to make Amsterdam UMC a key player in the pancreatitis field by creating strong collaborative networks with other research centers". The AGEM directors hope other research teams will be able to obtain such a strong position as well, and are currently assessing how they can most efficiently support this.

Recalling this goal, Van de Graaf mentions that where AGEM may have been somewhat more inwardly focused in the first years after its inception, "in 2021, we have surely started to shift attention towards collaborating with our neighbors, both within Amsterdam UMC as well as outside". The Dutch Translational Metabolism Conference (DMTC) series, initiated and co-organized by AGEM PI Riekelt Houtkooper and several PIs outside of Amsterdam, is an excellent example of a collaborative effort on a national scale. Further, AGEM and Amsterdam Infection & Immunity (AII) organized their first joint meeting to bring together researchers working in these fields, and AGEM and Cancer Center Amsterdam (CCA) jointly organized the HPBeter symposium, which already had strong ties with both regional and national hospitals.

Prof. dr. Stan van de Graaf

Despite these successful events, the directors also recognize that COVID-19 was still very much present. Next to the short-term effects of COVID-19, the directors feel that the long-term impact of the pandemic became more visible too. “Having to work from home for such a long period of time, without being able to see your colleagues, really started to take its toll in 2021” says Van de Graaf. He notices that social interaction through a computer screen is difficult: “Mostly the small things, like making a joke or the little chit-chats before meetings. Those unplanned moments, the spontaneity and creativity that we so desperately need in research, slowly disappeared”.

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Even though Van de Graaf feels it is a pity that several aspects of AGEM’s core business were hindered by COVID-19, such as face-to-face symposia and the very successful international student fellowship program, he feels proud that the institute was again able to quickly adapt to the continuously changing COVID-19 situation: “in 2021, we were able to allocate four innovation grants instead of two. All four projects will add something useful to AGEM as a whole, meaning researchers can reap the benefits from these investments for years to come”.

The directors are also proud of AGEM PI Louis Vermeulen, who won the Ammodo Science Award for fundamental research in 2021, and on Sanne van Neerven, PhD-student in the Vermeulen group, who won the Birnstiel award. “We also nominated AGEM PI Marlies Schijven for the Societal Impact Award”, Van de Graaf adds, “and I am proud she made it to the final four final nominees”.

Next to nominating promising AGEM candidates for several awards in- and outside of the Amsterdam UMC, the AGEM directors were again involved in several strategic decisions through their membership in the Amsterdam Research Board (ARB) in 2021. In these meetings, the directors are acting as representatives of all AGEM researchers, creating a lobby towards the Board of Directors of the Amsterdam UMC.

Furthermore, the lack of possibilities for physical events in 2021 also gave the institute time to reflect on their achievements of the past years and to critically look at its future. “This mid-term evaluation,” Van de Graaf explains, “nicely showed us that our initial goal for AGEM – reunite both houses into one AGEM at the Amsterdam UMC – has been achieved”. The reorganizational waves, where several AGEM-affiliated departments merged with their counterparts at the other location, has greatly contributed to achieving this goal. These waves have also stimulated departments to learn from each other by looking at best practices from both houses. Van de Graaf believes this will undoubtedly lead to improvements in healthcare provision, diagnostics and research in the coming years.

“So, even though AGEM might have seemed more idle due to cancelled activities in 2021”, Van de Graaf states, “we definitely have been working very hard behind the scenes on improving AGEM to be able to even better facilitate all gastroenterology, endocrinology and metabolism researchers and research at Amsterdam UMC”.

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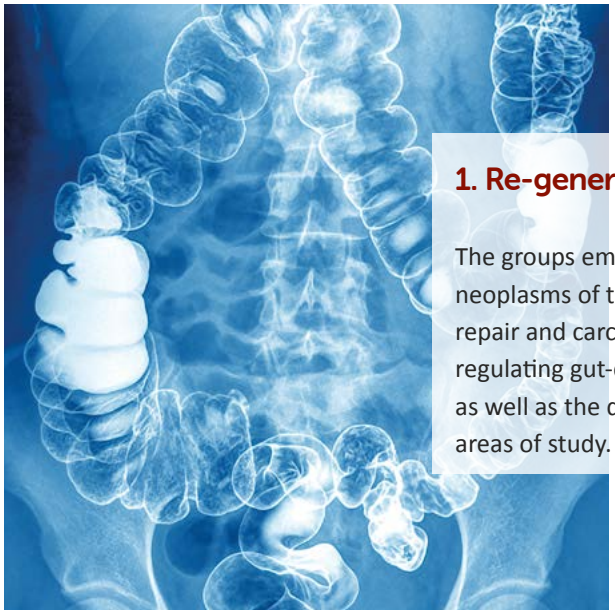
Prof. dr. Gerd Bouma

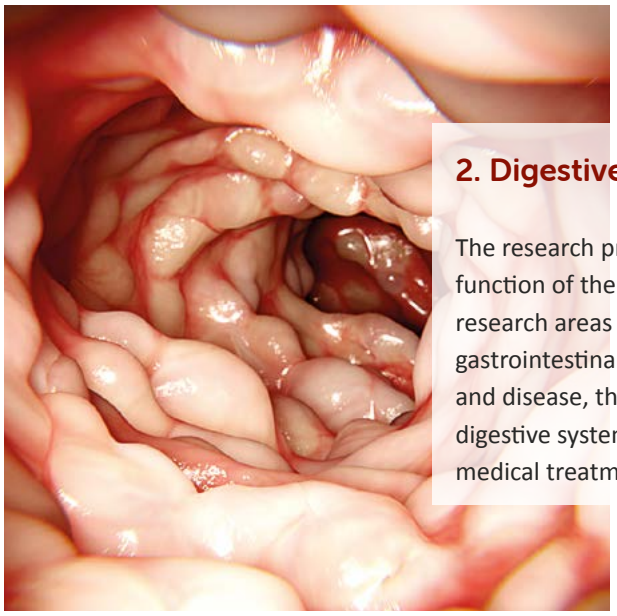
AGEM Research Programs

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



1. Re-generation and neoplasms of the digestive system

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

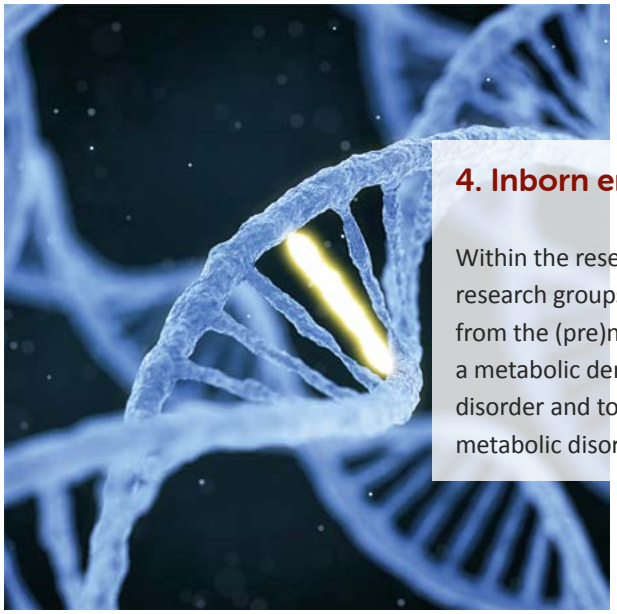


2. Digestive function and pathology

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

3. Endocrinology, metabolism and nutrition

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



4. Inborn errors of metabolism

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

AGEM Research Board 2021

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

New to the AGEM Research Board

Joris Erdmann

Since November 2021, Joris Erdmann, joined the AGEM research board. Joris was trained as a transplant and HPB surgeon (liver, bile duct and pancreas) and was previously involved in organ transplant and perfusion research. Since 2018 he joined the HPB team in Amsterdam and his clinical and research focus lies on primary liver tumors, liver function, failure and regeneration.

What I want to achieve with the AGEM research institute…

As a clinician and surgeon I believe that my main task is to translate the problems we face in the treatment of our patients to the research departments. Furthermore we should collect samples and facilitate research as much as possible. The clinicians can interconnect the various research groups and bring relevance to the great work that is done in the research laboratories. Together we are here to optimally treat the patients of today and improve that of the patients of tomorrow.

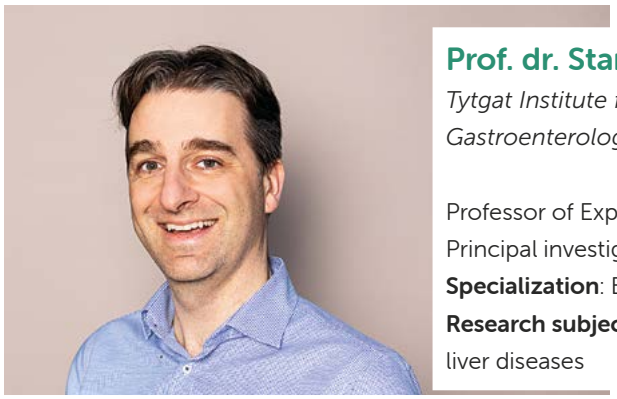
Dr. Joris Erdmann

AGEM directors

Prof. dr. Gerd Bouma

Department of Gastroenterology and Hepatology

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



Prof. dr. Stan van de Graaf

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

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

AGEM Research Board members

Dr. Anje te Velde

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

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

Prof. dr. Annemieke Heijboer

Endocrine Laboratory & Department of Clinical Chemistry

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

Prof. dr. Marc Besselink

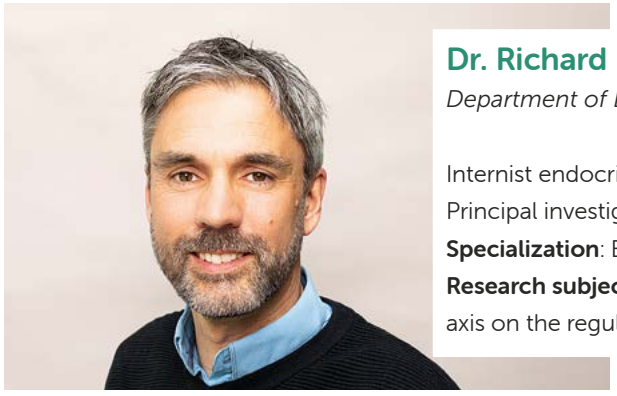
Department of Surgery

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

Prof. dr. Annet Bosch

Department of Pediatric Metabolic Diseases

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



Dr. Richard IJzerman

Department of Endocrinology

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

Dr. Hilde Herrema

Department of Experimental Vascular Medicine

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

Prof. dr. Hans Waterham

Laboratory Genetic Metabolic Diseases

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

Dr. Joris Erdmann

Department of Surgery

Hepatobiliary and pancreatic surgeon
Specialization: Surgery
Research subject: To study liver function, regeneration and failure within the field of liver surgery.

AGEM office

Dr. Eva Dirkx-Beuling

Amsterdam Gastroenterology Endocrinology Metabolism (AGEM)

Policy officer AGEM

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

Linda van den Noord

Amsterdam Gastroenterology Endocrinology Metabolism (AGEM)

Secretary AGEM

AGEM Science Impressions 2021

To give an impression of the research conducted at the AGEM research institute, five couples of young investigators and their supervisors were invited to present the research projects they worked on in 2021.

Paving the way to study gut maturation in a dish

Vanesa Dijkstra-Muncan and Francesca Giugliano

We are not born with a fully functional intestine. It still needs time to mature. Especially the first 1000 days of life, from conception till the second birthday are very important to establish a healthy, well-functioning intestine. When something goes wrong in this period, for example in premature or undernourished babies, or babies exposed to external factors which can modify the gut maturation, this will have both short and long term effects on health. In my research team we are interested in the gut maturation process in pre-and term infants from birth up to the weaning phase and how this is influenced by early life nutrition, microbial products and drugs. When we started this research line, we first had to set up an in vitro/ex vivo model in which we can study the impact of external factors on the gut maturation process. So we started with the rodent model because in rodents the gut maturation has been extensively described and the period of maturation is much shorter than in humans, only 30 days upon birth. To develop an in vitro model, we were interested to investigate whether primary fetal mouse epithelial cells grown as enteroids will mimic in vivo epithelial maturation when cultured ex vivo for 30 days. An enteroid culture is 3D or 2D in vitro system that enables the outgrowth of intestinal epithelial cells derived from mouse and human tissues into ever-expanding mini-guts. We discovered that enteroids, derived from mouse gut just prior to birth, display the characteristic of immature intestine at the beginning of culture. During 30 days of culture they undergo transition to adult epithelium, which corresponds to the pattern of development that mice normally undergo in the transition from milk to solid food. So we were able to mimic mouse gut maturation in vitro and we can now use this model to study the effect of drugs and nutritional concepts on gut maturation process.We ultimately want to have a human model that will mimic human maturation process. That quest was assigned to MD Francesca Giugliano that had already completed her specialization in pediatrics in Italy before she joined our lab as PhD in 2018. Since there is not much known about temporal change of intestinal epithelial function associated with maturation in pre-and neonatal stage of life, her first goal was to assess human gut development in vivo and define a set of maturation markers specific for human intestinal maturation. With the help of Joep Derikx ,from pediatric department who provided tissue specimens from pre and term infants that underwent surgery, we performed an extensive tissue profiling of different stages of human intestinal development. That enabled us to define a set of human gut maturation markers. For example expression of brush border enzyme alkaline phosphatase (ALP) and disaccharidases is highly upregulated during human gut development. ALP performs a defense function such as inactivation of bacterial lipopolysaccharide contributing to the

Vanesa Dijkstra-Muncan and Francesca Giugliano

barrier defense. Disaccharidases: sucrase-isomaltase (SIS) and lactase (LCT) are enzymes responsible for sugar processing prior to absorption. Although these enzymes can be detected in the intestine around 10 weeks of gestation, their expression increases at birth. Any defective expression of these enzymes can lead to intestinal diseases ranging from severe clinical phenotypes with osmotic diarrhea and failure to thrive to milder malabsorption conditions such as lactase deficiency. She used these markers to validate whether human fetal enteroids derived from human fetal intestine staged from 13-22wk against human in vivo development. In other words she looked whether the enteroids derived from fetal intestine would intrinsically turn to adult intestine during prolonged culture as it happened with mouse fetal enteroids. After lots of weeks of culture she discovered that human fetal enteroids retain a stabile fate for up to 20 weeks of culture. That meant that we can't simply use fetal enteroids and culture them in time to study how the human maturation process is unfolding. We needed to look for extra epithelial factors that are necessary for human gut maturation. We focused our attention to the immune compartment and her data shows that a set of secreted factors originated from immune cells can increase intestinal barrier function by increasing transepithelial resistance and activity of disaccharidases to the level seen in adult intestine.

Data from this project revealed which intestinal functions change during human intestinal maturation. We believe that the aligning the intrinsic feature of pre/postnatal intestinal adaptations during maturation process in vivo with in vitro would set human in vitro culture as a future golden standard for studies on intestinal epithelial maturity and diseases associated with challenged gut conditions. Importantly, the establishment and validation of such in vitro cultures from the intestine could lead to the development of specific interventional concepts able to modulate the maturation process and to prevent onset of maturation related diseases.

The curious case of lipid metabolism in cardiovascular and metabolic diseases

Noam Zelcer and Sebastian Hendrix

www.zelcerlab.eu

Dept of Medical Biochemistry, AMC

Lipids are everywhere. They form the cell membrane of each cell in the body. They surround intracellular organelles and vesicles. They are the primary constituents of circulating lipoproteins, and they can also act as critical signaling biomolecules to exert a wide array of responses. There are thousands of lipid species, many of which we still know very little about. Complicating matters further, the cellular composition of lipids can be rapidly modified in response to metabolic cues, extracellular signals (e.g. inflammation), or just as part of normal cellular physiology. How is this complexity controlled and lipid homeostasis maintained?

In our group at the Department of Medical Biochemistry, we study the molecular regulation of metabolism, primarily focusing on the (post)-transcriptional control of lipid metabolism. We address key questions in lipid metabolism, such as how does a cell know how much cholesterol or fatty acids it has, and what is the cellular response to elevated or decreased levels? How are these lipids trafficked between different compartments in the cell? How do cells dynamically reshape their lipid landscape in response to signaling cues, and vice versa how does the lipid composition dictate signaling output? Which genes regulate lipid metabolism? We approach these questions through a basic science lens. Yet given the involvement of lipid metabolism in all facets of cellular physiology, its dysregulation is at the epicenter of numerous human diseases, most notably cardiovascular and metabolic diseases that are the focus of our research. This makes our work a gateway into translational research as well.

There are three ongoing lines of research in our group, each studying a different aspect of lipid metabolism using cell- and mouse-based models in conjunction with human genetics. Specifically, we investigate (1) the role of the sterol-sensing transcription factors LXRs, (2) the role of the ubiquitin proteasomal system in post-transcriptional regulation of lipid-associated events, and more recently (3) we introduced the use of genome-wide functional genetic screens to interrogate cellular lipid metabolism.

Sebastian's PhD project, which is supported by an NWO VICI grant, starts with one such genome-wide screen that was geared towards identifying unknown genetic determinants of cholesterol biosynthesis. In this screen we discovered an uncharacterized open-reading frame that had no known function, and which our results suggested is essential for production of cholesterol and fatty acids by cells. Together with others in the lab he was able to determine that this gene is involved in the activation of the master transcriptional regulators of lipid metabolism, SREBPs, and that when absent SREBP-dependent signaling is severely impaired. The aim of the PhD project was therefore to understand the contribution of this new gene, which we christened as SREBP-RegulatINg Gene (SPRING), to lipid metabolism and to explore possibilities for SPRING-focused therapeutic interventions.

SPRING is a small membrane protein that is located in the Golgi, which begs the question as to how it regulates the transcriptional activation of SREPBs? SREBPs must undergo a two-step cleavage process in the Golgi before the transcriptionally active SREBP domain can travel to the nucleus to induce its transcriptional program. In a series of ongoing experiments Sebastian has found that SPRING is indispensable for the first cleavage event of SREBPs, as it is needed for the activity of the responsible proteolytic enzyme. Hence, when SPRING is absent, SREBPs cannot be proteolytically processed and activated, and in cells this abrogates, amongst others, cholesterol and fatty acid synthesis.

Sebastian Hendrix and Noam Zelcer

To address whether our observations in cells holds *in vivo,* Sebastian has developed mouse models lacking Spring. Global loss of *Spring* turned out to be embryonic lethal. SREBP signaling is prominent in the liver, and hence the project is now focusing on studying mice with liver-specific ablation of *Spring*. In initial experiments we have confirmed that loss of *Spring* in the liver results in marked attenuation of SREBP signaling, as was seen in cells. Moreover, in this model we observed multiple beneficial metabolic outcomes, and are now testing whether absence of hepatic *Spring* may protect mice from development of NAFLD and obesity. As loss of hepatic *Spring* in mice seems to lead to a beneficial metabolic phenotype, and there is an indication that genetic variation in human *SPRING* may have a comparable outcome. In the near future we are planning to explore therapeutic targeting of hepatic *Spring* using siRNAs. If successful, these results may support developing *SPRING* as a therapeutic strategy in lipid-associated diseases.

Sebastian's project could not have moved forward without the help of several close colleagues, Anke Loregger, Josephine Tan, Masoud Valiloo, Jenina Kingma, and Roelof Ottenhoff and without input from other AGEM members. In the coming years we hope to bring a new SPRING into lipid metabolism.

Unraveling the mechanisms of colorectal anastomotic healing and leakage

Joep Derikx and Claire van Helsdingen

Colorectal anastomotic leakage (CAL) is one of the most feared complications after colorectal surgery for various diseases, such as cancer, inflammatory bowel diseases (IBD) and diverticulitis. After resection of the affected part of the intestine, the cut ends are joined which is called the anastomosis. In most patients the anastomosis will heal properly, however in some patients the anastomosis does not heal well and they develop CAL. When a patient develops CAL, bowel content leaks into the abdominal cavity and can lead to postoperative ileus, peritonitis, sepsis or even death. CAL often requires one or more re-intervention, leading to increased length of hospital stay, higher health care costs and decreased health-related quality of life. In patients with colorectal cancer, CAL is associated with an impaired oncological prognosis. Despite the extensive research into CAL and the improvement of surgical techniques the incidence remained unchanged over the last years.

In our research group we work with the samples from the REVEAL-study (pREdic-tiVE factors for colorectal Anastomotic Leakage) in which we collaborated with Prof. Nicole Bouvy (Surgeon, Maastricht UMC+). This study is a large prospective multicenter cohort study of patients who underwent colorectal surgery with creation of a primary anastomosis for colorectal carcinoma (CRC) in MUMC+, Zuyderland and VieCuri Medical Centre. We collected patient and surgery-related characteristics, preoperative computed tomography (CT) scans and pre- and postoperative stool and blood samples from 526 patients.

Within CAL research we focus on three different topics. First, improving the preoperative prediction of the risk of CAL. Multiple risk factors for CAL, such as male gender, smoking and malnutrition have been identified. However, the prediction of the risk of developing CAL for the individual patient remains inaccurate. Previous research indicated that the gut microbiome composition may play a role in the development of CAL and might be of predictive value, therefore preoperative stool samples were analyzed with the help of Mark Davids from the MiCA and in close collaboration with Prof. Wouter de Jonge and Konstantina Zafeiropoulou from the Tytgat Institute for Liver and Intestinal Research. These data will contribute to both improving the prediction and understanding the pathophysiology. Another risk factor that may contribute to the prediction of CAL is the distribution of body fat and muscle. This body composition is measured on routinely performed preoperative CT-scans in collaboration with radiologist Dr. Robert Hemke (Amsterdam UMC). The outcomes of the microbiome analyses, together with body composition analyses, preoperative blood analyses and patient characteristics will lead to a dataset which will be analyzed via a multi-omics approach with the help of Horaizon B.V. to predict the preoperative CAL risk. Improvement of this preoperative risk assessment will aid surgeons to choose the optimal treatment strategy.

Second, we aim to find new biomarkers for the early diagnosis of CAL. The clinical presentation of CAL varies from subfebrile temperature and mild abdominal pain to sepsis with multiorgan failure. Due to the heterogeneous clinical presentation of CAL and the lack of specific additional laboratory tests, there is often a delay in the diagnosis and treatment of CAL which is associated with increased morbidity and mortality. The postoperatively collected blood samples will be analyzed to find new protein biomarkers using Olink proximity Extension Assay technology. Identification of new specific biomarkers for monitoring anastomotic healing, will help clinicians with earlier detection of derailment of healing and consequently leading to timely intervention and minimizing severe complications.

Third, we want to gain insights into the mechanism of anastomotic healing and leakage. Knowledge on intestinal wound healing is mainly derived from studies that have investigated cutaneous wound healing. However, there are differences such as the

Joep Derikx and Claire van Helsdingen

types of collagen that are present and the microbial environment. The unpredictability of CAL and the lack of specific biomarkers for CAL can be party attributed to the fact that the underlying fundamental processes of colorectal anastomotic healing and leakage are still not properly understood. We will investigate the role of the intestinal microbiome on the development of CAL with the use of human samples but also in animal models. This fundamental research is necessary as a better understanding of the fundamental processes that drive anastomotic healing will give leads for better predictive tools, preventive measurements, interventions that stimulate healing and new biomarkers for early diagnosis.

For the clinical research questions we also closely work with Prof. Pieter Tanis (Surgeon, Amsterdam UMC/ Erasmus MC, Dr. Roel Hompes (Surgeon, Amsterdam UMC), Kevin Talboom and Kiedo Wienholts on the IMARI study (Multi-Interventional program for prevention and early Management of Anastomotic leakage after total mesorectal excision in Rectal cancer patIents) which aims to improve the one-year anastomotic integrity rate with a multi-intervential program.

Altogether unraveling the multifactorial mechanisms of CAL needs a multidisciplinary approach with the goal to improve the perioperative care of patients.

Brain microglial cell dysfunction in obesity and diabetes

Chun-Xia Yi and Felipe Correa da Silva

Chun-Xia Yi group

Not until recently, we gained knowledge that the mechanism of the development of metabolic disease is beyond the canonical concept that brain metabolic sensing and regulation is dominated by the role of neurons and pathways controlled by neurons. The microenvironment in which neurons live is supported and maintained by other cells. In this microenvironment, microglia function as the immune homeostatic keeper, by clearance of debris and metabolic waste produced by different cells and initiate immune response. At the level of intercellular communications, we aim to delineate specific cellular interactions between neurons and microglia. We are also interested in understanding how microglia balance their phagocytic activity and inflammatory response under different pathophysiological conditions.

For translational studies, we are working with post-mortem human brain tissue donated by obese, type 1 or type 2 diabetes, and Prader-Willi Syndrome individuals, to profile gene or protein expressions associated with disease and treatment. By comparing type 2 diabetic individuals and non-diabetic controls, we have found a loss of key clock-regulatory neuropeptides and the intermingled neuron-supporting glial cells that are of utmost importance for a proper functioning of the neuronal clock network. Our findings suggest that disturbances in the daily physiology of type 2 diabetic patients, such as those in the sleep/wake cycle and glucose metabolism, may be due to an impaired functioning of the central master clock in the hypothalamus.

Moreover, we also take technical challenges in the microglial research field, to explore how to modify microglial function with biocompatible and biodegradable nanomaterials-assisted genetic and pharmacological approaches. Recently, we established a novel method to allow microglia to take up nanomaterials-carried siRNA to modify their immune response and phagocytosis. Powered with this novel technique, we are now ready to explore microglial intracellular pathways at specific brain region that is related to specific diseases.

Research on Prader-Willi Syndrome builds the bridge from bench to bedside

Prader-Willi Syndrome (PWS) is a neurodevelopmental genetic disorder due to the lack of expression of genes on the paternally inherited chromosome 15q11.2-q13 region. The phenotypic features of PWS are multisystemic and include a wide range of clinical features with age-dependent manifestations. The clinical features of PWS includes a certain degree of intellectual disabilities, hampered linguistic and motor milestones, and a wide number of endocrine abnormalities, which among others lead to metabolic disruption and gross obesity. Hypothalamic dysfunction is so far recognized as a hallmark of its pathophysiology and extensively suggested as one of the causative factors in the disease appearance and progression.

There are different types of PWS chromosomal deletion. Different locations of chromosomal breakpoints lead to the identification of two sub-genotypes, named as Type I and Type II deletions. In the PWS Type I deletion subjects a larger chromosomal portion that involves four additional genes is lost. Phenotypically, Type I deletion was found to have more aggressive and severe cognitive problems when compared to Type II. However, the genotype-phenotype relationships in the brain disruption in PWS sub-genotypes is still poorly explored and understood.

Extensive studies in rodents and humans demonstrated that hypothalamic malfunctioning, especially in energy homeostasis controlling neurons promotes the obese phenotype. This englobes the dysfunction and/or loss of neurons located at the infundibular nucleus (the human equivalent to the arcuate nucleus), and the hypothalamic paraventricular nucleus of the hypothalamus. This neuronal loss is well documented in the human hypothalamus in obesity and diabetes, and in PWS. These processes are multifactorial and notably orchestrated via an inflammatory process coordinated by microglia cells. Surprisingly, very few studies explored hypothalamic microglia activity in PWS.

Chun-Xia Yi and Felipe Correa da Silva

In our PWS project, we teamed up with the Department of Pathology and the Netherlands Institute for Neuroscience. PhD student Felipe Correa da Silva aimed to profile hypothalamic microglia and neuronal populations in Type I and Type II subjects. So far, we have observed extreme dysmorphic microglia in PWS Type I subjects. This dysmorphism has implications to disrupted phagolysosome capacity of these microglia. Whereas in Type II subjects, we found morphological intact microglia without disturbances in their phagolysosome capacity. These data suggest a possible participation of the four additional genes that are only lost in PWS T1 deletions. Among these four genes, we hypothesized that Cyfip1 could be one of the causative genes of the disruptive microglia phenotype that we observed since this gene participate in cytoskeleton regulation. To test this hypothesis, we generated two murine models that mimics the genetic haploinsufficiency of Cyfip1 gene, throughout the whole body or only in the microglial cells in the brain. In both models, we found disruptive microglial morphology and phagocytosis, even in a steady state without any obesogenic challenge. Our findings point to a distinct microglial immunity associated to PWS sub-genotype. Our results suggest the brain immune cells are promising targets to treat the behavioral disorders of PWS patients with Type I deletion.

Intestinal failure in children

Merit Tabbers and Aysenur Demirok

Intestinal Failure Team

Amsterdam University Medical Centers (Amsterdam UMC) is an international and national expertise center for children and adults with intestinal failure. Dr. Merit Tabbers is a pediatric gastroenterologist at the Emma Children's Hospital/ Amsterdam UMC and head of the pediatric intestinal failure & home parenteral nutrition team. Research is characterized by its international collaboration, which is provided by the European Reference Network for rare Inherited and Congenital (digestive and gastrointestinal) Anomalies (ERNICA) and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) - Network of Intestinal failure and Transplant in Europe (NITE). Merit Tabbers is chair of the intestinal failure working group of ERNICA. Due to the low prevalence of intestinal failure, international collaboration is of great importance to investigate diagnostics and therapies within this field. Her research and work include areas such as composition of parenteral nutrition, prevention of catheter related thrombosis and infection, non-invasive diagnostic tools of parenteral nutrition associated liver disease, health related quality of life, transition from pediatric to adult health care and guideline development and developing core outcome sets.
The intestinal failure team has the aim to improve quality of life and disease specific health conditions by a multidisciplinary approach. The pediatric and adult teams are collaborating in order to bridge the gap between pediatric and adult health care. This will create a safe and effective transition and will help to continue complex patient care in this specific group.

Intestinal Failure

Intestinal failure is most commonly defined as the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation, i.e. parenteral nutrition, is required to maintain health and/or growth. It is a rare, complex medical condition, with a prevalence of children on home parenteral ranging from 9.6 to 27 children per million. The most prevalent underlying conditions leading to chronic intestinal failure in children are; 1) short bowel syndrome, 2) intestinal neuromuscular motility disorders such as pediatric intestinal pseudo-obstruction syndrome and 3) congenital enteropathies. In our intestinal failure team we treat patients who are dependent on intravenous support for months to years. Patients are at risk for complications from administration of parenteral nutrition as well as from their underlying intestinal failure causing disease.

Improvement of clinical and research setting

Aysenur Demirok started her PhD in the pediatric intestinal failure & home parenteral nutrition team in 2022 and she followed up Sjoerd Nagelkerke, who defended his thesis in April 2022.The ultimate goal of her research is the improvement of clinical and research setting in this field. The focus of her projects is to improve the supportive catheter care and management of transition from pediatric to adult care. Besides that, she is performing an national observational study to gain more insight into diagnostics, therapy and outcomes of children with pediatric intestinal pseudo obstruction. Furthermore, she contributed to the development of a core outcome set which can be used in future research in this field.
Although the care for patients with intestinal failure improved greatly over the years, it will remain a chronic disease which needs efforts in improving supportive care. Prospective research into the most effective and safe strategies to prevent catheter-related infection and -thrombosis in pediatric intestinal failure is necessary to prevent these complications. This is of great importance for this patient group, as this is the lifeline for these children, making it more important to prevent loss of vascular access. Currently, the efficacy and safety of prophylactic anticoagulants are not known and clinical practice varies between centers. Therefore, an international, multicenter prospective study within ERNICA led by our group, is currently ongoing to gain more insight into the efficacy and safety of prophylactic anticoagulants.
The pediatric intestinal failure team will participate in an important international register: Intestinal Failure Registry (IFR).This is a multicenter, prospective, observational and longitudinal registry of children diagnosed with intestinal failure due to short bowel syndrome and treated by intestinal rehabilitation programs from centers around the world. This is set up in Canada by the Intestinal Rehabilitation and

Merit Tabbers and Aysenur Demirok

Transplant Association and by The Transplant Society, a non-for-profit organization. The IFR will provide an infrastructure for multicenter data collection, address knowledge gaps in intestinal failure and will provide valuable information to inform the development of evidence-based treatment modalities. This will contribute to optimal management for patients with intestinal failure and better understanding of current trends and outcomes in this field.

Another important aim of the research project is to gain more insight into pediatric intestinal pseudo obstruction (PIPO), which is a rare congenital disorder characterized by gastrointestinal motility dysfunction. Prevalence of PIPO in the Netherlands is unknown, nor which treatments they have received and their presenting and current symptoms. As pediatric intestinal pseudo obstruction has a wide range of symptoms, it leads to personalized medicine, making it more difficult to standardize and compare disease management. Therefore, a study across all academic centers in the Netherlands is performed to gain more insight in this disease. Furthermore, an international project has been performed within ERNICA to investigate diagnostic and therapeutic management in centers across Europe.

Past decades, mortality and morbidity have decreased due to improvements in care with many children growing into adult care. Although transition is an important and challenging process for this patient group, no standardized transition protocol exists. Therefore, the aim is to create a more standardized transition protocol for this patient group. This will be obtained by input from key stakeholders in this field including patients, parents and health care professionals from various disciplines across European centers during consensus meetings of ERNICA and ESPGHAN NITE.

For pediatric intestinal failure, research is scarce and the majority of the performed research is of small sample size. A great heterogeneity exists in outcome reporting, which makes it impossible to synthesize the results of different research studies. Therefore, a core outcome set for pediatric intestinal failure is created. Development of this COS can reduce heterogeneity in outcome-reporting, enhance comparability between studies and will represent different key stakeholders involved. This will ultimately lead to development of evidence-based management guidelines for children suffering from intestinal failure which is of great importance for this chronic, heterogeneous disease.

AGEM Grants 2021

In 2021, AGEM awarded five types of grants. Like previous years AGEM awarded the *AGEM talent development grant* for exceptionally talented researchers who are in the first 5 years after obtaining a PhD-degree and want to start their own research line (VENI-profile) or who want to further develop their own research line (VIDI-profile, max 8 years after PhD graduation), the *AGEM innovation grant* for innovative ideas beneficial to the AGEM research institute as a whole, the *AGEM international student fellowship* for (bio-)medical students (in their MSc-program or just graduated) to participate in a research internship for a 6-12 months at an international top institute, the *AGEM PhD-student course project* for the group of PhD-students that wrote the best proposal during the AGEM PhD-student course, and the *AGEM contribution printing costs of theses* of AGEM PhD-students.

The AGEM talent development grant 2021 (€75.000)

VENI-profile: Dirk Jan Stenvers

Role of the central brain clock in the pathophysiology of insulin resistance

Dirk Jan Stenvers

I am trained as a clinical internist-endocrinologist, but also as a basic circadian biologist. My research focus is the clinical application of circadian knowledge to improve metabolic and endocrine health. My PhD research was partly funded by a ZonMW Agiko Stipend, and my PhD thesis 'Light, the circadian timing system, and type 2 diabetes' (2017) was awarded two prestigious national PhD thesis awards (Dr. C.J. Roos award and Dr. F. Gerritzen award). Since 2021 I have an appointment as a staff endocrinologist at Amsterdam UMC. I combine clinical work with research and education. I lead a research group at the Amsterdam UMC and the Netherlands Institute of Neuroscience, consisting of currently 7 PhD students, 2 master students and 2 bachelor students. My team uses a variety of techniques including animal models, clinical intervention studies, retrospective cohort studies, questionnaire studies, human functional brain imaging, and molecular analyses of human tissues (including transcriptomics).

The AGEM talent development grant allows me…

…to develop a cutting-edge 7T fMRI protocol to visualize the central brain clock in the human hypothalamic suprachiasmatic nucleus (SCN). The SCN coordinates daily rhythms in sleep/wake behaviour, fasting/food intake, insulin secretion and insulin sensitivity. Based on animal studies and post-mortem studies, I hypothesized that the central brain clock is involved in the pathophysiology of type 2 diabetes (T2DM). Thanks to the AGEM talent development grant I was able develop a 7T fMRI protocol and subsequently use this protocol to assess the daily rhythm of SCN activity in people with increasing stages of insulin resistance in a observational cohort study (registered at clinicaltrials.gov NCT05314855). I was able to consolidate my collaboration with dr. Wietske van der Zwaag from the Spinoza Institute for Neuroimaging. By combining the AGEM grant with other funding I had the possibility to appoint the talented PhD student Esther Speksnijder, and to fund the fMRI scans. I will use the data from the study funded by the AGEM talent development grant to apply for future grants including the ZonMW Veni grant.

Esther Speksnijder and Dirk Jan Stenvers

VIDI-profile: Georges Janssens

What is the mechanism driving the NAD+ decline that occurs with aging?

Georges Janssens

Georges Janssens (1985) is Assistant Professor in the Laboratory Genetic Metabolic Diseases, at the Amsterdam UMC, location AMC in the Netherlands. His work is focused on multi-omics data integration studying the molecular determinants of healthy aging. His research education has taken place in California, the UK, Sweden, and the Netherlands. During his postdoctoral work at the Karolinska institute in Stockholm, he pioneered transcriptome-based machine-learning enabled drug screening, an approach he continues to expand upon today in his independent research line. Dr. Janssens has been awarded several prestigious fellowships including the FEBS (2017) and the VENI (2019). He has authored over 30 publications, with recent first authorships in journals including Cell Metabolism and Cell Reports, and recent corresponding authorships in journals including EMBO Molecular Medicine, Aging Cell, and Biogerontology. He writes a popular-science blog that distills myths on aging (AgingIsBeautiful.com) and is passionate to develop healthy aging diagnostics and interventions that are accessible to the public.

The AGEM talent development grant allows me…

… to hire a research technician that will explore molecular factors influencing NAD+ levels and help cover laboratory costs for the experiments. This work will be especially focused on how NAD+ levels change with age, how this is transcriptionally controlled, and what novel gene targets can modulate NAD+ levels.

Georges Janssens

The AGEM innovation grant 2021 (€50.000)

Sanne van Neerven, Jan Koster and Louis Vermeulen

A real-time atlas of intestinal differentiation

Sanne van Neerven

Sanne van Neerven is a molecular biologist with expertise on the regulation of intestinal stem cells in homeostasis and cancer. During her PhD in de lab of Louis Vermeulen, she specifically focused on the competition between normal and mutant stem cells, and revealed that modulation of this competition can prevent tumour initiation. This approach can be used to develop novel chemoprevention strategies for patients with heritable cancer syndromes. Currently, she is a postdoc in the lab of Ben Simons at the Gurdon Institute (University of Cambridge), where she will continue her work on cell competition and cancer.

Jan Koster

Jan Koster is group leader in applied bioinformatics within the CEMM at the Amsterdam UMC. His collaborative research group focusses on using bioinformatics techniques to understand the underpinnings of the cancer genome. With his team, he has conceived and is actively developing the R2 genomics analysis and visualization platform (https://r2.amc.nl), a web-based tool that allows any scientist to perform data mining without the need of bioinformatics expertise. R2 is also a core facility of the Amsterdam UMC.

Louis Vermeulen

Louis Vermeulen is professor of Molecular Oncology and medical oncologist at the Amsterdam UMC. Both his research and clinical work focus on intestinal malignancies. His research group studies the interaction of the cancer cells with their environment, the heterogeneity of colorectal cancers as well as the very first steps of tumor development in the gut. Besides the support from AGEM the work in the laboratory is supported by the ERC, ZonMw (Vici) and KWF grants.

The AGEM innovation grant allows us…

The development of single-cell (multi)omics techniques has aided the identification and characterization of cell types across many, if not all, tissues. Many studies attempted to infer differentiation trajectories based on these 'static' single cell profiles in pseudo-time. However, pseudo-time analysis relies on many assumptions to tackle in computational frameworks and due to low cell coverage, rare transitioning cell types and events that influence cell fate decisions can easily be missed. We therefore proposed to create a 'real-time' single cell atlas by combining in vivo lineage tracing methods with single cell RNA transcriptomics to study the differentiation trajectories of intestinal stem cells during homeostasis.

Using the AGEM innovation grant, we created this comprehensive cell atlas and now have a unique catalogue all cell types present in the intestine that enables us to study real-time lineage relations of intestinal stem cells. This atlas will provide a basis for several studies in our lab and will be made publicly available to the AGEM community via the R2 genomics platform.

Jan Koster and Louis Vermeulen

Torsten Scheithauer and Melanie Bénard

Anaerobic culturing for large scale studies into microbiota function

Torsten Scheithauer

Torsten Scheithauer studied Nutrition and Biomedicine at Technical University in Munich. His research at Amsterdam UMC focused on the gut microbiota in metabolic diseases. He joined the group of prof. Max Nieuwdorp to study the effect of intestinal bacteria on insulin-producing beta-cells in type 2 diabetes. After his PhD, he studied the immunogenic potential of bacteriophages in metabolic diseases under the supervision of dr. Hilde Herrema. He is trained as a wet-lab scientist with expertise in different sequencing techniques, animal research, and (anaerobic) microbiology.

Melanie Bénard

Melanie Bénard is a medical doctor (trained at Amsterdam UMC) and PhD candidate in the field of Gastroenterology. Her research trajectory focuses on fecal microbiota transplantation (FMT) as a treatment of ulcerative colitis (UC). She coordinates a clinical multi-center RCT in which anaerobically prepared donor FMT is compared to anaerobically prepared autologous FMT in UC patients with mild to moderately active disease. This research is led by prof. C.Y. Ponsioen. Furthermore, she is investigating the impact of different conditions of feces processing on the viability of (anaerobic) bacteria.

The AGEM innovation grant allows us…

… to gain more knowledge about the gut microbiota in human physiology. A dedicated anaerobic in vitro infrastructure at Amsterdam UMC will accelerate insight into the functioning of the gut microbiota in health and disease. For example, these techniques allow studying the interaction of microbes with medication, microbial conversion of (dietary) precursors into metabolically relevant metabolites, transkingdom community interactions, or optimizing the composition and efficacy of fecal microbiota transplantation. We will integrate common anaerobic culture systems such as reusable Hungate tubes, anaerobic jars, and an anaerobic chamber (available via Microbiota Center Amsterdam). We welcome scientists with an interest in using the proposed infrastructure.

Melanie Bénard and Torsten Scheithauer

Hans Waterham and Georges Janssens

Development of a user-friendly in silico comparative transcriptome analysis platform to facilitate drug screening and provide insight into disease mechanisms

Hans Waterham

Hans Waterham is Professor Functional Genetics of Metabolic Diseases, Principal Investigator, and Clinical Laboratory Geneticist in the Laboratory Genetic Metabolic Diseases at the Amsterdam UMC, location AMC in the Netherlands. His research is aimed at understanding consequences of genetic defects on cellular processes/metabolism and to use this for developing therapeutic approaches with focus on peroxisomal disorders and disorders of cholesterol/isoprenoid biosynthesis. As Clinical Laboratory Geneticist, he is involved in clinical DNA diagnostics for inherited metabolic diseases. He is co-founder and co-director of the United for Metabolic Diseases consortium, which unites patient organisations and clinicians, researchers and laboratory specialists of all 6 Netherlands Academic Metabolic Expertise Centers to improve diagnosis, prevention, treatment and care for patients with inherited metabolic disorders.

Georges Janssens

Georges Janssens (1985) is Assistant Professor in the Laboratory Genetic Metabolic Diseases, at the Amsterdam UMC, location AMC in the Netherlands. His work is focused on multi-omics data integration studying the molecular determinants of healthy aging. His research education has taken place in California, the UK, Sweden, and the Netherlands. During his postdoctoral work at the Karolinska institute in Stockholm, he pioneered transcriptome-based machine-learning enabled drug screening, an approach he continues to expand upon today in his independent research line. Dr. Janssens has been awarded several prestigious fellowships including the FEBS (2017) and the VENI (2019). He has authored over 30 publications, with recent first authorships in journals including Cell Metabolism and Cell Reports, and recent corresponding authorships in journals including EMBO Molecular Medicine, Aging Cell, and Biogerontology. He writes a popular-science blog that distills myths on aging (AgingIsBeautiful.com) and is passionate to develop healthy aging diagnostics and interventions that are accessible to the public.

The AGEM innovation grant allows us…

…to develop a user-friendly computational drug screening platform. The platform will be accessible to AGEM researchers and eventually the broader scientific community. It will allow researchers to (1) identify unique transcriptional signatures of effective drugs, compared to non-effective drugs, (2) screen for small molecules that modulate specific genes of interest relevant for a disease, and (3) identify compounds that might reverse more global transcriptional changes occurring in diseases.

Georges Janssens and Hans Waterham

Annet Bosch, Noam Zelcer and Sacha Ferdinandusse

Elucidating Classical Galactosemia; the search for modifier genes

Annet Bosch

Annet Bosch is a pediatrician for metabolic diseases. She is the head of the division of pediatric metabolic diseases and Professor of Pediatrics, Metabolic Diseases at the University of Amsterdam. She obtained her PhD on the thesis “Classical Galactosemia Revisited” at the University of Amsterdam in 2004. Her major research topics are galactosemia, phenylketonuria, riboflavin transporter deficiency and newborn screening.

Noam Zelcer

Noam Zelcer is a molecular biologist and specializes in studying the role of lipid metabolism in the development of lipid-associated diseases. After completing his postdoctoral fellowship in UCLA he joined the Department of Medical Biochemistry in 2010 (AMC) where he is a Professor of Molecular Regulation of Metabolism. His research group investigates the (post)-transcriptional regulation of lipid metabolism, with a focus on development of NAFLD and atherosclerosis.

Sacha Ferdinandusse

Sacha Ferdinandusse is a Clinical Laboratory Geneticist and specialized in the enzyme diagnostics and functional studies for peroxisomal disorders, mitochondrial fatty acid oxidation disorders, disorders of amino acid metabolism and carbohydrate metabolism, including galactosemia. She did her PhD, postdoctoral studies and training as Clinical Laboratory Geneticist in the Laboratory Genetic Metabolic Diseases, where she is now a member of the staff. Her work focuses on the development of functional tests for the aforementioned disorders to optimize diagnostics, to enable severity prediction and personalized care, and to study the underlying pathological mechanisms.

The AGEM innovation grant allows us…

Classical Galactosemia (CG, OMIM (230400)) is a disorder of galactose metabolism caused by a severe deficiency of the enzyme galactose-1-phosphate uridyltransferase (GALT). The pathophysiology of the long-term complications in CG is poorly understood, and the lack of biomarkers and prognostic factors severely hampers development of new therapeutic modalities. There is a high variability in patient outcome independent of the genetic mutation. Unfortunately, early diagnosis and dietary treatment do not prevent long-term complications in CG, which warrants development of other therapeutic strategies.The AGEM innovation grant allows us to develop a clinically-relevant cellular model for CG and to apply a genome-wide CRISPR/Cas9-based genetic screening approach to identify genetic modifiers of the CG cellular phenotype. The developed CG model can also be used for subsequent functional studies with therapeutic potential as a guiding line. Development of the CG cellular model and elucidation of modifier genes will enable prognostication and stimulate development of new therapeutic options in Classical Galactosemia.

Heleen te Brinke, Amber Meurs, Lodewijk IJlst, Sacha Ferdinandusse, Noam Zelcer and Annet Bosch

The AGEM international student fellowship 2021 (€500/month)

Erik Kroesbergen

From metabolic to neurodegenerative disease: impaired glymphatics?

People with metabolic diseases show increased risk for neurodegenerative disorders later in life, characterized by accelerated waste accumulation (i.e. amyloid-beta, tau, alpha-synuclein, Lewy bodies) in the parenchyma. As the relatively highest energy consumer and cell-signaling organ, the brain demands flexible and adaptive solute transport and waste clearance. Similar to peripheral lymphatics, the Nedergaard lab discovered specific cerebral-spinal fluid (CSF) pathways regulated by astrocytes, which supply and remove solutes to the parenchyma, currently known as the glymphatic system. Surrounding the pial and penetrating arteries, CSF can easily flow from the subarachnoid space along the donut-shaped perivascular spaces throughout the parenchyma. Exchanging nutrients and waste, the CSF is finally drained via peri-venous and peri-neural spaces into the cervical lymph nodes, to be expelled via the cardiovascular and excretory system. As glymphatic flow is highly affected by physiological parameters including heart rate, respiration, blood pressure, sleep and circadian rhythm, I am investigating the CSF flow and waste clearance in mice models of diabetes, small vessel disease and Alzheimer's disease. Using in vivo transcranial wide-field fluorescent microscopy combined with laser Dopler flowmetry, we hope to further understand the impact of metabolic and cardiovascular changes on the glymphatic system, and uncover a clear pathway from metabolic to neurodegenerative diseases.

The AGEM PhD-student course project 2021 (€5.000)

Maurice Kroon, Sarah van Eeghen, Richie Goulding and Jeska Fritsche

Unravelling the etiology of sex differences in the intestinal microbiome: a role for the sex hormones? A study in transgender individuals.

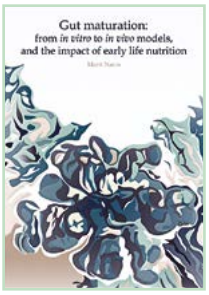
In January/February 2021, we attended the Amsterdam Gastroenterology Endocrinology Metabolism Course. The final goal of the course was to write a proposal for a study design in which the different fields of interest of the PhD candidates would come together. Many interesting presentations of the different speakers fueled inspiring ideas. However, after the introduction of all the PhD students from our group we quickly came to the realization that a study design between the gender dysphoria and endocrinology departments could be of interest. It is known that there are differences in gut microbiota between men and women, however the reason why is still not well researched. Transgender individuals often receive hormone therapy to obtain the secondary sex characteristics of the identified gender. Transmen (female assigned sex at birth, male identified gender) are treated with testosterone, whereas transwomen (male assigned sex at birth, female identified gender) receive estrogen often combined with an antiandrogen. The administration of sex hormones in a relatively young and healthy population may provide novel insights on the effects of sex hormones on the gut microbiota. Therefore, we proposed the following research question: Could sex hormones be responsible for the difference in gut microbiota between men and women?

Richie Goulding, Sarah van Eeghen, Maurice Kroon and Jeska Fritsche

The microbiome is analyzed using a fecal sample collected in 20 trans men and 20 trans women at least two years after the start of hormone therapy and after gonadectomy. The results are compared with the already known bacterial colonization of the gut in cis females and men. The hypothesis is that the intestinal microbiome of trans women will look more like cis women and the microbiome of trans men will be similar to that of cis men due to the effect of the gender affirming hormone therapy, as well as the gonadectomy.

Our pilot study has since been approved by the MEC and until now 9 participants have been included in the study of which the fecal samples have been stored waiting for analysis. We are excited to include more participants now that the pandemic is easing off and hope to publish our data soon!

The AGEM contribution printing costs of theses 2021 (€250)

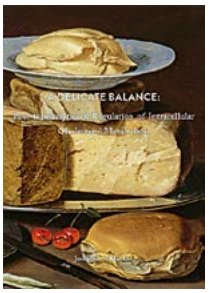


Marit Navis

Date of thesis defence: January 15th 2021

Gut maturation: From in vitro to in vivo models, and the impact of early life nutrition

The fundament of lifelong health is built in the first 1000 days of life, a critical window for gut development. In this thesis we aim to study the impact of various factors on early life gut maturation. We first develop a new model to study gut maturation in the laboratory, in organoids, including the interactions with food and bacteria/viruses. In the second part we show that minimal heat treatment during milk processing for infant nutrition can be beneficial for the developing gut.



Josephine Tan

Date of thesis defence: January 28th 2021

A Delicate Balance: Post-Transcriptional Regulation of Intracellular Cholesterol Metabolism

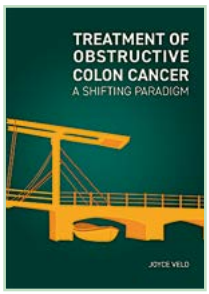
Cholesterol is indispensable for cellular function. Yet, disturbed cholesterol homeostasis is linked to a manifold of diseases. Mammalian cells are therefore working continuously to maintain the balance between too little and too much cholesterol. In this thesis, multiple genome wide screens have been performed to identify new players that act in cellular cholesterol metabolism. Characterizing the targets investigated in this thesis helps to advance our understanding of how cells maintain optimal cholesterol homeostasis.

Sem Aronson

Date of thesis defence: February 26th 2021

Gene therapy for inherited jaundice

This thesis describes experimental and clinical studies that bring viral vector mediated gene therapy for inherited jaundice a step closer toward clinical application. This may prevent the need of life-long phototherapy in patients suffering from Crigler-Najjar syndrome, caused by an enzyme deficiency impairing bilirubin metabolism. In addition, this technology may relieve symptoms and prevent the need of liver transplantation in patients suffering from progressive familial intrahepatic cholestasis, which results from a transport defect involved in bile formation.

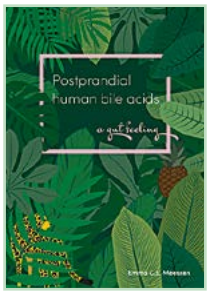


Joyce Veld

Date of thesis defence: March 11th 2021

Treatment of obstructive colon cancer: a shifting paradigm

In patients with obstructive colon cancer, resection of the tumour in the emergency setting may result in high morbidity and mortality rates. In this thesis, two alternative 'bridge to elective resection' techniques are investigated: placement of a colonic stent through the tumour, or the construction of a decompressing stoma. Both bridging techniques show several favourable outcomes in comparison to an emergency resection, although no conclusions can be drawn yet regarding the best bridging technique. Patient and tumour outcomes as well as patient preferences should therefore be taken into account when considering treatment for obstructive colon cancer.

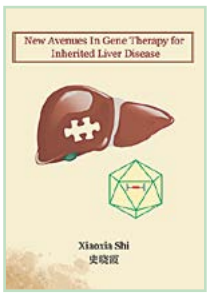


Emma Meessen

Date of thesis defence: March 26th 2021

Postprandial human bile acids: a gut feeling

This dissertation encompasses different translational observational- and intervention studies in which we investigated the postprandial bile acid response. In part 1, we reviewed the physiology of the postprandial (inflammatory) response. Part 2 contains three observational studies where we focused on the postprandial bile acid responses under different "physiological" conditions including day-to-day variability, fasting and intravenous meal infusion. In part 3, we aimed to improve metabolic health via the modulation of postprandial bile acid responses with different interventions.

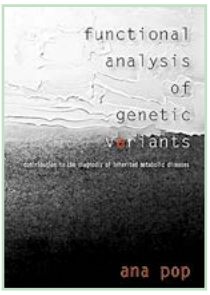


Xiaoxia Shi

Date of thesis defence: April 1st 2021

New avenues in gene therapy for inherited liver disease

In this study, we demonstrated that immune suppression at the time of AAV administration can prevent neutralizing antibodies thereby allowing effective re-treatment. AAV gene therapy also appeared effective in a model for PFIC type 3. A Crigler-Najjar mouse model, neonatal lethal, was rescued upon deleting on Bvra, which warrants the development Bvra inhibitors as alternative treatment.

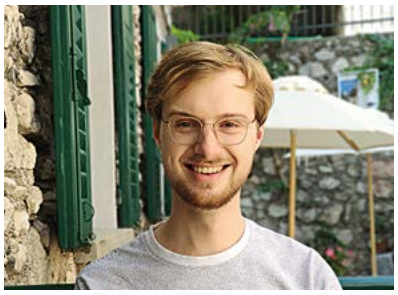


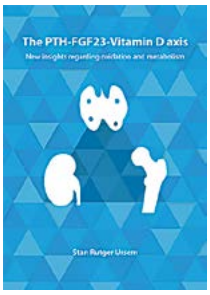
Ana Pop

Date of thesis defence: April 7th 2021

Functional analysis of genetic variants: contribution to the diagnosis of inherited metabolic diseases

The number of genetic variants of unknown clinical significance (VUS) is continuously increasing, especially because of the intensive use of high throughput sequencing techniques (often applied earlier in the diagnostic process). The pathogenicity interpretation of VUS is often challenging but is crucial for a complete diagnosis. Aiming at providing a diagnostic tool to clinicians, the studies presented in this thesis focus on functional characterization of missense VUS in genes associated with rare inherited metabolic disorders.



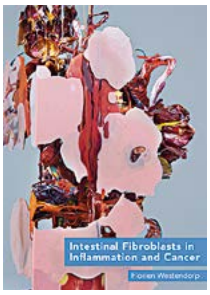


Stan Ursem

Date of thesis defence: May 26th 2021

The PTH-FGF23-Vitamin D axis: new insights regarding oxidation and metabolism

In this thesis, we researched several aspects of the hormones PTH (parathyroid hormone), FGF23 (fibroblast growth factor 23) and vitamin D. We studied the possibilities and limitations of a new method measuring only non-oxidized (bio-active) PTH in different (clinical) studies. In addition, we studied the relation between the bone-derived FGF23 and glucose metabolism. Lastly, we investigated in randomized controlled trials what the effect of vitamin D supplementation is on its metabolism.



Florien Westendorp

Date of thesis defence: May 28th 2021

Intestinal Fibroblasts in inflammation and cancer

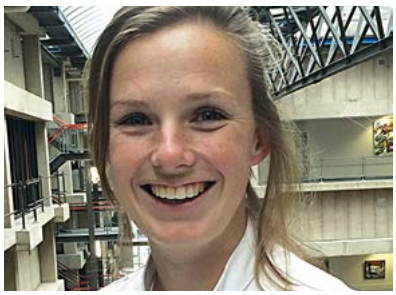
This thesis provides an addition to the exciting evidence that intestinal fibroblasts fulfil crucial roles in immunity, cancer development and stem cell maintenance, directed by signaling pathways such as the Hedgehog pathway. We show that the Hedgehog pathway signals from the epithelium to fibroblasts, via which it suppresses intestinal carcinogenesis and CXCL12-driven inflammation. Interestingly, we identify CD90 as a marker for fibroblasts that surround stem cells and provide support through the expression of class-3 semaphorins.

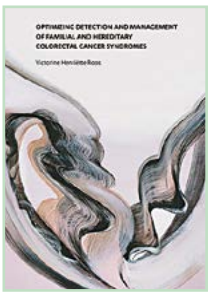
Kevin Stroek

Date of thesis defence: May 28th 2021

Optimization of established and assessment of novel newborn screening strategies in the Netherlands

Newborn screening (NBS) is an important method for prevention of severe disease or death in newborns with inborn disorders. A challenge in NBS is to find a balance between disease detection and unneeded referral of healthy newborns. We performed literature research and analyzed Dutch data for evaluation and optimization of NBS strategies. We proposed a screening method for one disorder to be included in the Dutch NBS and introduced improvements of current methods to reduce the number of unneeded referrals.



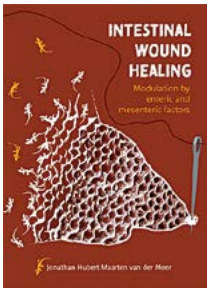


Victorine Roos

Date of thesis defence: June 18th 2021

Optimizing detection and management of familial and hereditary colorectal cancer syndromes

This thesis demonstrates that the addition of an online family history questionnaire (followed by genetic counseling) to the existing Dutch colorectal cancer (CRC) screening program, did not improve its diagnostic yield, nor significantly increased the detection of individuals with hereditary or familial CRC syndrome. Furthermore we estimated the effects of family history on the CRC risk. Lastly, we evaluated the safety and effectiveness of endoscopic and chemopreventive treatments in patients with hereditary CRC syndromes.

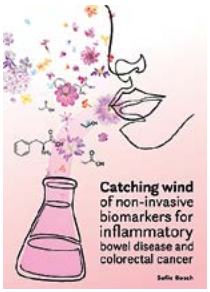


Jonathan van der Meer

Date of thesis defence: September 17th 2021

Intestinal wound healing: Modulation by enteric and mesenteric factors

Regeneration of the intestine is pivotal for one's well-being, as intestinal barrier defects are associated with a wide spectrum of diseases. By means of experiments in organoids and in mice and by clinical studies, we investigate factors that influence wound healing from within the intestinal tissue, as well as factors from the mesentery, which supports the intestinal tissue.



Sofie Bosch

Date of thesis defence: September 20th 2021

Catching wind of non-invasive biomarkers for inflammatory bowel disease and colorectal cancer

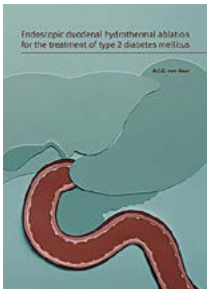
This thesis highlights the potential of faecal VOC analysis for the detection of IBD and the prediction of its disease course. Its potential for CRC and adenoma detection is presented and proposed to be a reliable tool for intra-individual surveillance and to estimate endoscopy timing after polyp removal. We have described combined omics panels to increase diagnostic accuracy for detection of both CRC and adenomas compared to the use of solely one omics platform.

Christel de Blok

Date of thesis defence: September 24th 2021

Let's talk about breasts: Breast care in transgender people from an internal medicine perspective

Breasts are considered an important symbol of femininity in Western societies and therefore are an important topic to most trans women. In this thesis, we studied breast care in transgender healthcare including hormone treatment induced breast development, the position of the breasts on the chest wall, satisfaction of trans women with their gained hormone induced breast development, breast cancer risk, and the occurrence benign breast lesions.

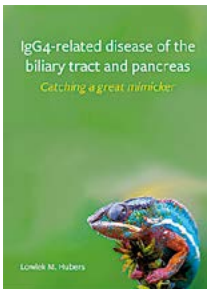


Annieke van Baar

Date of thesis defence: October 15th 2021

Endoscopic duodenal hydrothermal ablation for the treatment of type 2 diabetes mellitus

This thesis includes the first safety, feasibility, and efficacy studies of the endoscopic duodenal mucosal resurfacing (DMR) procedure for the treatment of type 2 diabetes mellitus (T2DM). DMR involves hydrothermal ablation of the duodenal mucosa, whereafter this mucosa regenerates. We show that DMR is safe and can be performed by experienced endoscopists. Efficacy is demonstrated by a decrease in HbA1c levels (representing glucose levels over 2-3 months) and improvements in additional parameters of metabolic health.

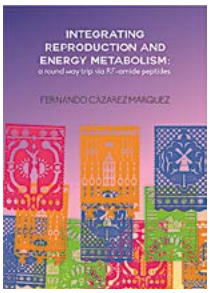


Lowiek Hubers

Date of thesis defence: October 22nd 2021

IgG4-related disease of the biliary tract and pancreas: Catching a great mimicker

IgG4-related disease (IgG4-RD) is a recently described inflammatory disorder of unknown origin. The biliary tract and pancreas are most frequently affected. IgG4-RD is notoriously difficult to distinguish from other biliary/pancreatic diseases, including primary sclerosing cholangitis (PSC) and biliary/pancreatic malignancies. As a consequence, misdiagnosis and incorrect treatments are common. This thesis aimed to improve the diagnostic process and unravel pathophysiological mechanisms in IgG4-RD.

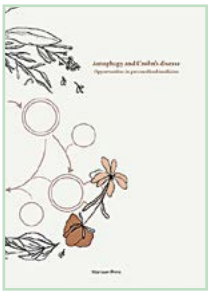


Fernando Cazarez Marquez

Date of thesis defence: November 2nd 2021

Integrating reproduction and energy metabolism: a round way trip via RF-amide peptides

In natural conditions many organisms are exposed to daily and seasonal changes in daylength, food availability and environmental temperature. In this work we investigated whether the neural systems controlling mating behavior are also involved in regulating feeding behavior and the body weight balance. In seasonal hamsters and laboratory rats we investigated whether two “reproductive neuropeptides” produced in the hypothalamus of the brain, i.e. Kisspeptin and RFRP-3, would affect food intake and body weight.



Marileen Prins

Date of thesis defence: November 5th 2021

Autophagy and Crohn’s disease: Opportunities in personalised medicine

Crohn’s disease is a chronic intestinal disease characterized by recurrent inflammation of the gastrointestinal tract. A third of patients inherited a genetic variant from both parents, that increases the chances of developing Crohn’s disease: the ATG16L1 T300A SNP. This impacts the autophagy capacity of cells: the recycling- and degrading system. In this thesis the effects of autophagy on the immune cells and epithelial cells of the gut are studied, aiming to contribute to personalized medicine.

AGEM Events 2021

AGEM PhD-student course

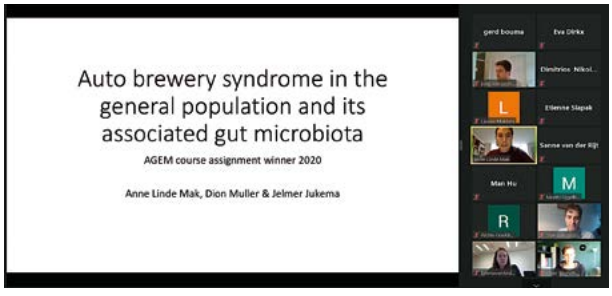
JANUARY FEBRUARY 25th - 5th

AGEM PhD-student course 2021

Online via ZOOM

In January and February of 2021, after a successful first edition in 2020, AGEM offered for the second time a course specifically developed for PhD-students that perform research in the field of gastroenterology, endocrinology and/or metabolism. This course aims to inform (starting) PhD-candidates about gastroenterology, endocrinology and metabolism, including those topics that are not necessarily within the scope of the PhD-candidates' own research. The course was coordinated by five AGEM members, Anje te Velde, Dries Kalsbeek, Sarah Siegelaar, Riekelt Houtkooper and Maarten Soeters, and more than 40 teachers gave lectures during the course.

Due to the COVID-19 regulations, the course was online via ZOOM and runned for two weeks. In the first week, all participants were given an overview of general insights and methodology applicable to gastroenterology, endocrinology and metabolism in daily lectures with subjects ranging from the pathophysiology of oesophagal diseases from clinic to cell biology, to imaging techniques for insulin resistance, and from epigenetics, to macrophage metabolism.

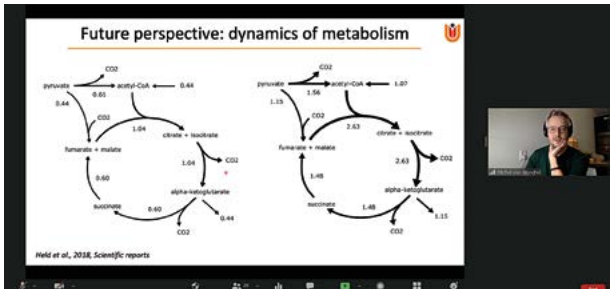


Presentation by Anne Linde Mak

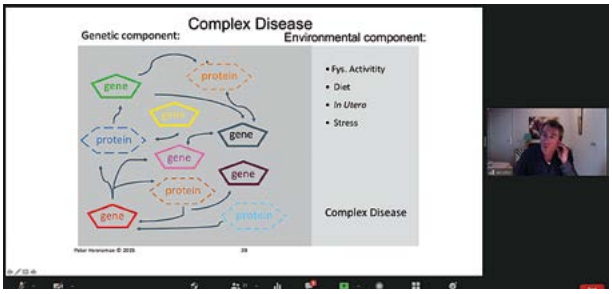
Presentation by Aart Nederveen

Presentation by Bas Teusink

Presentation by Eveline Bruinstroop



Presentation by Michel van Weeghel



Presentation by Wouter de Jonge

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

At the beginning of the course the PhD-students were given an assignment in small groups of three or four students. During the course the PhD students wrote a multidisciplinary grant proposal that was, well-prepared by the pitch workshop given in the first week, pitched to all participants on the last day of the course. Judged by the course coordinators, Group G (Jeska Fritzsche, Maurice Kroon, Richie Goulding and Sophie Schaper) wrote the best grant proposal “Unravelling the etiology of sex differences in the intestinal microbiome: a role for the gonadal hormones?” and they were given the opportunity to perform the research proposed in their project (See: AGEM Grants 2021 - The AGEM PhD-student course project 2021).

AGEM annual retreat

JUNE 3rd - 4th

AGEM retreat 2021

Eenhoorn Amersfoort and Online via ZOOM

We evolved the hybrid way!

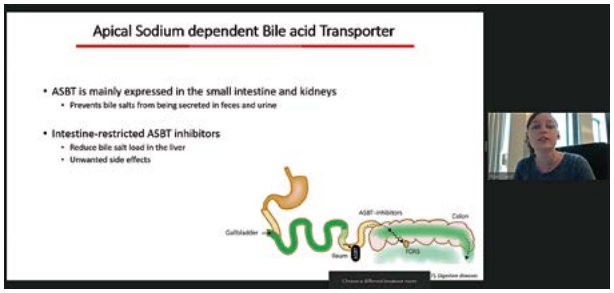
The goal of the AGEM retreat is to discover, share and learn from each other's research. After a completely online event in 2020, due to COVID-19, we were happy to be able to organize a hybrid retreat in 2021.

On Thursday June 3rd, the speakers of the morning session gathered in the Eenhoorn Meeting Center in Amersfoort. Over fifty participants followed the livestream from the ease of their own home. After a short introduction of AGEM director Prof. Stan van de Graaf, Dr. Joep Beumer from the Clevers lab at the Hubrecht Institute in Utrecht enlightened us on how human intestinal organoids can be used as a model to study gut hormone production, a topic nicely covering multiple AGEM research pillars. After Joep's talk, the AGEM grant 2021 laureates (see AGEM grants 2021) shortly presented their projects. In the thirty minutes that followed, Annieke van Baar, Yama Issa, Marte Molenaars, Sanne van der Veen en Sanne Verberk battled for the AGEM Best Publication 2020 Award. Sanne van der Veen became the proud winner of the award. The morning session was closed by Remco Kersten and David Trampert who gave a duo-presentation entitled "The biliary bicarbonate umbrella screening: A high-throughput approach to identify novel therapeutic targets for cholestatic liver diseases".

In the afternoon, the retreat continued online via ZOOM with 46 AGEM PhD candidates presenting their research in five parallel sessions. Given the success of

Presentation by Dr. Joep Beumer

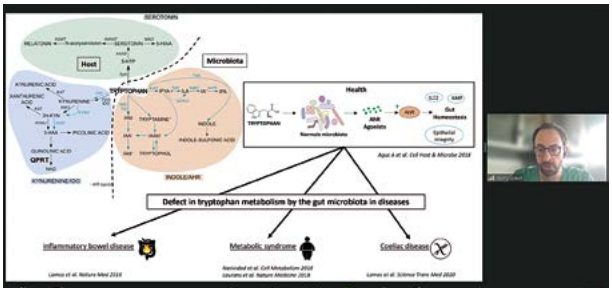
Presentation by Remco Kersten and David Trampert



Presentation by Roni Kunst

Presentation by Workshop Huis van Verbeelding

Winner best Presentation Award Frouwkje Politiek



Presentation by Prof. Harry Sokol

the (online) workshops from previous years, we offered the attendees workshops from an array of relevant topics. The options offered this year were: “Making (remote) working together work”, “Business drawing (huis van verbeelding)”, “Scientific outreach and how to use it for public awareness” and “Present with Humor”. The first day of the retreat successfully ended with an online escape room challenge to strengthen the ties between various AGEM affiliated departments.

On Friday June 4th, we started the afternoon with seven AGEM PhD candidates who presented their research in an alternative way and battled for the Best Presentation Award. By using drawings, Frouwkje Politiek was voted the winner of this award. After a short break, Prof. Harry Sokol from the Sorbonne Université, Centre de Recherche Saint-Antoine and Saint Antoine Hospital in Paris, France, presented work showing that manipulating the gut microbiota to modulate the tryptophan metabolism and particularly the AhR pathway could be of therapeutic interest for many human diseases. The AGEM retreat 2021 ended with another round of online workshops: “Making (remote) working together work”, “Business drawing (huis van verbeelding)”, “Scientific outreach and how to use it for public awareness” and “Present with Humor”.

Thank you all for making this a great AGEM retreat in 2021. We look forward to seeing you again (hopefully in person), and to welcome new participants at future retreats.

The AGEM retreat 2021 committee

AGEM symposia

NOVEMBER 2nd

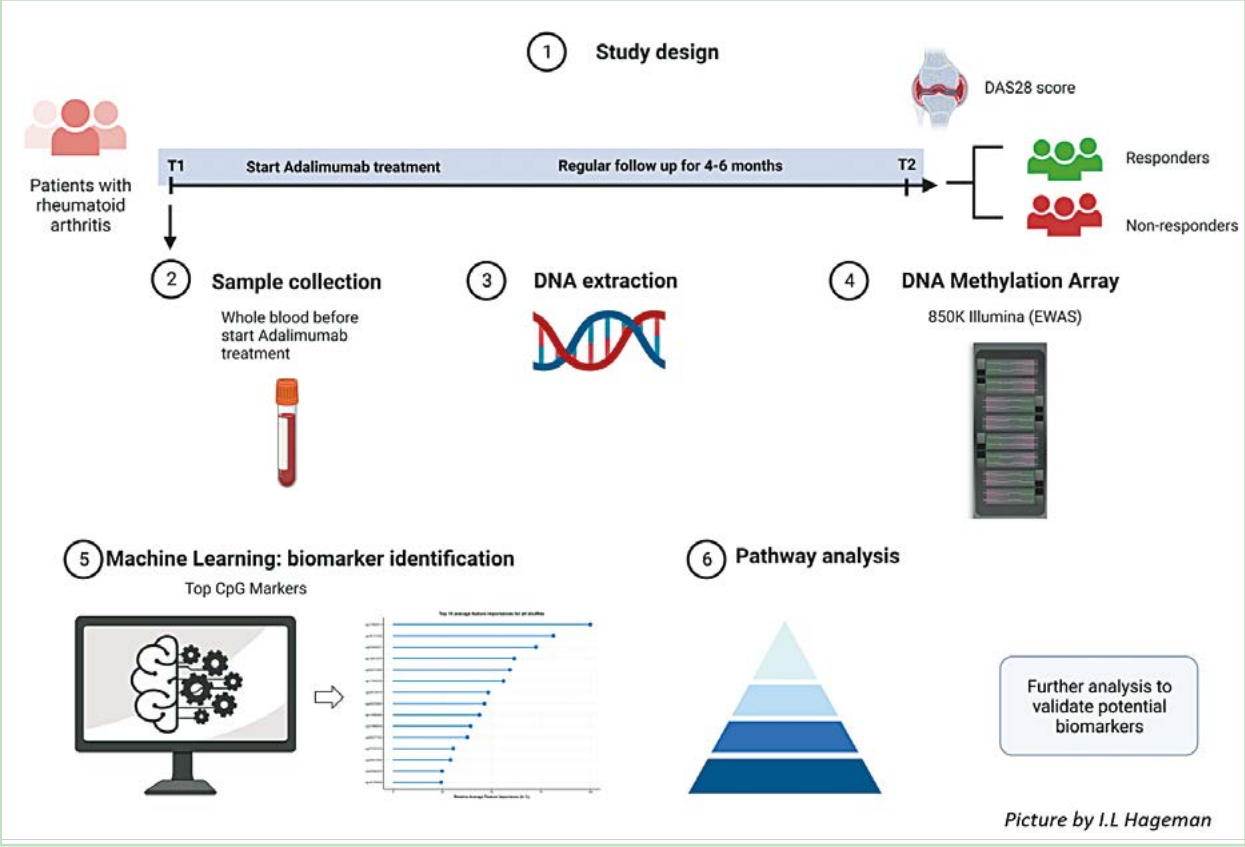
AGEM – AII meet and greet

CASA Amsterdam

On November 2nd, 2021 in the short timeframe where it was possible to organize meet and greets on location we met with PIs from the AII in CASA Amsterdam. This first meeting was to get to know each other and to see how we can initiate interaction and possible cooperation between groups of AII and AGEM. PIs from several departments (Rheumatology and Clinical Immunology, Tytgat Institute, Experimental Immunology, Center for Experimental and Molecular Medicine, Molecular Cell Biology and Immunology, Clinical Chemistry and Pediatrics, Sanquin, Internal Medicine-Infectious Diseases, Genetic Metabolic Diseases, Dept. of Endocrinology and Metabolism) presented in a short pitch their research. The focus was on diseases with an immunological basis and how PIs could contribute to the promotion of collaboration to unravel basic immunologic principles of chronic diseases. A good example of already ongoing collaboration was shown by Prof. Dr. Wouter de Jonge who presented insights in a collaborative project between the departments of Gastroenterology and Rheumatology on DNA methylation markers to predict treatment success of biologicals in IBD and RA.

This first meeting is hopefully the start of intensifying ongoing and of new collaborations between AGEM and AII.

PIs from AII: Sander Tas and Conny van der Laken
PIs from AGEM: Anje te Velde and Gerd Bouma
Supported by Yvonne Duiker (AII) and Eva Dirkx (AGEM)



Collaborative project AGEM and AII presented by Prof. Wouter de Jonge

DECEMBER 10th

AGEM – CCA symposium: "HPBeter"

Online streamed from O|2 building, Amsterdam UMC

In 2020, the hepatopancreaticobiliary ("HPB") departments of the AMC and VUmc were formally merged. This December, the new department hosted its first ever joint symposium, called "HPBeter." Through the Amsterdam UMC HPBeter symposium we hoped to familiarize ourselves with each other's research activities and stimulate collaboration between all disciplines that are involved in HPB research. Although we were unable to bring everyone physically together due to COVID-19 restrictions, we believe the "hybrid" HPBeter symposium was an inspiring day and a success.

The symposium hosted colleagues from the gastroenterology and hepatology, radiology, pathology, oncology, surgery, and translational lab research disciplines. Leading principal investigators presented inspiring overviews of their research lines which spanned the fields of biliary-, hepatocellular-, and pancreatic malignancies, as well as, colorectal liver metastases, benign liver tumors and translation lab research. In addition, PhD students gave in depth presentations on ongoing research and published work. Furthermore, the overarching role of the Cancer Center Amsterdam (CCA), Amsterdam Gastroenterology, Endocrinology and Metabolism Institute (AGEM) and the HPB Biobank was reiterated. Finally, the day was topped off by our keynote speaker, Professor Marjolein van Egmond, who advised us "how to survive in the media" in the event that our departments' merger leads to the emergence of famous researchers.

Overall, this fusion has brought together experts of all fields involved in HPB research. We are uniquely positioned to measure ourselves with other top-level academic institutions, to keep improving our HPB research and most importantly, to improve our patient care.

We would like to thank our speakers, moderators and the audience for their efforts and participation. On to the next HPBeter symposium, and on to a 'Beter HPB at the Amsterdam UMC'.

The organizing committee: Rutger-Jan Swijnenburg, Gitta Kuipers, Linda van den Noord, Nina Wesdorp, Charlotte van Veldhuisen, Jeska Fritzsche, Remco Kersten, Mark Dings, Boris Janssen and Esther Pijnappel

Presentation by Marjolein van Egmond


Speakers and organizing committee

AGEM Tager Lectures 2021

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.

Online via ZOOM

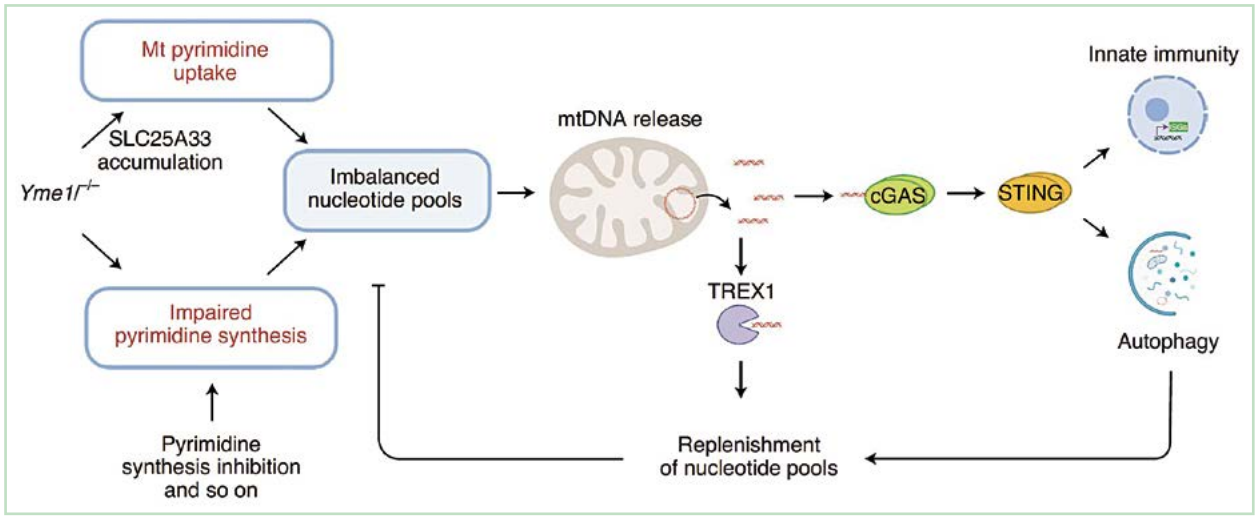
OCTOBER 28th

Dr. Hans-Georg Sprenger
Whitehead Institute for Biomedical Research & Massachusetts Institute of Technology, Cambridge, USA

"Mitochondrial Proteostasis and Inflammation"


Dr. Hans-Georg Sprenger

Cytosolic mitochondrial DNA (mtDNA) elicits an inflammatory response implicated in several pathologies. Signals triggering the release of mtDNA from mitochondria remain enigmatic. Here, I discussed our recent findings, demonstrating that mtDNA release into the cytosol and inflammation can occur as a metabolic response to cellular pyrimidine deficiencies. The mitochondrial protease YME1L preserves pyrimidine pools by supporting de novo nucleotide synthesis and by proteolysis of the pyrimidine carrier SLC25A33. Thereby, YME1L prevents mtDNA release and activation of an innate immune response.



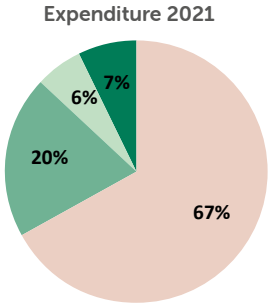
Research infographic by Hans-Georg Sprenger

AGEM Numbers and Facts 2021

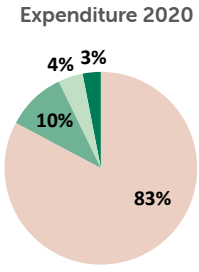
AGEM finances 2021

For 2021, the AGEM research institute was provided with €562.289,00 (€253.789,00 from board of directors VUmc and €308.500,00 from board of directors AMC). In the table below is shown how this money was budgeted and spend. Most of the 2021 budget was used for the AGEM grants.

	Income 2021
AMC	€ 308.500,00
Vumc	€ 253.789,00
Total	**€ 562.289,00**



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



	Income 2019
AMC	€ 308.500,00
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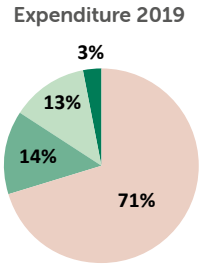
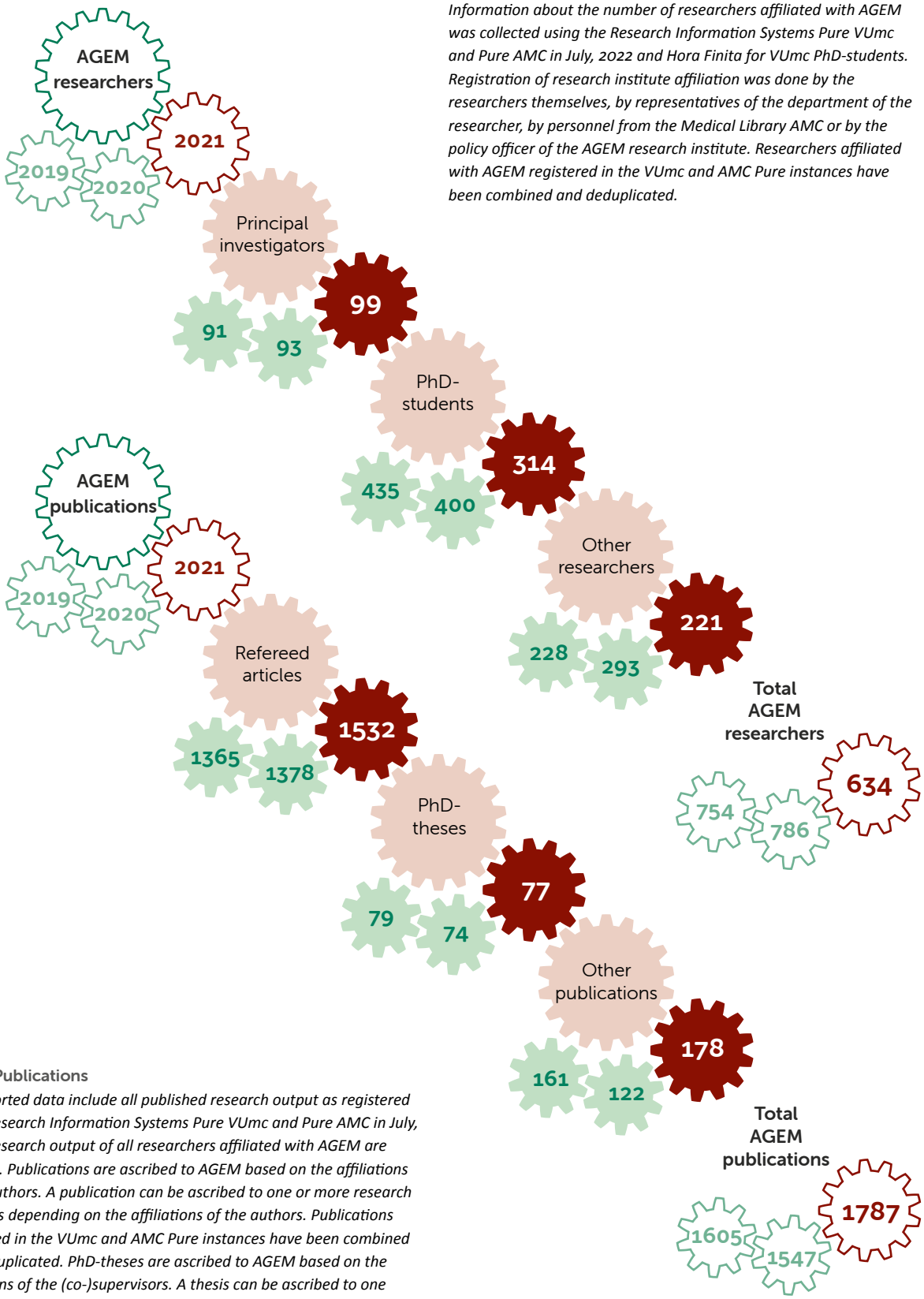
Total	**€ 558.500,00**



AGEM grants *Personnel* *Meetings* *Miscellaneous*

AGEM numbers 2021



AGEM Researchers

Information about the number of researchers affiliated with AGEM was collected using the Research Information Systems Pure VUmc and Pure AMC in July, 2022 and Hora Finita for VUmc PhD-students. Registration of research institute affiliation was done by the researchers themselves, by representatives of the department of the researcher, by personnel from the Medical Library AMC or by the policy officer of the AGEM research institute. Researchers affiliated with AGEM registered in the VUmc and AMC Pure instances have been combined and deduplicated.

AGEM Publications

The reported data include all published research output as registered in the Research Information Systems Pure VUmc and Pure AMC in July, 2022. 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 2021

Prof. dr. Annet Bosch

Pediatrics, Metabolic Diseases

Picture by Kirsten van Santen

On January 5th 2021, Annet Bosch was appointed professor of Pediatrics, Metabolic Diseases. She delivered her inaugural lecture "Beter Maken" on May 13 2022.
Annet is a pediatrician for Metabolic Diseases and head of the Department of Pediatric Metabolic Diseases of the Amsterdam UMC, location AMC. Besides her work in the Amsterdam UMC, Annet Bosch is a member of the Board of the Dutch Medicines Evaluation Board (CBG-MEB).
Her clinical and translational research focusses on Classical Galactosemia, Phenylketonuria and Riboflavin Transporter Deficiency. The AMC is an international Center of Expertise for all three inborn errors of metabolism. She is the AMC representative for the European Reference network for Hereditary Metabolic Disorders (MetabERN). Annet enjoys a large international network, through among others the Galactosemia Network (Gal-Net) of which she is a board member, and through the European Phenylketonuria Guidelines group.
She is involved in the organization of Newborn Screening for inborn errors of metabolism in the Netherlands, as a member of the Adviescommissie Neonatale Screening voor Metabole Ziekten (ANS-MZ) and the Programmacommissie Neonatale Hielprik Screening (PNHS). In close cooperation with the laboratory for Newborn Screening located in the AMC age she performs research aimed at the evaluation and optimization of the Dutch Newborn Screening program.

Did you know that... (1)

... AGEM PIs Prof. **Max Nieuwdorp** and Prof. **Stan van de Graaf** received an NWO VICI grant.

... the first results of the project of the AGEM talent development 2017 grant awarded to AGEM researcher **Daniël Miedema** were published in JAMA Network Open on April 26, 2021.

... AGEM PI **Louis Vermeulen** won the Ammodo Science Award 2021.

... Immunologist **Hergen Spits**, former AGEM PI, was appointed "Ridder in de orde van de Nederlandse Leeuw".

... AGEM PI **Marlies Schijven** and her team received the Medical Inspirator Prize 2020-2021.

... **Sanne van Neerven** received the Birnstiel Award for outstanding early career scientists based on her research accomplishments in the lab of AGEM PI Prof. **Louis Vermeulen**.

Prof. dr. Stan van de Graaf

Experimental Hepatology and Metabolism

On May 18th 2021, Stan van de Graaf was appointed professor of Experimental Hepatology and Metabolism. Stan van de Graaf studied Chemistry at the Radboud University in Nijmegen. He did his PhD in the Department of Physiology of the Radboud University Medical Centre on the regulation of epithelial calcium transport. After a postdoc in Münster, Germany, he went to UMC Utrecht, and shifted his scientific interest from kidney/gut to bile acid transport in gut/liver.
Upon his move to the Amsterdam UMC (then AMC) he expanded his group (supported by Vidi/ERC and AMC Fellowship grants), and his research interest. His research team now aims to unravel and exploit processes controlling hepatic/intestinal transport and metabolism. The ultimate goal is to translate basic/fundamental concepts to a clinical application in the field of cholestatic and metabolic liver diseases. To this end, molecular studies are combined with integrative systems biology. His group is funded by a VICI grant and the drug development aspect is executed in collaboration with the Center for Drug Design and Discovery (Leuven).
Stan is Director of Amsterdam Gastroenterology Endocrinology Metabolism (AGEM) since 2017 and Head of the Tytgat Institute for Liver and Intestinal research since February 2022.

Did you know that... (2)

... the Metabolic Laboratory (ML, VUmc) and the Genetic Metabolic Diseases Laboratory (lab GMZ, AMC) continued together as the Genetic Metabolic Diseases Laboratory (GMZ) at location AMC.

... a team of researchers consisting of **Ronella Grootens** (LUMC), **Mira Staphorst**, **Irma Hein** and AGEM PI **Hans van Goudoever** (Amsterdam UMC) received a ZonMw Pearl for their collaboration in making scientific research more accessible to children.

... Rubicon grants were awarded to three AGEM top scientific talents: Sanne van Neerven, Yasmine Liu and Josephine Tan

... Dr. **Vanesa Dijkstra-Muncan**, Dr. **Anne Eskes**, Dr. **Krisztina Gecse**, Dr. **Ramon Gorter**, Dr. **Nordin Hanssen**, Dr. **Jeffrey Kroon**, Dr. **Tim de Meij**, Dr. **Merit Tabbers** and Dr. **Rogier Voermans** were appointed as (AGEM) PI in 2021.

Future perspectives for the AGEM research institute

Overall, 2021 has once again been an interesting year for AGEM. COVID-19 forced the institute to adapt: moving activities online, redirecting funds from international fellowships to innovation grants and re-evaluating the institute's own strategy and vision on the future.

"The air is buzzing with excitement to see each other face-to-face again in 2022", prof. dr. Van de Graaf, co-director of AGEM, says, "a striking example of this is that we already have an unprecedentedly high number of enrollments for our annual AGEM retreat that will take place in March 2022".

> "The air is buzzing with excitement to see each other face-to-face again in 2022"

The directors recognize that the plans they have for AGEM in 2022 are mostly along the same lines as their vision on 2021. "Of course, without COVID-19, we would have already managed to start executing these plans, whereas now we had to lay low for a year", Van de Graaf explains. Nevertheless, the drive to improve AGEM is still very much there and, once society reopens, the directors plan to start running. "What I look forward most," Van de Graaf says, "is to look at all the things we are nót doing yet at AGEM – to see where we can fulfill unmet needs and how we can grow as an institute". In order to do so, the directors have two main focus areas for 2022.

The first one is a path that AGEM has already started to walk on in 2021, namely to look over the institute's own walls and increase multidisciplinary collaboration with external partners. "I think we really have to start looking at our strengths," says Van de Graaf, "We have harmonized both houses, now it is time to start thinking about in which areas AGEM is leading and can take a central role, both nationally and internationally". Through awards, grants and symposia, the directors hope to be able to help launch AGEM researchers into the international research field. Van de Graaf: "I hope we can slowly transition from: AGEM events are aimed at AGEM people, to: AGEM events are organized by AGEM people, for a national, or even international, audience". An important prerequisite of this goal is to make AGEM an interesting collaborative partner for academic partners, the (pharmaceutical) industry and small business owners. In 2022, Van de Graaf hopes that the institute can work towards this goal more structurally, by stimulating Public Private Partnerships (PPPs) and strengthening IXA with AGEM-dedicated business developers.

Prof. dr. Gerd Bouma

"We have harmonized both houses, now it is time to start thinking about in which areas AGEM is leading and can take a central role, both nationally and internationally"

The second theme the directors feel deserves extra attention in 2022, is talent policy. "We know that we have a lot of talented researchers in our institute" says Van de Graaf. He explains it is important that the institute keeps track of these talented individuals, to know when, where and how to support these researchers. Especially those researchers who are in the transition phase from postdoc to a staff position as group leader deserve extra attention, according to the directors. In 2021, the institute has already redirected its Talent Development grant, by broadening its aim to pre-veni and pre-vici researchers alike. In 2022, the directors want to keep exploring how to best support all researchers in AGEM, including these early-career talents, with efficient, transparent and fair talent policy. "However, we cannot do this all by ourselves", Van de Graaf explains. Therefore, the directors are striving and lobbying for an overarching talent policy across Amsterdam UMC, with specific attention to the early-career talents.

"We know that we have a lot of talented researchers in our institute"

Prof. dr. Stan van de Graaf

Next to these goals, the AGEM directors stress that they have a lot of ambitious plans for AGEM in 2022: to facilitate clinical research, stimulate talent development, visualize the continuum of innovations for animal-free research and advanced animal-models for human diseases, and many more. On top of that, the institute will also start preparing its six-yearly external evaluation, which will be used to rethink and fine-tune AGEM's strategy and strategic plans for the next six years.

Gerd Bouma, AGEM director
Stan van de Graaf, AGEM director
Eva Dirkx-Beuling, AGEM policy officer
Maartje Schots, AGEM policy officer

Amsterdam UMC
University Medical Centers

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