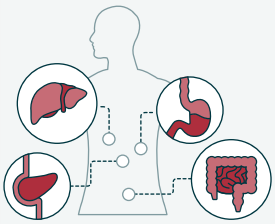
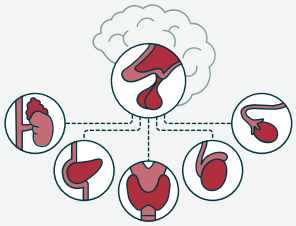
Amsterdam UMC

Amsterdam Gastroenterology Endocrinology Metabolism

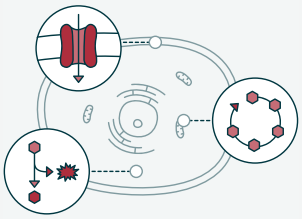
AGEM Annual report 2024



Gastroenterology



Endocrinology



Metabolism

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Contents

Directors looking back

It's Thursday afternoon, and as tradition goes, Nanne de Boer (AGEM director) joins Anita Boelen (AGEM director) and the two policy officers of AGEM at the AMC location. Only this week, instead of reflecting on our AGEM week, we take some time to look back on our AGEM year.

It comes as no surprise that the compatible duo, who describe each other as "fresh" and "energetic", agree on what they value most in a research institute: the feeling of togetherness, of belonging to something. "Something that is stimulating," de Boer adds. That is exactly what they hope researchers experience as part of AGEM. In addition, they want researchers to feel that AGEM supports their needs. In that vein, they reflect on all the ways AGEM tries to support collaboration, such as the annual AGEM retreat and the PI events. "That is also why we set up the AGEM database in 2024, with everyone's research and skillset," they point out, exemplifying a concrete initiative from this past year.

For de Boer, looking back at 2024 means reflecting on the moment he actually started as AGEM director. While he says you never quite know what to expect in a role like this, he remembers things going smoothly from the beginning. "The atmosphere was very relaxed, informal, pleasant, and safe." Boelen agrees, adding, "Everything felt lighthearted, and I felt a lot of enjoyment." She also believes that having both a clinician and a basic scientist as AGEM directors has been an essential and positive change. Alongside their strong professional connection, de Boer says it was easy to begin working toward the institute's goals. "I joined during the SEP, so a lot of the groundwork had already been done. That made things very clear for me: where we were coming from, what the issues were, and what we would be tackling in the years ahead. It was, really, an ideal starting point."

Both Boelen and de Boer speak positively about their experiences as AGEM directors. Looking back at everything that happened in 2024, they pause to truly reflect on the year. There were many meaningful and uplifting moments. One of the first that comes to mind for both is a true premiere: the very first Grant Award Ceremony, which took place in May. They agree it was a festive event and a well-deserved celebration of the hard work and dedication of AGEM researchers.

A longstanding tradition that continued at a high level in 2024 was the series of Tager Lectures and the Grand Rounds in Digestive Diseases. Boelen attends the lectures at the AMC, while de Boer joins those at the VUmc, largely due to their respective office locations. While this physical divide can sometimes present logistical challenges or a sense of separation, it also widens the AGEM community by reaching researchers across both Amsterdam UMC sites. de Boer notes that his arrival at AGEM helped reinforce the link between AGEM and the Gastroenterology program. "That's partly because in my role I've been able to point out to people in the gastroenterology department what AGEM is and that it exists," he says.

The PI events also continued in 2024, with a variety of themes. One of de Boer's personal favorites was the Liver Disturbances session. "Even though it wasn't the most well-attended, that session was a real highlight, because it brought the basic scientists and clinicians together again. You could really see how happy the liver researchers were that we organized it."

Boelen also recalls 2024's edition of *De Anatomische Les* with a lot of enthusiasm. That year, AGEM's nominated speaker, Sadaf Farooqi, was selected to give the keynote. This was an honor and allowed AGEM to participate in a series of inspiring activities. In preparation, Boelen and colleagues traveled to

Prof. dr. Nanne de Boer and Prof. dr. Anita Boelen

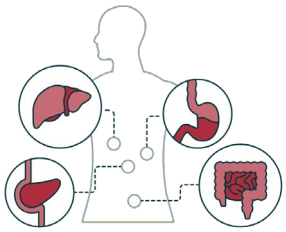
Cambridge to meet with Farooqi. “She’s very efficient. We were only there for an hour, and she already completely understood what she needed to do. I do think she appreciated it, and it helped her see how important it was,” Boelen says. The event itself, including a nationally recognized masterclass, made a lasting impression. “What an amazing and special day it was,” Boelen remembers. De Boer agrees, adding, “Her lecture was really strong.”

A lot of positives to look back on in 2024. Their final thoughts this afternoon touch on valorization. De Boer wraps up the interview by reflecting on the current movement taking place across Amsterdam UMC, and within AGEM too. “The focus is shifting away from just the financial side of valorization, and more towards asking: what does your discovery or research actually contribute? Especially in a societal sense. I think that’s a really positive development.” There is still work to be done, Boelen points out, but de Boer agrees that the growing conversation around valorization has been a refreshing step.

Overall, both directors sense a fresh energy within AGEM, and not just from their own perspectives. “The collaboration between the four of us, and especially with Anita, has been smooth and without any issues,” de Boer says. Boelen adds, “People tell me that there’s a lot of positive energy in us as a team.” That atmosphere of trust and enthusiasm has defined their experience throughout 2024.

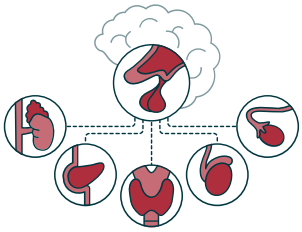
Research Programs

Within the AGEM research institute three research programs have been defined and are extensively described on the AGEM website.



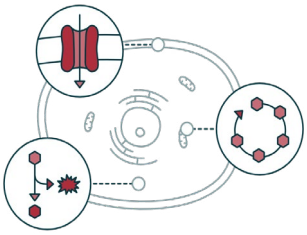
Gastroenterology

The research program "Gastroenterology" focusses on the function of the human digestive system in health and disease.



Endocrinology

The research program "Endocrinology" focusses on the effect of hormonal regulation on the human body.



Metabolism

The research program "Metabolism" focusses on metabolic disorders, both common and rare, manifesting from (pre)neonatal period into adulthood.

Research Board 2024

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

The Young AGEM committee consists of five members and each research board meeting at least one of the Young AGEM members is present to represent Young AGEM.

New to the AGEM research board 2024

Nanne de Boer

Since January 2024, Nanne de Boer joined the AGEM research board as director. He is a gastroenterologist and professor of inflammatory bowel disease (IBD), on the topic of optimal medicine use, at the Amsterdam UMC.

His research aims at cost-conscious care, with effective and personalized IBD treatment focused on efficiency and sustainable outcomes, also by means of drug rediscovery and repurposing.

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

I want to spark enthusiasm for science and research, aiming at collaboration in our own research AGEM institute but also between the other institutes. I truly believe that we can excel by working together, using basic, translational and clinical research. Our institute facilitates and supports fantastic research that really has impact, I think we can really proud of all our achievements. Raising attention to our successes, for example by use of (social) media, is one of my main focus points.

Nanne de Boer

Manon Wildenberg

Since December 2024, Manon Wildenberg joined the AGEM research board as research board member. She performed her PhD studies at the Erasmus MC, department of Immunology, focusing on myeloid cells in local tissue immune processes. This interest was further solidified in her postdoctoral project (LUMC) studying specifically the intestinal immune system in inflammatory bowel disease (IBD).

She has been at the Amsterdam UMC since 2011 currently as associate professor and principal investigator. Her research group is strongly focused on translational studies, collaborating with both clinical gastroenterology and surgery. Current topics of investigation include the role of extra-intestinal tissues (mesentery/appendix) in IBD and wound healing processes in both intestinal inflammation and surgical complications in IBD.

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

Like my own research, the AGEM research institute contains both very basic, translational and clinical science. As an AGEM RB member I hope to contribute to the collaborations within the institute as well as with other research institutes and partners. Due to the increasing complexity of science, joining forces in terms of knowledge, materials and data will be essential to break new barriers and improve healthcare as well as health itself.

Manon Wildenberg

Valentina Bravo

Valentina Bravo joined AGEM at the very end of 2024, starting on December 1st as one of the two Policy Officers. Although she wasn't always sure where her place in healthcare would be, working in the field has long been an aspiration. Her interest in nutrition and physiology brought her to study Sport and Exercise Medical Sciences at the University of Exeter, England, where she discovered a passion for both nutrition and science communication.

This science communication passion stemmed from creating educational resources for the medical field, but spanned more societal and political issues during her master's degree in Science Education and Communication at Utrecht University. With the big question "What's the point of science if it never reaches the public appropriately?" in mind, Valentina became inspired to be part of the bridge between science and society.

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

At AGEM, one of the two policy officers focuses primarily on communication, the role I was hired to take on. I think continuing to strengthen the sense of belonging within the institute for the researchers through internal communications is important. One way of doing this is by contributing to the development of (new) communication events (lectures, campaigns, meetings, etc.), and another is by making researchers feel valued. I hope to do this by improving both the quality and the reach of AGEM's external communications. At this renowned institute in this prestigious medical center, inspiring and groundbreaking research is being done from all directions, and it should reach other experts in the field as well as the general public. My goal will be to create and implement a science communication strategy that allows this research to improve gastroenterological, endocrinological, and metabolic health.

Valentina Bravo

AGEM directors 2024

Prof. dr. Anita Boelen

Department of Clinical Chemistry, Endocrine Laboratory

Professor of Thyroid Hormone Metabolism, in particular molecular and diagnostic aspects
Specialization: Thyroid hormone, neonatal screening
Research subject: The role of thyroid hormone metabolism in innate immune cells and the pathogenesis of congenital central hypothyroidism.

Prof. dr. Nanne de Boer

Department of Gastroenterology and Hepatology

Professor of Gastroenterology and Hepatology, in particular on efficient and optimal use of IBD medicines
Specialization: Inflammatory bowel disease
Research subject: Cost-conscious IBD care, with effective and personalized treatment focused on efficiency and sustainable outcomes, also by means of drug rediscovery and repurposing.

AGEM Research board members 2024

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. 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

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

Associate professor

Specialization: Cardiometabolic disease
Research subject: Translational and integrative research into development of obesity, diabetes and fatty liver disease. Gut microbiome.

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.

Prof. dr. Noam Zelcer

Department of Medical Biochemistry

Professor of Molecular regulation of metabolism

Specialization: (Post)transcriptional regulation of lipid metabolism
Research subject: The regulation of lipid metabolism and the role this has in NAFLD and CVD.

Prof. dr. Joep Derikx

Department of Pediatric Surgery

Professor of pediatric surgery

Specialization: Neonatal abdominal surgery and pediatric thyroid gland surgery
Research subject: Studying the pathophysiological consequences of intestinal anastomotic healing and disturbed healing; neonatal gut maturation and inflammation; develop markers that can be used to diagnose intestinal damage.

Prof. dr. Stephan Kemp

Department of Clinical Chemistry

Professor of Inherited Neurometabolic Disorders and Newborn Screening
Specialization: Inherited neurometabolic diseases
Research subject: Lipid metabolism and neurotoxicity with a focus on X-linked adrenoleukodystrophy.

Dr. Manon Wildenberg

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

Associate professor
Specialization: Inflammatory bowel disease
Research subject: Optimization of IBD therapy through translational studies on medication mode of action, the role of extra-intestinal tissues and surgery.

Young AGEM Committee 2024

Dr. Signe Mosegaard Nielsen

I am a postdoctoral Fellow at the Laboratory Genetic Metabolic Diseases. My research focuses on the development of stem cell derived models for rare inherited metabolic diseases and using these to detect novel disease mechanisms and testing alternative treatment strategies.

Dr. Patrick de Jonge

I am a postdoctoral researcher at the department of experimental vascular medicine, where I started after obtaining my PhD from Utrecht University in 2020. My main research focus are viruses of microbes called bacteriophages and how they interact with bacterial populations in the human gut.

Dr. Anne van der Spek

I am currently a postdoctoral researcher in the Department of Endocrinology, focusing on (autoimmune) thyroid disease and thyroid hormone action. Besides my research I am also a medical doctor specializing in internal medicine and endocrinology.

Dr. Jeska Fritzsche

I am a medical doctor currently training to become a gastroenterologist. In addition to my clinical work, I am pursuing postdoctoral research at the Department of Gastroenterology and Hepatology, focusing on the endoscopic management of (pre)malignant lesions of the biliary tree.

Dr. Mohammed Ghiboub

I am a postdoctoral researcher at the Tytgat Institute for Liver and Intestinal Research and the Department of Pediatric Surgery at Amsterdam UMC, where I started after obtaining my PhD from the University of Amsterdam in 2022. My research focuses on identifying novel metabolomic and epigenetic signatures as biomarkers and therapeutic targets in inflammatory bowel disease (IBD) and colorectal cancer.

AGEM Office 2024

Dr. Eva Dirkx-Beuling

Amsterdam Gastroenterology Endocrinology Metabolism (AGEM)

Policy officer AGEM (June 2015 – present)

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

Esther de Regt, MSc.

Amsterdam Gastroenterology Endocrinology Metabolism (AGEM)

Policy officer AGEM (September 2023 – November 2024)

MSc. Biology & Science Communication and Society

Valentina Bravo, MSc.

Amsterdam Gastroenterology Endocrinology Metabolism (AGEM)

Policy officer AGEM (December 2024 – present)

MSc. Science Education & Communication (Biology)

Dr. Ric van Tol

Amsterdam Gastroenterology Endocrinology Metabolism (AGEM) and Innovation Exchange Amsterdam (IXA)

Business Development & Innovation Strategy

Specialization: Nutrition and GI Health, Industrial Research Management

Science Impressions 2024

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 2024.

Targeting cellular metabolism to treat cystinosis

Fanny Oliveira Arcolino and Elena Levtchenko

Cystinosis is a rare, multisystemic disorder caused by mutations in the CTNS gene, which encodes cystinosin, the lysosomal cystine transporter. The disease is characterized by the accumulation of cystine in lysosomes, initially affecting kidneys and later on several other organs, including the eyes, thyroid, muscles, pancreas, liver, and brain. Current treatment with cysteamine helps to reduce lysosomal cystine accumulation but does not prevent disease progression, leading patients to end-stage renal disease, dialysis, and transplantation. These observations motivated researchers to look beyond cystine accumulation and focus on broader cellular mechanisms that may underlie cystinosis pathophysiology.

At Amsterdam AMC, within Emma Center for Personalized Medicine, cystinosis has been identified as one of the rare diseases of focus. In this context, our Pediatric Nephrology team has investigated the metabolic landscape of cystinosis, revealing a fundamental impairment in cellular energy metabolism. In a recent study, we focused on podocytes—specialized kidney cells crucial for glomerular filtration—and observed significant mitochondrial and metabolic dysfunction. Patient-derived and isogenic podocytes generated by knocking out the CTNS in healthy cells displayed altered tricarboxylic acid (TCA) cycle activity, diminished ATP levels, and fragmented mitochondrial networks. Notably, we found a marked sensitivity to ferroptosis, a regulated form of cell death driven by lipid peroxidation. Mitochondrial reactive oxygen species (ROS) played a central role in triggering this process.

We showed that pharmacological inhibition of mitochondrial ROS or lipid peroxidation using MitoTEMPO or Liproxstatin-1 significantly improved podocyte adhesion and permeability in vitro. Furthermore, these compounds restored glomerular proteinuria in a zebrafish model of cystinosis. These results, recently published (Berlingerio et al., Journal of Translational Medicine, 2025), suggest that ferroptosis is a key mechanism of kidney disease in cystinosis, and highlight mitochondrial dysfunction and redox imbalance as critical contributors to disease progression.

Building on these novel findings, we are currently studying proximal tubular epithelial cells (PTECs). These cells are essential for reabsorbing metabolites in the nephron, and their dysfunction contributes to the severe renal phenotype observed in patients. Our ongoing work involves metabolic profiling of cystinosis PTECs using Seahorse flux analysis, stable

isotope-labeled metabolomics, and NAD+ quantification. Preliminary results show a significant reduction in mitochondrial respiration and glycolytic capacity, accompanied by intracellular depletion of nicotinamide adenine dinucleotide (NAD+), a key metabolic cofactor. To address this, we are testing nicotinamide riboside (NR), a vitamin B3 derivative and NAD+ precursor. Early findings suggest that NR supplementation can improve ATP levels, basal glycolysis, and compensatory glycolysis in PTECs, enhancing their overall bioenergetic profile. Given that NR is already approved for human use, this strategy represents a promising translational approach.

By integrating the data from podocytes and PTECs, our research novel metabolic pathways in cystinosis. Rather than viewing the disease solely as a lysosomal storage disorder, we propose that mitochondrial impairments and ferroptotic cell death are fundamental contributors to its pathogenesis. This broader perspective opens the door to combination therapies that go beyond cystine depletion and aim to restore cellular homeostasis.

This work is the result of a close collaboration between the Laboratory of Pediatric Nephrology, conducted by Dr. Sante Princiero Berlingerio and led by Prof. Elena Levtchenko and Prof. Fanny Oliveira Arcolino, and the Laboratory of Genetic Metabolic Diseases, directed by Prof. Riekelt Houtkooper and Dr. Fred Vaz. Conducted within the framework of the Emma CPM, coordinated by Prof. Clara van Karnebeek, it brings together nephrology, metabolism, and research on rare diseases in a shared effort to translate mechanistic insights into patient-centered solutions.

The objective is not only to understand cystinosis in depth, but to identify effective, accessible, and mechanism-based interventions. The use of NAD+ precursors such as NR, alongside approaches to prevent ferroptotic damage, may represent a new therapeutic direction capable of preserving kidney function and improving long-term outcomes for patients with cystinosis (Figure 1). Moreover, similar mechanisms are likely to play a role in a broader spectrum of kidney disorders.

As we continue this work, we are reminded of the words of Seneca: “There is no enjoying the possession of anything valuable unless one has someone to share it with.” And now, with new tools in hand, we are preparing for the next step: transforming metabolic insight into tangible benefit for cystinosis patients.

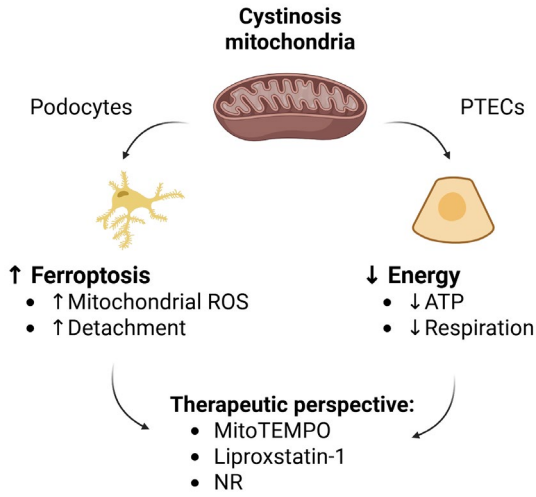
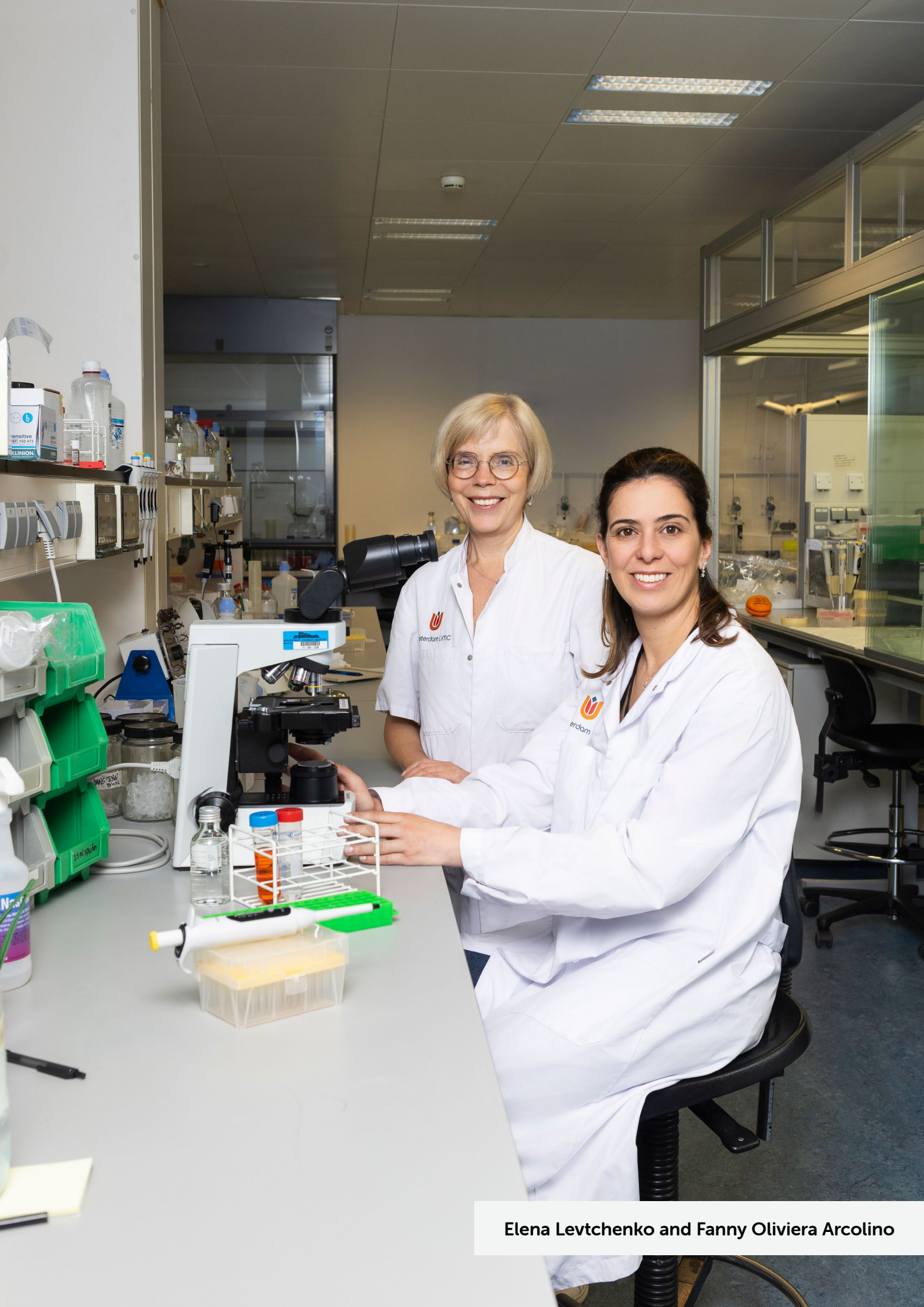


Figure 1. Mitochondrial dysfunction in cystinosis drives ferroptosis and energy deficiency. Targeting these pathways with MitoTEMPO/ Liproxstatin-1 and nicotinamide riboside (NR) offers a promising translational approach.

Fanny Oliveira Arcolino, Elena Levtchenko and Sante Princiero Berlingerio



Elena Levtchenko and Fanny Oliviera Arcolino

Endocrine regulation of liver metabolism

Xinru Zhang and Eveline Bruinstroop

In 2025, I was honored to be appointed Principal Investigator within AGEM. My research line focuses on the endocrine regulation of liver metabolism, employing a translational approach that spans in vitro models, liver biopsies, and patient studies using advanced MR-spectroscopy techniques to measure hepatic fat content. My work has a particular emphasis on metabolic dysfunction-associated steatotic liver disease (MASLD).

MASLD has become the most prevalent liver disease worldwide, fueled by the increasing epidemics of obesity and type 2 diabetes. With a global prevalence of approximately 30% in the general population—and alarmingly, up to 3% in children—it is imperative to invest in translational research now to mitigate the long-term consequences, including liver failure, hepatocellular carcinoma, and an associated surge in cardiovascular disease risk.

Within my group, we investigate the regulatory role of estrogens and thyroid hormones on liver metabolism. Within the Menopause Consortium, which was led by Professor Peter Bisschop and recently awarded a €9.4 million grant, we will study the effects of menopause across three domains: sleep and mental health, physical health, and work. Clinically, it is well recognized that women exhibit a degree of protection against MASLD before menopause, a protection that diminishes thereafter. Intriguingly, hormone therapy in transgender individuals has been shown to significantly alter their liver phenotype, as we demonstrated recently (Tebbens, JCEM 2023). As work package leader within the consortium, I coordinate the development of novel in vitro models to dissect the hormonal regulation of hepatic insulin resistance, steatosis, inflammation, and fibrosis and work together with Sarah Siegelaar and Peter Bisschop to design a human intervention trial investigating menopause-related changes in diabetes and liver disease. PhD candidates Merel Goedkoop and Rona Brokkelkamp, and Post-doc Maarten Steinz focus on the impact of menopause on diabetes and liver metabolism.

In addition to estrogen, a major focus of my research lies on thyroid hormone (TH) signaling in MASLD. Our previous work has contributed to the development of liver-specific TH-ß analogs, which in 2024 became the first FDA-approved pharmacological treatment for MASLD (Ratziu, Scandall and Bruinstroop, Journal of Hepatology 2024). These analogs target the thyroid hormone receptor beta (TR-ß) in hepatocytes, aiming to circumvent systemic side effects mediated by the alpha isoform (TR-ß) in heart and bone tissue. However, while these treatments effectively reduce hepatic fibrosis, the precise cellular mechanisms behind their anti-inflammatory and anti-fibrogenic effects remain elusive. Our research seeks to unravel these mechanisms.

Clinically, I am the lead investigator for Amsterdam UMC in the multicenter nation-wide T3-4 HypoTrial (https://t3-4-hypotrial.nl), wherein we examine whether patients with hypothyroidism with persistent symptoms on levothyroxine show beneficial effects of addition of the bioactive hormone T3 on quality of life. Within Amsterdam UMC, we examine whether supplementation with T3 improves intrahepatic lipid content, assessed through MR-spectroscopy.

Within the laboratory I work closely together with Professor Anita Boelen to study how TH signaling affects various hepatic cell types. Recent bulk RNA sequencing data have shown that TR-ß signaling progressively declines during MASLD development (Kendall et al. 2023 Nature Medicine). While hepatocytes—the dominant cell type in the liver—express TR-ß predominantly, non-parenchymal cells such as macrophages also appear to be important targets. PhD student Esmee Hoen is currently investigating TH effects on macrophages, which are

important in the context of inflammation resolution and fibrosis regression.

I am proud to highlight the research of PhD candidate Xinru Zhang, who focuses on the role of thyroid hormone metabolism within hepatocytes during MASLD progression. A key enzyme in this process is deiodinase type 1 (Dio1), which converts the pro-hormone T4 into the bioactive T3 form. Our earlier studies showed a compensatory upregulation of Dio1 in the early stages of MASLD, suggesting an adaptive response to maintain local TH signaling despite systemic metabolic derangements. Xinru's project aims to elucidate the molecular regulation of this compensatory mechanism, with a specific focus on the role of nutrient signals and the hepatic transcription factor HNF4A.

To this end, she is developing and utilizing in vitro hepatocyte models to mimic the nutrient-rich environment characteristic of early MASLD. In parallel, she collaborates with international partners at Friedrich Schiller University Jena and the University of Lille, as well as with several AGEM research groups investigating thyroid hormone metabolism in human liver biopsies. Through these efforts, Xinru seeks to define the pathways by which nutrient overload and hormonal (dys)regulation intersect to impair hepatocellular function. A deeper understanding of Dio1 regulation and its interaction with key transcriptional networks such as HNF4A may open new therapeutic avenues to reinforce the liver's intrinsic defenses against steatosis and fibrosis.
By bridging clinical studies and molecular research, our group aims to contribute to a more precise, cell-specific understanding of hormonal regulation in liver disease, ultimately striving to improve the lives of patients affected by MASLD.

Eveline Bruinstroop and Xinru Zhang

Gender affirming endocrine treatment in transgender adolescents

Lidewij Boogers and Sabine Hannema

An increasing number of transgender and gender diverse (TGD) adolescents seek medical care to align their body with their gender identity. During puberty the development of secondary sex characteristics that are incongruent with gender identity can cause great distress. Treatment with a gonadotropin-releasing hormone (GnRH) analogue can be used to suppress sex steroid production and stop further development of such characteristics in a reversible manner. From age 15-16 years sex hormone treatment can be used to induce pubertal development in line with the gender identity. Medical treatment is always preceded by a holistic assessment by a mental health professional and counselling about treatment options and their benefits and risks.

Evidence in this relatively new field is still limited. To further inform treatment guidelines and to optimise counselling of adolescents and their families we perform clinical studies evaluating a range of outcomes of hormonal treatment in TGD adolescents. Since transgender care has become the topic of societal and political debate it is all the more important to provide further scientific evidence on the efficacy and safety of treatment. Over the past few years we have studied treatment trajectories and continuation rate of hormone treatment, effects on growth, body composition, bone mineral density, the development of secondary sex characteristics and satisfaction with treatment effects. For these studies we have used prospectively collected data, existing clinical data as well as data from national registries. Transgender care is truly multidisciplinary care and this is reflected in our research for which we have collaborated with colleagues from both paediatric and adult endocrinology, child psychiatry, psychology, gynaecology, plastic surgery, otorhinolaryngology, speech therapy and medical technology.

Since large prospective studies in TGD adolescents are scarce, we initiated the ENIGI Adolescents study in 2021. This international collaboration between gender clinics in Ghent, Florence, and Amsterdam offers a broad range of research opportunities. Prospective data are collected at the participating hospitals through objective measurements such as grip strength, voice frequency and a 3D scan of the chest, complemented by self-reported information gathered via questionnaires. Adolescents can be included when they start either GnRH analogue treatment or gender affirming hormone treatment, i.e. testosterone or estradiol.

This comprehensive data collection enables us to explore a wide variety of research topics concerning TGD adolescents. For instance, by tracking prospective changes such as voice deepening, breast development, and muscle growth, we can evaluate the progression of these physical effects over time. Additionally, the impact of factors like the tempo of gender-affirming hormone dose increase and different methods of administration can be assessed. Beyond physical outcomes, the questionnaire data provide valuable insights into treatment-related side effects, as well as changes in body image and mental well-being. In addition information on life style and on their ideas regarding fertility and fertility preservations is collected.

The multi-centre design of the study also facilitates comparisons of treatment strategies across participating clinics, which differ to some extent in their approaches. Furthermore, the long-term nature of this project allows for the adaptation of the study protocol in response to emerging research questions or evolving concerns from the TGD community itself.

Currently, more than 400 individuals are participating in the study. Recently the first publication of results

of the ENIGI adolescents study has appeared, focussing on the attitudes of TGD adolescents and their parent regarding fertility, parenthood, and fertility preservation before the start of GnRH analogue treatment or gender affirming hormone therapy. We found that many TGD adolescents express a desire for future parenthood yet experience decisional conflict about their reproductive options, even after receiving comprehensive fertility counselling prior to the start of hormonal treatment.

Analyses of other outcomes has started, providing novel insights, for example into the variability in the decrease of voice frequency in response to testosterone treatment in adolescents. We also investigate non-medical interventions that TGD adolescents use, such as the use of binders, i.e. tight tops to compress the breasts and give the chest a masculine appearance. We found this practice is very common among late pubertal TGD adolescents and binders are worn for many hours a day. We are currently looking at its determinants and health consequences.

In response to the rising demand for gender-affirming treatment among TGD adolescents, the ENIGI Adolescents study is fulfilling the need for prospective data on the effects and safety of GnRH analogue and gender affirming hormone treatment. This will improve counseling, helping adolescents and their families to make evidence-based healthcare decisions together with the multidisciplinary team while also paving the way for further advancements in the field.

Lidewij Boogers and Sabine Hannema

Deciphering Disease Severity in X-linked Adrenoleukodystrophy Through Lipidomics

Yorrick Jaspers and Stephan Kemp on behalf of Team ALD

At Team ALD our research is centered on X-linked adrenoleukodystrophy (ALD) - a severe, inherited metabolic disorder caused by pathogenic mutations in the ABCD1 gene. These mutations impair peroxisomal function, resulting in the systemic accumulation of very long-chain fatty acids (VLCFAs). While the biochemical basis of ALD is well understood, the clinical presentation is strikingly variable. Males with ALD are at high risk for adrenal insufficiency, spinal cord disease, and leukodystrophy (CALD)—a rapidly progressive brain disorder that often leads to severe disability or death. Females may also develop symptoms, most commonly spinal cord involvement later in life.

Although treatments such as hormone replacement and hematopoietic stem cell transplantation (HSCT) can be effective, timing is everything. In the case of CALD, for example, good outcomes from HSCT depend on very early detection, before the onset of neurological symptoms. Therefore, early diagnosis combined with long-term follow-up is essential.

In 2023, the Netherlands became the first country in Europe to introduce newborn screening for ALD. Every newborn boy is now tested with a multi-step screening algorithm using dried blood spots, which allows presymptomatic diagnosis. While this is a major advance, it also poses a profound clinical dilemma: we can identify the disease, but we cannot predict how it will progress. Boys identified through newborn screening may remain asymptomatic for years, while others may develop adrenal dysfunction or CALD before the age of 10 years. There is no test to predict which boys will develop these symptoms. This uncertainty creates significant challenges for patients, families and clinicians.

Our research in Team ALD aims to fill this gap by developing molecular tools that better reflect or predict disease severity. For example, we have focused on lipidomics, the large-scale analysis of lipid molecules in biological samples. Because VLCFAs are incorporated into many different lipid species in the body, lipidomics allows us to characterize disease-specific remodeling of the lipidome.

In 2024, researcher Yorrick Jaspers led a study that illustrates the power of this approach. The paper, published in Communications Medicine, used high-resolution mass spectrometry to analyze the plasma lipidome of 92 male and 65 female ALD patients and 24 healthy controls. The goal was to explore how VLCFAs are embedded in complex lipids-and whether these patterns correlate with clinical disease burden.

We found that VLCFAs are incorporated into a variety of lipid classes, including lysophosphatidylcholines (LPC), phosphatidylcholines (PC), sphingomyelins (SM), and triglycerides (TG). The levels of these VLCFA-containing lipids were significantly elevated in ALD patients. More importantly, the degree of elevation of these lipids correlated with disease severity: in males, higher plasma levels were associated with CALD, adrenal insufficiency, and severe spinal cord involvement.

This lipidomic signature was further supported by findings in a subset of CALD patients who had undergone HSCT. While treatment reduced plasma levels of LPC 26:0 (the diagnostic biomarker for ALD), levels did not normalize, suggesting persistent underlying metabolic dysfunction. These findings suggest that lipidomics not only reflects the

molecular burden of disease, but may also be useful in monitoring treatment response.

What makes this work particularly relevant today is its potential to complement newborn screening efforts. While current screening methods effectively identify pathogenic ABCD1 mutations and VLCFA elevations, they do not provide prognostic information. Lipidomic markers - if validated in prospective cohorts - may help fill this gap. By tracking VLCFA-containing lipids over time, we may eventually be able to distinguish patients at high risk for early cerebral disease from those who are likely to remain stable.

Importantly, these results were recently confirmed in a Minnesota study with 5-year follow-up of boys identified through newborn screening, showing that LPC 26:0 levels at screening may predict early disease onset in ALD. At present, these lipidomic signatures are not ready to guide individual treatment decisions. Although group-level trends are clear, there is overlap between symptomatic and asymptomatic individuals. However, the implications are promising. With further validation, lipidomics could become a clinically useful prognostic tool, adding a layer of molecular insight to existing diagnostic protocols.

The study also illustrates our broader vision of bridging cutting-edge analytical chemistry with real-world clinical needs. At Team ALD, we combine mass spectrometry, genetics and clinical data to develop biomarkers that are biologically meaningful and clinically actionable. We work closely with clinicians and patient communities to ensure that our findings address unmet needs and support better patient care.

Our work in 2024 is an example of this approach. This study shows how untargeted lipidomics can reveal meaningful differences associated with disease status, helping us move from descriptive to predictive diagnostics. As newborn screening becomes the norm and treatment options continue to evolve, our ability to stratify risk and personalize follow-up will be more important than ever.

In the coming years, we plan to build on these findings by following newborn-screened ALD patients longitudinally, developing targeted lipid assays, and integrating lipidomics with genomics and imaging. The ultimate goal is ambitious, but within reach: to transform ALD from an unpredictable disease to one whose progression can be mapped, monitored, and, if necessary, intervened upon with precision.

Stephan Kemp and Yorrick Jaspers

Duodenal ablation as treatment for type 2 diabetes

Céline Busch and Jacques Bergman

The duodenum, the first segment of the small intestine, plays an important regulatory role in glucose homeostasis. Prolonged exposure to a Western diet, high in fat and sugars is thought to induce changes in the duodenal mucosa that contribute to metabolic dysfunction. Studies have shown that patients with type 2 diabetes (T2D) experience significant improvements in insulin resistance and glycaemic control within days after undergoing Roux-en-Y gastric bypass surgery, well before significant weight loss occurs. These findings suggest that bypassing the duodenum itself may be a key driver of these rapid glycaemic and metabolic improvements.

This insight has paved the way for novel therapeutic strategies that target the duodenum to improve glucose control for T2D and possibly metabolic syndrome. Endoscopy offers a minimally invasive alternative to surgery, with the duodenum being easily accessible via upper gastrointestinal endoscopy. Addressing insulin resistance, the underlying cause of T2D, rather than merely treating the symptom, hyperglycaemia would represent a change in the treatment paradigm for T2D.

Duodenal ablation emerged as this minimally invasive endoscopic approach that targets the duodenal mucosa to improve glycaemic control. The first technique developed was duodenal mucosal resurfacing (DMR), using the Revita catheter (Fractyl Health Inc), see figure 1 A and B. This procedure involves hydrothermal ablation of the mucosa following submucosal injection of a protective buffer. Both open-label (Revita-1) and sham-controlled trials (Revita-2) in which our study group has participated have shown that DMR can significantly improve glycaemic control in patients with T2D.

More recently, another innovative technique has emerged, re-cellularisation via electroporation therapy (ReCET) using the Endogenex catheter (Endogenex Inc.) as portrayed in figure 1 C and D. This technique uses electroporation, meaning it applies pulsed electric fields to the superficial mucosa, inducing controlled cell apoptosis and subsequent duodenal mucosal renewal. Since only the superficial mucosal layers are affected, no submucosal buffer is required. In the EMINENT study, we investigated whether a single ReCET procedure, combined with a glucagon-like peptide-1 receptor agonist (GLP-1RA), could eliminate the need for exogenous insulin treatment in T2D patients. In this open-label study, we found that 86% of patients remained off insulin and achieved adequate glycaemic control one year after the procedure.

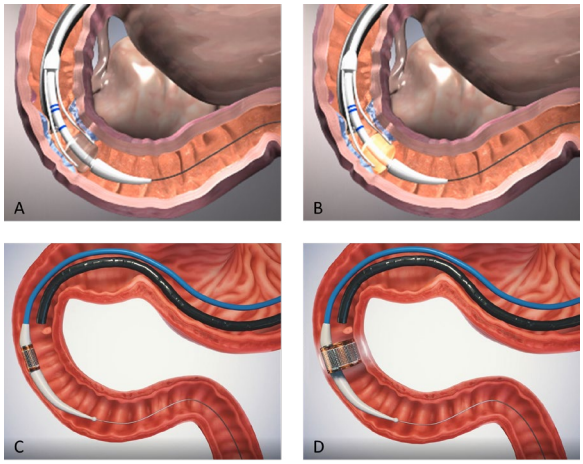


Figure 1. A. DMR procedure: after over a guidewire, placement of the catheter past the papilla of Vater a submucosal buffer is administered to lift the mucosa. B. After the mucosal lift the tissue is hydrothermally ablated. C. ReCET procedure: using fluoroscopic and endoscopic guidance, the catheter is advanced past the papilla of Vater. D. Pulsed electric field treatment is applied via the flex circuit after which the catheter is moved stepwise to Treitz.

The follow-up trial, the EMINENT-2, is a randomized controlled trial (RCT) designed to further evaluate the combination of ReCET and GLP-1RA, which is currently being conducted. Simultaneously we are performing the REMIND study, an RCT assessing DMR paradigm 1, a more intensive ablation sequence and also retreatment with DMR. In addition to all the clinical endpoints that we are assessing in the

EMINENT-2 and REMIND studies, several assessments will be performed to further our understanding of duodenal ablation and the metabolic role of the duodenum. These studies include:

- Large duodenal mucosal sampling using cold snare resection, enabling in-depth pathological and immunohistochemical analysis in tissue microarrays (TMAs)
- Single-cell RNA sequencing (scRNAseq) to identify transcriptomic changes at the cellular level
- Postprandial hormone response profiling to assess changes in enteroendocrine signalling
- Close-up endoscopic imaging to visualize possible macroscopic mucosal changes
- Oral and fecal microbiota analysis to identify shifts in gut microbial composition

All assessments are conducted both pre- and post-intervention, and include a sham arm. In case of the REMIND the post retreatment is also included, all allowing for more robust data.

Looking ahead, our team is planning to perform portal vein blood sampling to capture direct hormonal signalling from the gut to the liver. This will provide unique insights into the gut-liver axis and help refine therapeutic targets.
In parallel, we are exploring GLP-1 gene therapy, where GLP-1 is not delivered via injections (GLP-1RA) but the gene is delivered to a patient via a vector, enabling the pancreas to produce incretin hormones endogenously and sustainably.

As our understanding of the duodenum's role in metabolic regulation continues to grow and given the accessibility of the duodenum via upper GI endoscopy, gastroenterologists are about to get a new role in metabolic endoscopy. Duodenal ablation might set in a paradigm shift: rather than focusing solely on symptom-oriented interventions like endoscopic sleeves, it aims to address the root causes of T2D, such as insulin resistance, directly at the level of the intestinal mucosa.

Céline Busch and Jacques Bergman

Best Publication 2024

In 2025, AGEM once more organized the Best Publication battle. For this, all AGEM principal investigators (PIs) had the opportunity to nominate publications of their best researcher, PhD student or postdoc, that published as first author in a top journal in 2024.

Out of these nominees, members of the AGEM Research Board selected a top 3. These selected candidates were offered a pitch workshop and, with the skills learned, Heleen Jansen, Felipe Correa-da-Silva and Lotte Slooter pitched their publication during the AGEM award ceremony on May 22nd, 2025. After this so-called "AGEM Best Publication 2024 Battle", the attendants of the award ceremony voted for their ultimate favorite. The author of the publication with the most votes was named winner of the AGEM Best Publication 2024.

Meet the nominees for the AGEM Best Publication 2024

Heleen Jansen

Heleen Jansen was nominated by Wendy den Elzen and Annemieke Heijboer for her article published in Thyroid: *"Age-Specific Reference Intervals for Thyroid-Stimulating Hormones and Free Thyroxine to Optimize Diagnosis of Thyroid Disease".* Thyroid. 2024 Nov;34(11):1346-1355.

The motivation of Wendy den Elzen and Annemieke Heijboer for the nomination was: "It is a great achievement because it is a fantastic nationwide study in which an incredible amount of data from across the country has been used to establish age-dependent reference intervals for thyroid hormones and for all commonly used measurement methods. This leads to fewer cases of subclinical hypothyroidism and, as a result, less unnecessary care."

Felipe Correa-da-Silva

Felipe Correa-da-Silva was nominated by Chun-Xia Yi for his article published in Acta Neuropathologica: *"Microglial phagolysosome dysfunction and altered neural communication amplify phenotypic severity in Prader-Willi Syndrome with larger deletion".* Acta Neuropathol. 2024 Mar 31;147(1):64

The motivation of Chun-Xia Yi for the nomination was: "This study provides critical insights into how the larger Type 1 (T1) deletion in Prader-Willi syndrome (PWS), a severe genetic disorder characterized by obesity and endocrine dysfunction, leads to more pronounced hormonal, metabolic, and cognitive challenges compared to the smaller Type 2 (T2) deletion. By identifying key differences in brain cell function and structural changes linked to these symptoms, the research highlights the importance of precise genetic analysis to better understand individual variability in the disorder. These findings pave the way for more personalized care strategies and targeted therapies, offering hope for improved management of obesity and endocrine-related complications in individuals with PWS."

Lotte Slooter

Lotte Slooter was nominated by Ynte de Boer and Joost Drenth for her article published in Hepatology: *"Lack of complete biochemical response in autoimmune hepatitis leads to adverse outcome: First report of the IAIHG retrospective registry".* Hepatology. 2024 Mar 1;79(3):538-550.

The motivation of Ynte de Boer and Joost Drenth for the nomination was: "Because of Lotte's outstanding work on the multi center International Autoimmune Hepatitis Retrospective Registry (IAIHG-RR) analysis, which led to the publication of an article in the leading American Association for the Study of Liver diseases (AASLD) journal 'Hepatology' that firmly establishes the normalization of both IGG and ALT/AST as a therapeutic target that should be achieved in AIH. This study provides much needed proof for therapeutic endpoints in the new international AIH guidelines, currently under development."

AGEM Best Publication 2024 Winner

Heleen Janssen

Age-Specific Reference Intervals for Thyroid-Stimulating Hormones and Free Thyroxine to Optimize Diagnosis of Thyroid Disease

My name is Heleen Jansen and I have worked as a PhD candidate at the Endocrine Laboratory under supervision of promotors Annemieke Heijboer and Anita Boelen and copromotors Eveline Bruinstroop and Jacquelien Hillebrand at the subject of improving diagnostics for thyroid diseases, in which I specifically looked at pitfalls and improvements in laboratory measurements. In June 2024, I successfully defended my PhD thesis (cum laude) and I am currently working as resident in Internal Medicine. Thyroid diseases are highly prevalent in the general population and many people still experience difficulties in optimizing treatment to function well in daily life. Improving laboratory measurements of thyroid hormones can help in both diagnostics and treatment and can therefore be of great relevance to a large group of patients. This clear goal made, amongst others, my PhD trajectory so interesting.

The article that was awarded for the Best Publication 2024 Award made me very enthusiastic since our results could directly be used in clinical practice. In this project, we established age-specific reference intervals for thyroid-stimulating hormone (TSH) and free thyroxine (FT4). Reference intervals are established to distinguish abnormal results of a laboratory test from normal results and previous research has shown that TSH and FT4 concentrations can change physiologically with ageing.

We used retrospective data from 13 Dutch laboratories, thereby included 7.6 million TSH and 2.2 million FT4 results and we established age-specific reference intervals per decade using an indirect method. We showed that the upper reference limit of especially TSH significantly increased from 60 years in men, and from 50 years in women. Furthermore, we showed that the use of adult age-specific reference intervals resulted in a decrease in unnecessary diagnoses of subclinical and overt hypothyroidism in women over 50 and men over 60 years of age, highlighting the clinical relevance of using these age-specific reference intervals. Therefore, we concluded the article by recommending the implementation of adult age-specific reference intervals for TSH.

Heleen Janssen and Anita Boelen

Grants 2024

In 2024, AGEM awarded four 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-like-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, and the AGEM contribution printing costs of theses for AGEM PhD candidates.

AGEM Innovation Grant 2024 laureates

AGEM Talent Development Grant 2024 laureates


Effects of two eHealth applications on antibiotics use,
and microbiota of febrile children with acute, uncomplicated
Dutch primary care
NHAP-tool
FeverApp
Amsterdam Ga
Endocrinolog
Fueling t


Amsterdam UMC
Gut responses to nutrients
in humans with obesity
A randomized crossover MRI study
Team:
Sofieke de Jonge, PhD
Susanne la Fleur, PhD
Mireille Serlie, PhD, MD
Katy van Galen, MD
Amsterdam
Endocrinol
Fuelin


Exploring Esophageal Atresia through micro
• EA is a rare congenital anomaly characterized by a discontinuation of the esophagus
• Poorly understood condition with life long complications (Dysphagia, feeding disorders)
• Innovative, fundamental research required to develop new treatment strategies
• Through micro-CT imaging we will be studying the Neural network and Muscle buildup in 3D
Esophageal atresia
Tracheoesophageal fistula
msterdam Gastroer
Endocrinology Met
Fueling th

The AGEM talent development grant 2024 (€50.000)

Anne van der Spek (VENI-like-profile)

The GUT2GD study: do changes in the gut microbiome trigger Graves' Disease?

I am a clinical fellow as well as a postdoctoral researcher in the Department of Endocrinology. My research focuses on thyroid hormone metabolism and thyroid disease. Currently I am taking the first steps towards an independent research line focused on the role of the gut microbiome in the development of Graves' Disease, an autoimmune disease that stimulates the thyroid to produce excess amounts of thyroid hormone. With this new line of research I aim to understand the underlying cause of Graves' Disease and the role of the gut microbiome in its development. My ultimate goal is to identify new targets for Graves' Disease therapies, thereby improving treatment outcomes for my patients.

The AGEM talent development grant allows me to study whether the changes in the gut microbiome that are observed in Graves' Disease patients are not, as previously thought, a consequence, but a direct cause of the disease. Treatments for Graves' Disease have been unchanged for over 50 years, despite the standard treatment with anti-thyroid drugs achieving disease remission in only 50% of patients. Importantly, none of our available therapies target the underlying cause of Graves' Disease, the development of thyroid-stimulating autoantibodies. I will use a computer method to identify gut bacteria in Graves' Disease patients that are capable of confusing the immune system and could result in the production of the autoantibodies that trigger the disease. This project has the potential to advance the scientific understanding of Graves' Disease, help define new therapeutic targets and may ultimately lead to the first microbiome-based therapies for Graves' Disease.

Anne van der Spek

Mohammed Ghiboub (VENI-like-profile)

Histone serotonylation: The hidden epigenetic key to chronic fatigue in Crohn's disease

I am a researcher at the Tytgat Institute for Liver and Intestinal Research and the Department of Pediatric Surgery at Amsterdam UMC. My work focuses on unraveling immune-epigenetic mechanisms in inflammatory bowel disease (IBD), with the aim of identifying biomarkers and therapeutic targets that can improve patient outcomes. After obtaining my PhD from the University of Amsterdam in 2022, I established an independent research line investigating the role of recently discovered epigenetic modifications in IBD symptoms such as fatigue and abdominal pain.

The AGEM talent development grant allows me to investigate whether histone serotonylation (H3Q5Ser) — a newly identified epigenetic modification involving the covalent attachment of serotonin to glutamine 5 on histone H3—drives chronic debilitating fatigue in Crohn's disease (CD) during clinical remission. This modification is catalyzed by the enzyme Transglutaminase 2 (TGM2) and has been shown to alter chromatin accessibility and transcriptional output, suggesting a novel role for serotonin beyond its classical neurotransmitter function.

Preliminary data from my research reveal that fatigued CD patients in remission exhibit elevated levels of H3Q5Ser in immune cells, pointing to a persistent epigenetic imprint. With the support of the AGEM Talent Development Grant, I will apply a multi-omics strategy—including ChIP-seq, ATAC-seq, RNA-seq, and CyTOF—to (1) longitudinally assess whether H3Q5Ser is positively and persistently associated with debilitating fatigue in CD patients transitioning from active disease to remission, and (2) evaluate whether H3Q5Ser is a druggable epigenetic mark by identifying the gene programs it regulates that are associated with fatigue in immune cells.
By establishing H3Q5Ser as a fatigue-associated chromatin mark, this project could open new therapeutic avenues for targeting fatigue in IBD and potentially in other serotonin-related disorders.

Mohammed Ghiboub

Tim de Meij (VIDI-like-profile)

A Novel Tool for Therapeutic Drug Monitoring of Methotrexate in Children and Adolescents with Inflammatory Bowel Disease: A Prospective Multicentre Cohort Study

I am pediatric gastroenterologist and my clinical focus include the care for children with inflammatory bowel disease. I have a keen interest in translational research, focusing on microbiology and metabolomics in gastrointestinal inflammatory diseases. Current focus lies on development of novel, microbiota-related diagnostic biomarkers for gut inflammation, including necrotizing enterocolitis, inflammatory bowel disease and gut-derived sepsis. I incorporate these themes in my scientific work.

The AGEM talent development grant allows me to develop a more personalized treatment of methotrexate (MTX) in children and adolescents with Crohn's disease. Currently, there is substantial variability in therapeutic response and a high incidence of side effects during MTX treatment, which is partly due to the lack of therapeutic drug monitoring (TDM). Plasma concentrations are not suitable for TDM in low dose MTX due to their short half-life-time. However, intracellular methotrexate polyglutamate (MTX-PG) concentrations have proved to be effective for TDM in adult Crohn's disease and other immune-mediated inflammatory diseases (IMIDs), such as rheumatoid arthritis. We will provide insight into the pharmacokinetics of MTX by determining the accumulation patterns of MTX-PG and identify clinical and biological predictors influencing those accumulation patterns. Moreover, we will investigate the relationship between MTX-PG concentrations and therapeutic efficacy and toxicity. Ultimately, we aim to develop a predictive model that can predict the likelihood of treatment success and side effects prior to the start of MTX therapy. We expect MTX-PG to be a valuable TDM tool, improving clinical outcomes and minimizing side effects and together take a step towards a more personalized treatment in pediatric and adolescent Crohn's disease.

Tim de Meij

The AGEM innovation grant 2024 (€25.000)

Eefje Belt-van Zoen and Hilde Herrema

Reducing Antibiotic Use for acute, uncomplicated Upper Respiratory Tract Infections (URTIs) by eHealth Apps that encourage safe use of effective natural medicinal products (e.g. food supplements) for URTIs and phase-specific fever management

Eefje Belt-van Zoen is health scientist and program manager of the Master Advanced Nursing Practice at University of Applied Sciences Leiden. In her PhD research at Amsterdam UMC, she explores the role of fever, natural medicinal products, and the gut microbiome in early-life health and long-term disease prevention, contributing to sustainable healthcare and improved outcomes in pediatric populations. For this work, she collaborates with Microbiota Center Amsterdam and Leiden Centre for Applied Bioscience (LCAB).

Hilde Herrema is medical biologist and head of the Laboratory for Experimental Vascular Medicine (Amsterdam UMC) and the Microbiota Center Amsterdam. Her research resolves around the role of the gut microbiome in development of metabolic disease, with a particular interest in bacteriophages. Included are wet lab and computational approaches, as well as intervention studies in close collaboration with clinician scientists. She is core member of a large National Growth Fund initiative and co-leads a WP in a NWO-KIC consortium.

The AGEM innovation grant allows us to perform 16S sequencing of the stool samples collected for our RCT. This enables us to identify bacterial communities, offering insights that would otherwise remain inaccessible. In addition, the grant supports logistical improvements by allowing us to arrange for the secure and timely transport of samples. Ensuring that all biological material reaches the lab under optimal conditions is essential for data integrity and reproducibility. Finally, the grant contributes to our ongoing efforts to increase participant diversity and retention. This is particularly important in ensuring that our RCT is both representative and inclusive. Overall, the grant strengthens the scientific rigor and operational quality of our project, while aligning with our commitment to ethical and inclusive research.

Hilde Herrema and Eefje Belt-van Zoen

Chun-Xia Yi and Andries Kalsbeek

In-depth immunometabolic profiling of microglia in rats on Time-Restricted Eating using SCENITHBONCAT assay

Chun-Xia Yi's research explores how hypothalamic microglia contribute to common and syndromic obesity (e.g., Prader-Willi Syndrome). I discovered they respond early to obesogenic diets, triggering neuroinflammation before peripheral changes. I study neuron-microglia interactions and how disrupted microglial immunometabolism impairs neuronal function, sustaining obesity. I also develop genetic and pharmacological tools to modify microglia in vivo and study live microglia from obese animal models and postmortem human brains. My current focus is on microglial metabolic memory and its role in weight regain. I aim to understand how microglia lose metabolic flexibility and how reversing this could support lasting weight loss.

Andries Kalsbeek's research investigates how the circadian timing system (CTS) regulates bodily rhythms in physiology and hormone release, with a focus on energy metabolism. The endogenous circadian rhythm of the CTS master clock in the brain is synchronized to the exact 24h rhythm of the outside world by light, but most peripheral tissue clocks of the CTS are synchronized by food intake and (locomotor) activity. Our current experiments focus on the question how an optimal timing of exercise and the feeding-fasting cycle can strengthen the rhythm of the clock and prevent metabolic diseases such as type 2 diabetes and obesity.

The AGEM innovation grant allows us...

Shift work and late-night eating increase obesity risk by disrupting alignment between eating patterns and the body's circadian rhythm. Obesity is associated with hypothalamic inflammation, where microglia help maintain brain health by clearing toxins and supporting neurons. Time-restricted eating (TRE), especially when aligned with the active phase, is known to help manage obesity, but microglial involvement is not well understood. Our recent study found that rats fed during their inactive phase gained more weight than those fed during their active phase, despite equal food intake. Microglial gene analysis suggested that eating at the wrong time-of-day reprograms their metabolism toward a more inflammatory state. To investigate this in detail, the AGEM innovation grant allowed us to collaborate with Stienstra's lab at WUR, using their cutting-edge SCENITH-BONCAT technology. This method uniquely measures how microglia rely on specific metabolic pathways for energy, using fewer cells and accommodating fragile microglia better than traditional approaches like Seahorse-XF analysis. This addresses key technical barriers in studying microglial metabolism. Our results show that the timing and content of food intake shape microglial metabolism, with dark-phase TRE increasing glucose use and glycolytic capacity in high-fat diet conditions - highlighting microglial flexibility as a potential target in obesity treatment.

Andries Kalsbeek and Chun-Xia Yi

Ramon Gorter and Joep Derikx

Exploring surgical anatomy and embryology of Esophageal Atresia through micro computed tomography

I'm **Ramon Gorter,** a pediatric surgeon at Amsterdam UMC. I combine my clinical work with research to improve care for children. My focus lies in minimally invasive surgery, colon dysmotility and anorectal malformations. I'm passionate about using scientific insights to enhance surgical outcomes and patient recovery. Being both a surgeon and a researcher allows me to directly translate questions from the clinic into research projects—and bring results back to the bedside. This dual role helps me contribute to safer, more effective treatments and drives innovation in pediatric surgery. For me, research and clinical practice go hand in hand.

I'm **Joep Derikx,** professor and pediatric surgeon at Amsterdam UMC, where I lead research alongside my clinical work. My passion lies in understanding the underlying mechanisms of intestinal diseases in newborns and children, especially necrotizing enterocolitis and Hirschsprung disease. By combining patient care with fundamental and translational research, I aim to develop better diagnostics and treatments that truly make a difference. I believe that innovation in the lab should always connect back to the patient. As a professor, I also enjoy mentoring the next generation of clinician-scientists, fostering a culture where research and clinical care strengthen one another every day.

The AGEM Innovation Grant has allowed us to take a significant step forward in our research into esophageal atresia, which is currently underway at Amsterdam UMC. Using high-resolution micro-CT imaging, we are now able to study the muscle structures of the esophagus in exceptional detail. This advanced imaging technique gives us a unique opportunity to investigate the underlying anatomical differences that may contribute to the dysmotility disorders often seen in patients with esophageal atresia.

Our aim is to uncover subtle structural abnormalities in the esophageal wall that may not be visible through conventional methods. By doing so, we hope to better understand why many of these children continue to experience difficulties with swallowing and digestion, even after successful surgical repair. This research bridges clinical practice and scientific exploration, allowing us to translate patient experiences into targeted research questions—and potentially, into improved treatments.

As pediatric surgeons, we are driven by the challenges we encounter in daily care. Through this project, we hope to lay the groundwork for future innovations in diagnosis, therapy, and long-term management of esophageal dysmotility. The AGEM Innovation Grant has been instrumental in making this possible, and we're excited about the progress we're already seeing.

Joep Derikx and Ramon Gorter

Sofieke de Jonge, Susanne la Fleur, Katy van Galen and Mireille Serlie

Gut responses to nutrients in humans with obesity: a randomized crossover MRI study

Sofieke de Jong is a research fellow at the department of radiology and nuclear medicine of the Amsterdam UMC, specializing in MRI-based assessment of gastrointestinal motility. With a background in both medicine and engineering, her work bridges clinical need and technological innovation to improve understanding of gut function in health and disease. Her research include topics in the fields of MRI acquisition and quantification, gastrointestinal physiology, food, inflammatory bowel disease and functional gastrointestinal disorders.

Susanne la Fleur is a professor in Neurobiology of Energy Metabolism at the Endocrine Laboratory of the Amsterdam UMC. Her research group focuses on the interaction between energy metabolism and the brain in the development of obesity and type 2 diabetes, with a special emphasis on the effects of highly palatable nutrients on the brain. Her research bridges basic science and the clinic to translate findings from the rodent obesity model she developed to the human setting, showing how the brain responds to an overload of highly palatable nutrients. Her work is interdisciplinary ranging from psychology to biology and medicine.

Katy van Galen is a researcher, physician and medical specialist in training at the department of internal medicine of the Amsterdam UMC. Her PhD research investigated brain responses to variations in nutritional state, focusing on physiology and pathophysiology in human obesity. Her research showed that people with obesity exhibit disturbed brain responses and striatal dopamine release following intragastric nutrient infusions. Notably, these deficits were not ameliorated by clinically significant diet-induced weight loss, suggesting that such impairments may contribute to the pathogenesis of obesity and the high rate of weight regain observed after successful weight loss.

Mireille Serlie is an endocrinologist and Professor of Medicine at the Department of Endocrinology and Metabolism as well as a Professor of Medicine at Yale Medical School in the USA. Her translational research focusses on the interaction between the brain and body weight and the effects of nutrients and dietary treatment on brain centers that control food intake. She also performs studies on the molecular mechanisms of insulin resistance. Being a physician scientist puts her at the crossroads of bed and bench. Clinically, she treats endocrine patients and leads the Parenteral Nutrition and Intestinal Failure Center of Excellence.

The AGEM innovation grant allows us to investigate gut responses to nutrient in humans with obesity, using non-invasive MRI techniques. Small bowel motility is essential for proper digestion and nutrient absorption and is influenced by hormones released during and after meals. In obesity, hormonal response is altered, but very little is known about small bowel motility. This gap in knowledge is critical, as therapies that regulate gastrointestinal motility could play a role in obesity management.

Traditional methods to measuring small bowel motility are invasive and challenging. MRI enables non-invasive, targeted imaging of gut movement during a 20-second breath-hold, offering new opportunities for clinical research.

To explore this, we collaborate on a unique single-blinded, randomized-controlled, cross-over MRI study involving humans with healthy weight and humans with obesity. Participants underwent intra-gastric administration of glucose, lipid, or water, followed by MRI motility scanning before and after nutrient intake. The group with obesity also repeated the protocol after weight loss through dietary intervention. We will assess intra-gastric nutrient-induced changes in small bowel motility and explore associations with GLP-1 hormone response. This project will provide important insights into gastrointestinal function in obesity, guiding future research into targeted therapies and gut function modulation.

Sofieke de Jonge and Katy van Galen

The AGEM international student fellowship 2024 (€500/month)

Jutta van Crevel

Towards a patient-tailored approach for papillary adenomas

During my internship, I conducted a clinical research project on patients with sporadic papillary adenomas, a rare precursor of papillary carcinoma. These lesions are currently, preferably endoscopically, resected upon diagnosis to prevent malignant degeneration, followed by prolonged follow-up due to a high risk of recurrence. However, existing guidelines do not account for competing mortality risks, which may be relevant in this typically older, comorbid population.

The aim of this study was to assess patients' general condition and comorbidities using the age-adjusted Charlson Comorbidity Index (ACCI), and to evaluate its impact on all-cause mortality. I conducted a retrospective study using data from two tertiary referral centers (Westmead Hospital, Sydney and Amsterdam UMC). Primary outcomes were ACCI scores and all-cause mortality in patients who underwent resection of papillary adenoma. We also analyzed the effect of symptoms on survival. Secondary outcomes included outcomes in patients who did not undergo resection and adverse events following endoscopic papillectomy (EP).

Five-year survival was significantly lower in patients with a high ACCI score (>5) compared to those with a low score (<4), independent of symptoms. Adverse event rates after EP were similar across ACCI groups, indicating that while EP is generally safe, its long-term benefit may be limited in patients with substantial comorbidity. These results suggest the ACCI may serve as a valuable tool to support individualized decision-making regarding treatment and follow-up strategies in patients with papillary adenomas. In asymptomatic patients with high comorbidity, a conservative approach may be appropriate, however, further research is needed to confirm this hypothesis.

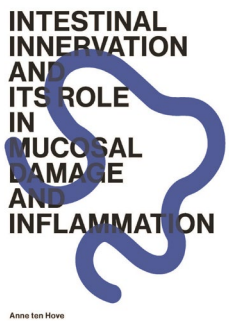
Ana Jiménez García

HLA-DRB-Associated Peptide Presentation and Its Role in Immunogenicity in IBD

Anti-TNF therapies, which have been in use for over 20 years in inflammatory bowel disease (IBD) management, continue to be widely regarded as first-line biological therapy for both Crohn's disease and Ulcerative colitis. However, almost half of the patients who respond will lose clinical benefits within the first year due to the development of antibodies against the drug molecule. These anti-drug antibodies (ADAs) are correlated with lower drug levels and treatment failure.
It is established that genetic predisposition related to antigen presentation to the immune system is associated with the development of ADAs. Genetic variation in the HLA-DR region, particularly the HLA-DRB1*01:03 allele, has been strongly associated with increased risk of ADA formation. While it is presumed that HLA-DR molecules may present anti-TNF drug-derived peptides to T cells, the broader context of how these HLA variants shape antigen presentation is poorly understood.

During my internship at the University of Oxford, we aim to characterize the naturally presented peptide repertoires of B cells and PBMCs from IBD patients carrying either the risk allele (HLA-DRB1*01:03) or the control allele (HLA-DRB1*01:01), using high-resolution Astral mass spectrometry.
By comparing the peptide landscapes presented by these HLA variants, we hope to uncover fundamental differences in immune presentation that may predispose risk allele carriers to enhanced immunogenicity, potentially explaining why they more frequently develop ADAs against biologic therapies. These findings could contribute to future strategies aimed at predicting ADA risk and designing less immunogenic biologics.

The AGEM contribution printing costs of theses 2024 (€250)

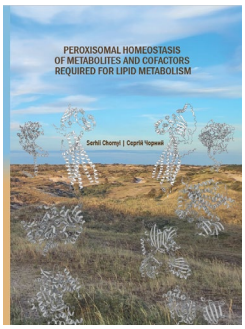


Anne ten Hove

Date of defense: January 12th, 2024

Intestinal innervation and its role in mucosal damage and inflammation

The regulatory role of the autonomic nervous system in intestinal inflammation and immunity is widely acknowledged. In this thesis, we investigated mediating pathways and demonstrated a pivotal role for the spleen. Further, we elucidated effects of sympathetic activity on intestinal mucosal homeostasis. Chemical sympathetic denervation led to enhanced intestinal inflammation, and impaired barrier integrity. In contrast, alpha2A specific adrenergic receptor stimulation led to increased proliferation and stem cell function.

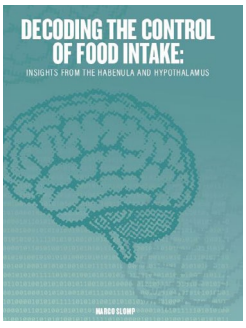


Serhii Chornyi

Date of defense: January 16th, 2024

Peroxisomal homeostasis of metabolites and cofactors required for lipid metabolism

The work presented in this thesis relates to two biochemical pathways: fatty acid beta-oxidation and de novo ether lipid synthesis. Enzymes involved in these pathways are localized in a single-membrane-bounded organelle called peroxisome. The peroxisomal membrane forms an impermeable barrier for most of the precursors and products of the biochemical pathways, and thus they have to be transported by specialized membrane proteins or converted to smaller metabolites inside the peroxisomal lumen. This thesis describes how certain metabolites, NAD(H) and CoA esters of fatty acids, are transported through the peroxisomal membrane and how a dysfunction of the transport affects peroxisomal metabolism.

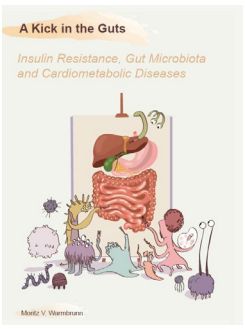


Margo Slomp

Date of defense: January 19th, 2024

Decoding the control of food intake: Insights from the habenula and hypothalamus

This thesis focused on the habenula and hypothalamus, two brain regions important for reward in general and food intake specifically. We studied the response of lateral hypothalamic neurons to sucrose drinking and how this was affected by a high-fat diet. Next, we focused on the lateral habenula and described that specific input from the central amygdala affects palatable intake. Finally, to add translational knowledge, we investigated the functional connectivity of the habenula in humans.

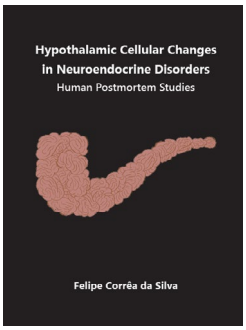


Moritz Warmbrunn

Date of defense: February 2nd, 2024

A Kick in the Guts: Insulin Resistance, Gut Microbiota and Cardiometabolic Diseases

In this thesis, we show that bacteria in the gut affect many aspects of health in prediabetes, diabetes and cardiovascular diseases. For example, we show that supplementation of the amino acid histidine, which is abundant in foods high in proteins such as nuts and meat improves blood sugar in patients with diabetes. This knowledge can help future diabetes patients to improve their diet and prevent disease complications.

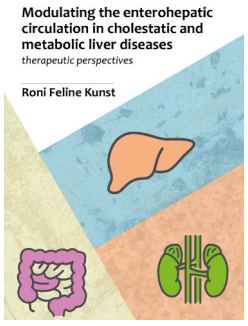


Felipe Correa da Silva

Date of defense: March 4th, 2024

Hypothalamic Cellular Changes in Neuroendocrine Disorders: Human Postmortem Studies

Hypothalamic dysfunction in Prader-Willi Syndrome (PWS) and type 2 diabetes mellitus (T2DM) was investigated using molecular and histological analyses of human postmortem tissue. We identified (1) disrupted circadian machinery and (2) cell-specific changes in PWS linked to subgenotypes, suggesting the need of personalized treatments. T2DM involves loss of oxytocinergic neurons, gliovascular uncoupling, and altered tanycytic lipid metabolism. These findings bridge animal model insights with human pathology, revealing cellular mechanisms underlying neuroendocrine metabolic disorders.

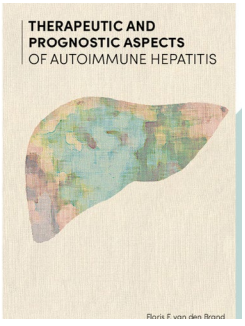


Roni Kunst

Date of defense: March 7th, 2024

Modulating the enterohepatic circulation in cholestatic and metabolic liver diseases: therapeutic perspectives

The enterohepatic circulation describes the circulation of bile salts from the liver towards the gall bladder, followed by the small intestine and the via the portal vein back to the liver. This process is driven by the presence of multiple bile salt transporters. In this thesis, we describe how modulating the enterohepatic circulation can contribute to treatment strategies against cholestatic and metabolic liver diseases.

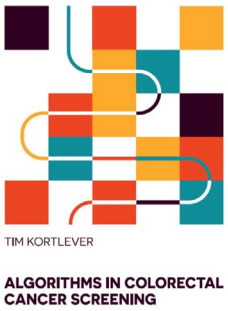


Floris van den Brand

Date of defense: April 8th, 2024

Therapeutic and prognostic aspects of autoimmune hepatitis

This thesis provides clinical insights for physicians treating autoimmune hepatitis by focusing on clinical aspects of autoimmune hepatitis regarding the prognosis, management and potential therapeutic targets, and assesses a web-based patient registry to facilitate for future studies.

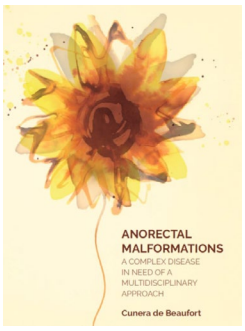


Tim Kortlever

Date of defense: April 10th, 2024

Algorithms in colorectal cancer screening

Screening for colorectal cancer (CRC) with the faecal immunochemical test (FIT) lowers the risk of CRC diagnosis or death. FIT is not optimal in detecting (pre)cancerous lesions. Algorithms that combine FIT with other markers for CRC may improve the yield of screening. This thesis examines several algorithms trialed in real-world screening programs. We found that the tested algorithms did not lead to an improved yield. Finding better working combinations should now be prioritized.

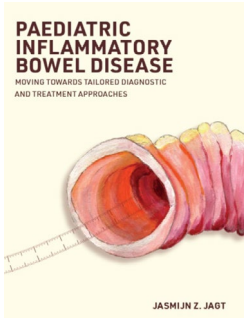


Cunera de Beaufort

Date of defense: April 19th, 2024

Anorectal malformations: a complex disease in need of a multidisciplinary approach

Research described in this thesis, entitled 'Anorectal malformations: a complex disease in need of a multidisciplinary approach', aimed to contribute to improvements in understanding of patient characteristics and complex additional anomalies that might be present in patients with anorectal malformations (ARM). Furthermore, despite available proposition papers, problems when entering primary school and the implementation of transition of care to adulthood were enlightened.

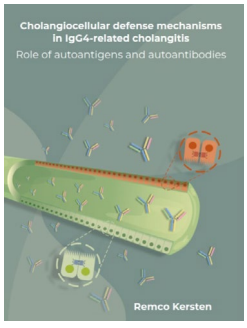


Jasmijn Jagt

Date of defense: April 26th, 2024

Paediatric inflammatory bowel disease: Moving towards tailored diagnostic and treatment approaches

This thesis aimed to investigate the role of the faecal gut microbiota and metabolomics in the pathophysiology of paediatric IBD. We explored whether changes in microbial and metabolomic profiles could develop into non-invasive diagnostic biomarkers (Part I). Additionally, we aimed to evaluate and optimise current treatments with thiopurines and infliximab. Also, we evaluated the Dutch clinical practice regarding surveillance strategies in children with UC (Part II). In the final part of this thesis (part III), we aimed to create a shared research agenda from the point of view of patients, caregivers, and healthcare professionals.

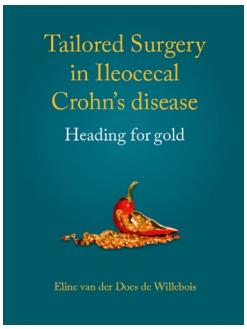


Remco Kersten

Date of defense: May 22nd, 2024

Cholangiocellular defense mechanisms in IgG4-related cholangitis: Role of autoantigens and autoantibodies

This thesis investigates IgG4-related cholangitis, a disease of the bile ducts that leads to extensive scarring and inflammation of these bile ducts. In IgG4-related cholangitis, antibodies were discovered that are directed against proteins of our own bodies. Here we demonstrate that some of these proteins play a protective role in bile duct cells and that autoantibodies can (potentially) inhibit these protective roles.

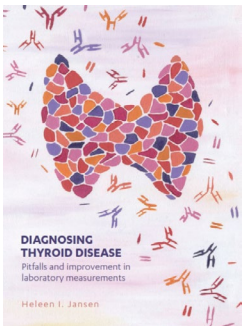


Eline van der Does de Willebois

Date of defense: May 24th, 2024

Tailored surgery in ileocecal Crohn's disease: heading for gold

Crohn's disease is a chronic inflammatory bowel disease that has a serious impact on the quality of life of a young population. This thesis entitled "Tailored surgery in ileocecal Crohn's disease – heading for gold", aimed to improve postoperative outcomes for IBD patients. In part I the role of the mesentery in IBD was investigated and part II discusses the challenges of adequate endoscopic scoring of disease recurrence. Finally, part III investigated the clinical relevance of an inflamed appendix in patients with ileocecal Crohn's disease.

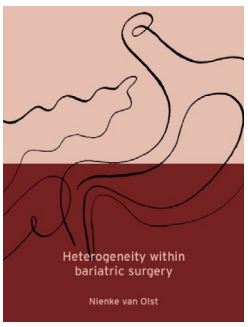


Heleen Jansen

Date of defense: June 11th, 2024

Diagnosing thyroid disease: pitfalls and improvement in laboratory measurements

This thesis demonstrates the extensive scope of laboratory measurements in diagnosing thyroid disease and its tendency towards a more personalized diagnostic approach. It shed light on potential pitfalls in specific populations and improvement opportunities. Lastly, the crucial interface between laboratory medicine and patient care was highlighted. The thesis emphasizes that collaboration between laboratory specialists and requesting medical specialists is vital for achieving optimal thyroid care.



Nienke van Olst

Date of defense: June 21st, 2024

Heterogeneity within bariatric surgery

This thesis covers various topics within the field of bariatric surgery: incretins, bile acids and the microbiome after bariatric surgery, the best surgery for patients with diabetes mellitus type 2, differences between men and women, and total weight loss. In the second part we dive into the topic of abdominal pain after bariatric surgery. What are the most common diagnoses and diagnostic tests and what is the role of pancreatic insufficiency and the microbiome.

Koos de Wit

Date of defense: June 27th, 2024

Risk factors and therapeutic interventions for decompensated cirrhosis affecting the gut-liver axis

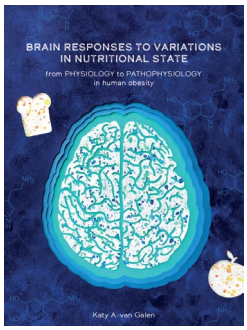
Koos de Wit performed research on risk factors and therapeutic interventions affecting the gut-liver-brain axis in patients with cirrhosis. In part 1, several cohorts of patients with complications of portal hypertension due to liver cirrhosis were studied. In part 2, the drug rifaximin was studied. The effects known in literature were systematically reviewed and the effects on human small intestinal cells were investigated. In the last part, various biomarkers in patients with liver cirrhosis were investigated.

Sabrina Oussaada

Date of defense: June 28th, 2024

Beyond the Scale: Novel Treatment Strategies and Health Impacts of Obesity

This thesis explores obesity as a chronic condition resulting from energy imbalance, leading to fat accumulation, and increased metabolic disorder risks. While some causes of obesity are understood, mechanisms driving excess intake remain elusive. The thesis investigates drug treatments like lorcaserin, vitamin D's role, and the link between obesity, inflammation, and insulin resistance. It highlights bariatric surgery's benefits and the impact of obesity on COVID-19 severity, emphasising personalised treatment approaches based on metabolic and genetic factors.

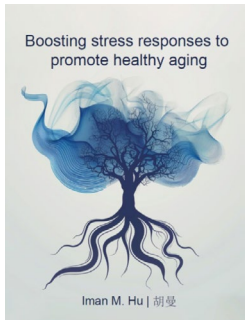


Katy van Galen

Date of defense: June 28th, 2024

Brain responses to variations in nutritional state: From physiology to pathophysiology in human obesity

Significant strides have been made in understanding how the brain regulates food intake and how disruptions lead to overeating and obesity. Most insights come from rodent studies, necessitating human context translation amid the global obesity crisis. This thesis aimed to enhance understanding of food intake regulation and brain mechanisms underlying obesity in humans, highlighting obesity as a condition where brain control over food intake is compromised. It examines cerebral responses to nutritional changes in humans with a healthy weight and humans with obesity. Our findings highlight the complexity of obesity and the need for multifaceted interventions.

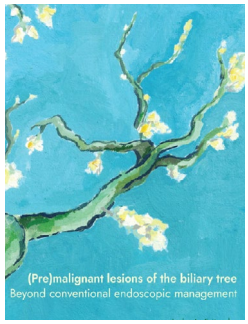


Iman Hu

Date of defense: September 19th, 2024

Boosting stress responses to promote healthy aging

Iman is focused on better understanding stress responses and how to leverage them to promote healthier living. During her Phd, she led several projects that combined computational and experimental approaches to investigate mitochondrial function and stress responses in aging, using model organisms such as C. elegans and mice.

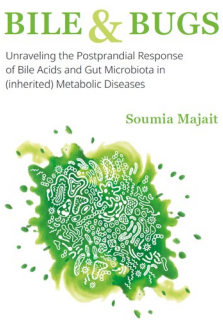


Jeska Fritzsche

Date of defense: September 20th, 2024

(Pre)malignant lesions of the biliary tree: Beyond conventional endoscopic management

Patients with (pre)malignant lesions of the biliary tree often present with biliary obstruction requiring endoscopic biliary drainage. This thesis explores clinical research aimed at optimising conventional endoscopic management of these lesions and beyond. It covers potential improvements in the treatment of papillary adenomas (a precursor lesion of periampullary carcinoma), the development of a new method to drain the bile duct using endoscopic ultrasound to create a new anastomosis (eus-guided choledochoduodenostomy), and advancements in the diagnosis and biliary drainage of intrahepatic and perihilar cholangiocarcinoma including the use of radiofrequency ablation inside the bile ducts.

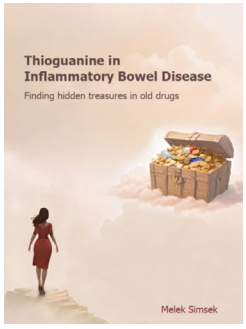


Soumia Majait

Date of defense: September 26th, 2024

Bile and bugs: Unraveling the postprandial response of bile acids and gut microbiota in (inherited) metabolic diseases

This thesis explores how bile acids (BAs) and gut bacteria work together to digest food. BAs help break down fats, but they also send signals to control how our bodies use energy. Gut bacteria can change BAs, which can affect these signals. This thesis studies how age, disease, and different diets can impact this process.

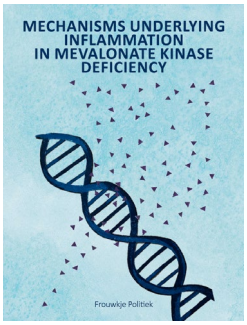


Melek Simsek

Date of defense: October 2nd, 2024

Thioguanine in Inflammatory Bowel Disease: Finding Hidden Treasures in Old Drugs

This thesis investigates thioguanine as a safe and effective treatment for inflammatory bowel diseases (IBD). Compared to azathioprine and mercaptopurine, thioguanine showed fewer side effects, with 80% of patients tolerating it well and 45% achieving steroid-free remission after 12 months. It also appeared safe during pregnancy, with outcomes similar to other thiopurines. Serious side effects, including liver toxicity, were rare at the current IBD dosing (0.2-0.3 mg/kg, maximum 25 mg/day).



Frouwkje Politiek

Date of defense: October 22nd, 2024

Mechanisms underlying inflammation in mevalonate kinase deficiency

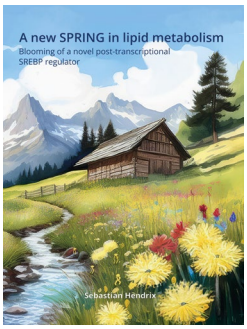
Mevalonate kinase deficiency is an autoinflammatory metabolic disorder caused by biallelic pathogenic variants in the MVK gene characterized by lifelong recurring and often unprovoked episodes of inflammation. This thesis reports the identification of several cellular processes and signaling pathways affected by mevalonate kinase deficiency in different cellular models, including patient-derived cells and CRISPR-CAS9-edited monocytic THP-1 cells. In addition, screening of a small compound library identified multiple compounds that increased mevalonate kinase levels in patient fibroblasts.

Jamie van Son

Date of defense: November 6th, 2024

From gut to brain: Exploring mechanisms and therapeutic targets of obesity

This thesis explores the pathogenesis and consequences of obesity, aiming to enhance prevention and treatment strategies. Part I discusses obesity's impact during illnesses like COVID-19. Part II studies the gut-brain axis and its role in metabolic health, linking imidazole propionate to blood pressure. Part III examines the relationship between autophagy and insulin sensitivity in obesity. Part IV focuses on the brain, exploring increased food cravings in obesity and bromocriptine's effects on glucose metabolism and central dopamine.

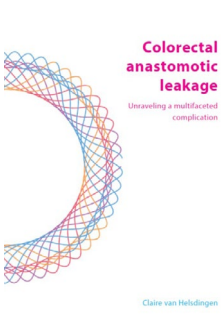


Sebastian Hendrix

Date of defense: November 6th, 2024

A new SPRING in lipid metabolism: Blooming of a novel post-transcriptional SREBP regulator

Cholesterol and fatty acids are essential fats for cell function that must be tightly regulated to prevent diseases like heart problems and cancer. This thesis identifies a protein called SPRING that helps control cholesterol and fatty acid levels by influencing the SREBP transcription factors responsible for these processes. Experiments show that without SPRING, SREBP activity decreases, lowering fat production and protecting against liver fat buildup. This research could lead to new treatments for lipid-related diseases.



Claire van Helsdingen

Date of defense: December 13th, 2024

Colorectal anastomotic leakage: unraveling a multifaceted complication

Colorectal anastomotic leakage is a serious and potentially life-threatening complication following colorectal surgery. It occurs when a newly created bowel connection (anastomosis) does not heal properly, leading to leakage of bowel contents into the abdominal cavity. This thesis investigates preoperative predictive factors to identify at-risk patients, evaluates new diagnostic biomarkers for earlier and more accurate detection and delves into the underlying biological processes of healing and leakage. By understanding these issues, surgeons can improve outcomes for patients undergoing colorectal surgery.

Events 2024

AGEM PhD candidate course

AGEM PhD candidate course 2024

Wednesday January 17th – Wednesday January 24th 2024

Amsterdam UMC, location AMC, Amsterdam

From Wednesday January 17th till Wednesday January 24th AGEM organized the AGEM PhD candidate course for the fourth time. 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 Annemieke Heijboer and Hilde Herrema and 15 teachers gave lectures during the course.

Wednesday through Friday of 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 intestinal diseases to organoids as model system for GI research, from transgender care to imaging techniques for insulin resistance, and from inborn errors of metabolism to macrophage metabolism.

During the course, eight interdisciplinary teams collaborated to develop a 1,500-word research proposal and craft a compelling pitch to present their ideas. All groups skillfully applied the insights they learned from the pitch workshop and pitched their proposals to all participants on the last day of the course.

This year, group D (Left: Jarne Jermei, Tianqi Mu and Miriam van der Werf) gave the best pitch and group H (Right: Karlijn Koops, Romy de Kroon and Han Jiao) wrote the best proposal.

AGEM annual retreat

AGEM retreat 2024

Thursday March 14th & Friday March 15th 2024

Bilderberg Hotel 't Speulderbos, Garderen

The AGEM Retreat 2024 took place on Thursday the 14th and Friday the 15th of March, 2024, at Bilderberg Hotel 't Speulderbos. The goal of the AGEM Retreat was for AGEM researchers, mainly PhD candidates, to meet their peers, to familiarize themselves with other research projects within the AGEM research institute, and to practice presenting their own research at a scientific conference. During three plenary sessions and two parallel sessions spread over two days, all PhD candidates and postdocs had the opportunity to present their own research to their peers. The presentation sessions were accompanied by interesting talks from keynote speakers.

On Thursday morning, Sue Gibbs, professor of Regenerative Medicine at the Amsterdam UMC who recently received the prestigious Willy van Heumen lifetime achievement award, gave a fascinating talk about innovative ways to replace animal models. An enlightening out-of-the-box lecture about AI possibilities in healthcare was given by Professor of Translational AI in Laboratory Medicine Martijn Schut. In addition, AGEM retreat participants could choose from one of five workshops, including workshops with research-related content like valorization and improving presentation skills, but also creative workshops such as action painting. Participants also got the chance to network with each other during a 'speed dating' workshop.


That's all Folks!

New this year was an organized forest walk in the foresty surroundings of the Veluwe near the Speulderberg, to provide some time for relaxation and networking among researchers. Additionally, more time was allocated for breaks in general, with the aim of improving participants' focus during the sessions. In the evening, participants enjoyed some friendly competition during the pub quiz, with a prize awarded to the esteemed winners. The evening concluded with a party themed 'Childhood Dream Job,' featuring a DJ.

On early Friday morning, a swimming bootcamp was conducted by two athletic committee members, followed by an interesting keynote lecture by Professor of Clinical Endocrinology Peter Bisschop. He discussed the effects of menopause on bone health, endocrine health, and metabolic health, as well as his efforts to improve health outcomes in perimenopausal women. After the last plenary presentation session, it was time to conclude this year's successful retreat with an award session!

The prize winners of the AGEM retreat 2024:

- Best classical presentation: Berith Balfoort
- Best elevator pitch: Etienne Slapak
- Best poster presentation: Lauri Borghuis
- Most contributing participant: Iman Hu
- Best outfit: Amber Mater (Frida Kahlo)

AGEM meetings 2024

AGEM symposium: "MASLD: gearing up for an ever more prevalent liver disease"

Thursday March 21st, 2024

Amsterdam UMC, location AMC, Lecture Hall 4, Amsterdam

On Thursday March 21st the third edition of the MASLD symposium was organized by the MASLD-NL consortium in collaboration with the AGEM research institute.

The symposium covered the full translational spectrum focused on 'MASLD: gearing up for an ever more prevalent liver disease'. During this symposium, five renowned speakers in the MASLD field shared their research. Prof. Lise Lotte Gluud form the Copenhagen University Hospital discussed the clinical and scientific challenges in the field of MASLD . Dr Geurt Stokman from TNO Metabolic Health Research talked about the technological advancements in MASLD research. Prof. Ellen Blaak from Maastricht University gave a presentation on metabolic phenotyping and precision nutrition in MASLD. Prof. Max Nieuwdorp from the Amsterdam UMC discussed MASLD and the gut-liver axis, and Prof. Vlad Ratziu for the Sorbonne University Paris presented the latest developments in pharmacotherapy for MASLD.

The rest of the program was filled with talks by other junior experts in the field. Arty Kovynev described the different effects of late versus early exercise training on MASLD. Hester van Mourik talked about extracellular cathepsins. Stan Driessen told us about the implementation of a comprehensive care path for MASLD, and patients screening on MASH was discussed by Vivian de Jong. The evening ended with a delicious networking dinner.

Young AGEM career lunch

Thursday April 11th, 2024

Amsterdam UMC, location AMC, K01-222-1, Amsterdam

On Thursday April 11th from 12.00-13.00hrs the Young AGEM committee organized her first event: the Young AGEM career lunch.

Dr. Eveline Bruinstroop (top), endocrinologist and clinical researcher on hypothalamic control of lipid metabolism and dr. Bruno Sovran (bottom), basic science researcher on pediatric intestinal diseases and recently appointed assistant professor at Emma Centre for Personalized Medicine elaborated on their career path and experiences thus far. Topics that were addressed varied from how to combine research with family/private life to the challenges that occur during the process of applying for grants. Afterwards plenty of questions were asked, accompanied by delicious sandwiches.

AGEM PI event “Advanced Diagnostics”

Thursday April 25th, 2024

Volkshotel, Amsterdam

On Thursday April 25th the second AGEM PI event “Advanced Dianostics” was organized. Around 20 AGEM principal investigators met up at the Volkshotel, this time to discuss their research related to “Advanced Dianostics”. The aim of the evening was to find thematic connection and synergies specifically within AGEM.

Researchers that were invited to present, informed the others on the existing research through various pitches on screening, diagnostics and/or monitoring. After the presentations given by Annemieke Heijboer, Gajja Salomons, Fred Vaz, Tim de Meij and Mark Lowenberg, more in depth discussions and networking were facilitated during a walking dinner with delicious bites.

AGEM Grant Award Ceremony

Thursday May 23rd, 2024

Amsterdam UMC, location AMC, Fonteynzaal, Amsterdam

Thursday May 23rd AGEM organized the very first Grant Award Ceremony! It was a fun event where the winners of the Innovation grants and the Talent Development grants were officially awarded their prizes

The program was further filled up by the Best Publication 2023 Battle and talks by three AGEM grant laureates: Eveline Bruinstroop, Joep Grootjans and Georges Janssens.

The award winners were:

- Innovation grant winners: Eefje Belt-van Zoen, Daniël Docter, Sofieke de Jonge, and Patrick van der Zande
- Talent Development grant winners: Anne van der Spek, Mohammed Ghiboub and Tim de Meij
- Best Publication 2023 winner: Sebastian Hendrix. Other nominees: Katy van Galen and Heleen Jansen.

AGEM symposium: "Food for Life"

Thursday October 10th, 2024

De Nieuwe KHL, Amsterdam

On Thursday October 10th the AGEM symposium: "Food for Life" took place in De Nieuwe KHL in Amsterdam. The afternoon was filled with talks on Perioperative nutrition, Early life nutrition and Chronic diseases & nutrition.

Greet van den Berghe (KU Leuven) talked about epigenetics and long-term effects of ICU nutrition. Hans van Goudoever (Amsterdam UMC) gave a presentation on the power of early nutrition for preterm and term born infants. Clara Belzer (WUR) discussed the nature and nurture of our microbiome. Dietary therapy for Crohn's disease was addressed by Nikki van der Kruk (Amsterdam UMC). And Emanuel Canfora (Maastricht University) explained how microbial metabolites are in control of body weight and insulin sensitivity. Arjen Brussaard ended the program with a pitch on valorization.

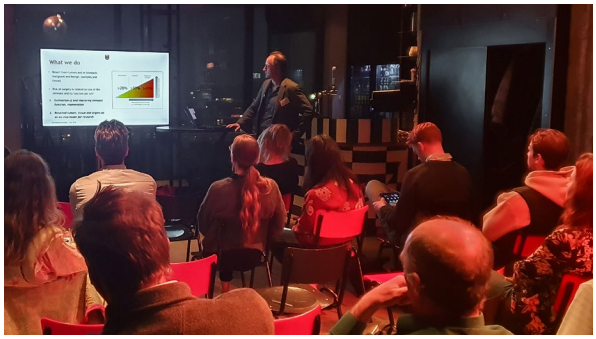
A special thanks to Stan van de Graaf and Ric van Tol for organizing and moderating the event.

The afternoon was concluded with a delightful vegetarian dinner, offering ample opportunity for fruitful networking.

AGEM PI event “Liver disturbances”

Thursday November 7th, 2024

Volkshotel, Amsterdam



On Thursday November 7th AGEM organized the third AGEM PI event! This time the theme was “Liver disturbances”, which resulted in six very diverse and interesting pitches by Anita Boelen (right), Noam Zelcer, Stan Van De Graaf, Zhixiong Ying (for Piter Bosma), Bart Takkenberg and Joris Erdmann (right).

Our goals to increase the awareness of research done by AGEM, network, and increase the AGEM community feeling were met and facilitated by the delicious walking dinner supplied by the Volkshotel!

AGEM – CCA symposium: "HPBetter Symposium 2024 / Together we can make HPB treatments better"

Friday November 22nd, 2024

O|2 building, Amsterdam UMC

On Friday November 22nd, the HPBeter multidisciplinary congress brought together diverse group of healthcare professionals. This congress day was organized to discuss, inspire and improve research projects and healthcare in the hepatopancreatobiliary (HPB) field.

The day was structured into four thematic sessions: colorectal liver metastases, primary liver diseases, and both malignant pancreatic and biliary diseases and benign HPB conditions. Each session was moderated by chairs who guided the discussions. Presentations ranged from clinical trials to fundamental research, alternated with healthcare pathways, case presentations and healthcare challenges. This comprehensive approach ensured that participants left with both a deeper understanding of the latest innovations and practical insights for daily practice.

It was a very well visited day, attracting healthcare professionals as well as researchers, medical specialists, residents (AIOS/Fellows), and nurse practitioners from all different fields. This year we also saw an increased attendance of care professionals from peripheral hospitals. The engagement and enthusiasm from this broad spectrum of participants contributed to the success of the day.

The day ended with a keynote presentation by Professor Sjoerd Repping, chairman of ZE&GG (Zorgevaluatie en Gepast Gebruik) at the Zorginstituut Nederland. His talk was both confronting and inspiring, challenging us to critically reflect on the type of research we conduct and the barriers we face when implementing our study results. By sharing his team's work on healthcare evaluation and appropriate use, Sjoerd Repping offered insights and inspiration for the future.

AGEM seminar series 2024

AGEM Tager Lectures

The AGEM research institute has a seminar series in the Amsterdam UMC, location AMC, focused on metabolism and endocrinology; 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, Noam Zelcer and Eveline Bruinstroop. Suggestions for future speakers for the Tager lecture are always welcome.

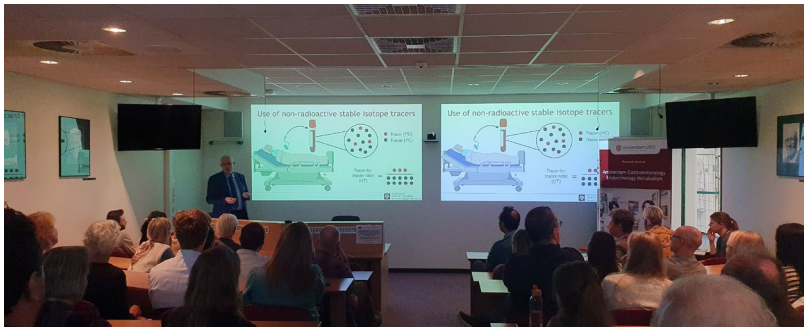
Tuesday January 9th, 2024

Amsterdam UMC, location AMC

Prof. dr. Nicolaas Deutz

Health & Kinesiology, Texas A&M University

"Stable isotope methods in human clinical research"



Thursday March 7th, 2024

Amsterdam UMC, location AMC

Dr. Sean Froese

Division of Metabolism, University Children's Hospital, Zurich

"Inborn disorders of folateand vitamin B12 metabolism: causes, consequences and the push for novel treatments"

Thursday May 23rd, 2024
Amsterdam UMC, location AMC

Prof. dr. Tony Lam

Toronto General Hospital Research Institute & University of Toronto

"A kidney-brain axis regulates food intake and body weight"

Tuesday July 2nd, 2024
Amsterdam UMC, location AMC

Prof. dr. Michela Deleidi

Laboratory of Mechanisms and Therapy of Genetic Brain Diseases, Institut Imagine, Paris

"Investigating Genetic Brain Diseases using Brain Organoids"

Thursday October 3rd, 2024
Amsterdam UMC, location AMC

Prof. dr. Kerstin Stemmer

Institute of Theoretical Medicine, University of Augsburg, Germany

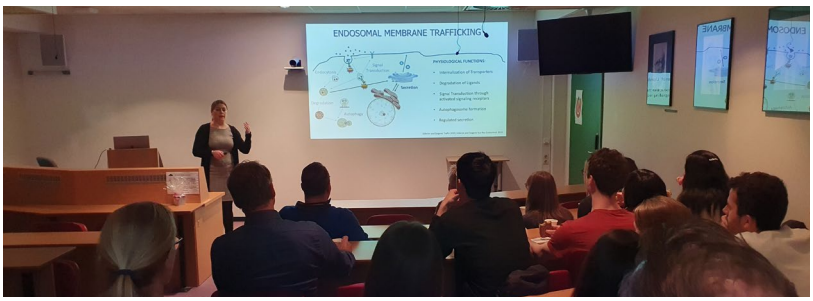
"Extracellular Vesicles: Emerging Key Players in Metabolic Diseases"

Thursday November 28th, 2024
Amsterdam UMC, location AMC

Prof. dr. Anja Zeigerer

Medical Faculty Mannheim and The European Center for Angioscience, University of Heidelberg, Germany

"Coupling membrane transport to metabolic control"



ImmunoMetNet Amsterdam UMC meetings 2024

Since 2022 ImmunoMetNet AUMC organizes a local ImmunoMetNet AUMC series where "young" Amsterdam UMC researchers from distinct disciplines and research institutes can present immunometabolism-related work. Hereby, the aim is to share expertise, tools and samples across the borders of the distinct Amsterdam UMC research institutes with immunometabolism as the unifying factor.

Tuesday January 30th, 2024

Amsterdam UMC, location AMC, Costerzaal, Amsterdam

The first meeting of ImmunoMetNet AUMC series of 2024 took place at location AMC (Costerzaal) on the 30th of January, where a crowd of about 30 researchers met and got to know the projects of four new young speakers of the network:

- Kaspar Bresser (Sanquin Research), postdoctoral researcher in the group of Monica Wolkers, opened the session with his preliminary work on metabolic enzymes as potential rheostats in T cell. dysfunction, a project for which he recently was awarded a CCA grant.
- Nico Hahn (AGEM/ACS), PhD candidate in the group of Jan van den Bossche, shared with the audience their most recent data on modulation of macrophages by metabolic interventions.
- Ramin Raoof (CCA), postdoctoral researcher in the group of Tuna Mutis and Niels van de Donk, provided a summary of a recently completed project on the role of monocytes in controlling cancer cell metabolism in multiple myeloma.
- The session was closed by Crescenzo Massaro (CCA), postdoctoral researcher in the group of Rubina Baglio, with their first results on high-dimensional immunometabolic profiling using spectral flow analysis with the aim of better personalizing the treatment for cancer patients.

As usual, AGEM organized a very nice catering afterwards where we could enjoy drinks and food while discussing with the participants.

Tuesday September 24th, 2024

Amsterdam UMC, location AMC, Costerzaal, Amsterdam

On the 24th of September, the last ImmunoMetNet AUMC Seminar of 2024 was held in the Costerzaal at location AMC with around 30 attendants and four junior researchers as speakers.

- Yumna Butt, PhD student in the group of Iosifina Foskolou at Sanquin, shared their data on the role of m6A RNA metabolism on T cells.
- Nina Mezgec Mrzlikar, PhD student in the group of Joep Grootjans at AMC/VUmc, gave a talk on metabolic profiling of human peritoneal macrophages, with the specific aim of finding novel treatment targets for peritoneal metastasized cancer.

- Beatriz Fernandes Corte-Real, postdoc in the group of Jan Van den Bossche at VUmc, presented the Metabocode, which consists of the characterization and modulation of the metabolism of tumor-associated macrophages.
- Daan Kloosterman, PhD in the group of Leila Akkari at NKI, shared a story on macrophage-mediated recycling of cholesterol-rich myelin debris, which fuels brain cancer malignancy.

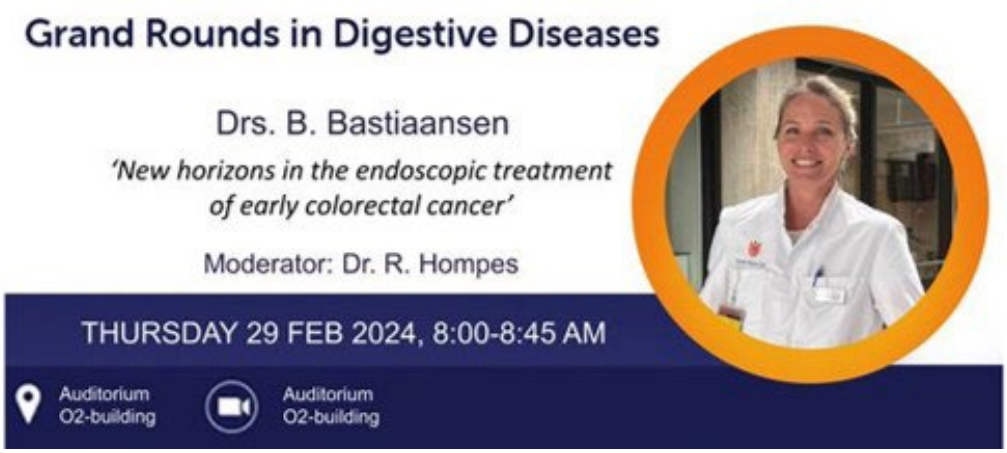
The session was followed by casual discussion over bites and drinks provided by AGEM.
Keep an eye on www.immunometnet.com and the @immunometnet Twitter profile or reach out to immunometnet@amsterdamumc.nl for more information on future ImmunoMetNet seminar series!

Grand Rounds in Digestive Diseases 2024

From the origins of colorectal cancer, to duodenal resurfacing for the treatment of diabetes or spatial omics to decipher the role of macrophages in liver disease. These are just a few examples of the series of lectures organized by the Department of Gastroenterology & Hepatology, entitled 'Grand Rounds in Digestive Diseases'.

In monthly Thursday morning sessions, top-level scientists from the Amsterdam UMC and beyond provide a broad audience with an overview of the recent scientific advances in their research field. In addition to purely scientific Gastroenterology & Hepatology-related presentations, sometimes more general topics are covered.

These series of lectures have been initiated by Prof. Geert D'Haens and Dr. Joep Grootjans from the department of Gastroenterology & Hepatology. Topics are selected by a steering committee which includes clinical and basic scientists from the departments of Surgery, Paediatrics, Radiology, Pathology and the Tytgat Institute. The Grand Rounds are hosted both on-site at location VUmc (Auditorium, O2-building) and online via zoom Thursday mornings from 8.00AM to 8.45AM.



Thursday February 29th 2024	**Barbara Bastiaansen** New horizons in the endoscopic treatment of early colorectal cancer
Thursday March 28th 2024	**Jacco van Rhenen** Intravital microscopy of GI cancer
Thursday April 25th 2024	**Gijs van den Brink** Facing fearful odds: turning molecules into medicines
Thursday May 30th 2024	**Lissy de Ridder** Investigator Initiated Research in the paediatric IBD field

Thursday June 27th 2024	**Guus van Dongen** Fibrobodies and Fibrobody-Drug Conjugates: a vision for diagnosis and therapy of fibrosis
Thursday October 3rd 2024	**Myriam Chalabi** Immunotherapy for colorectal cancer: are we there yet?
Thursday October 24th 2024	**Mariëtte van den Hoven** Ethical dilemmas in Artificial Intelligence (AI)
Thursday November 28th 2024	**Geert Litjens** AI for GI: possibilities of computational pathology?
Thursday December 19th 2024	**Philip Chiu** Advancing Third Space Endoscopy – From Endoluminal to Full Thickness Resection

EKZ Grand Rounds & Inspirational Sessions

At the end of 2023, the science committee of the Emma Children's Hospital was established in order to organize the monthly Grand Rounds in Pediatric Research. These EKZ Grand Rounds provide a platform for the wonderful scientific projects and developments in and around the Emma Children's Hospital, as well as increase cooperation and visibility of (young) researchers. These Grand Rounds are open to all employees of the Amsterdam UMC. Especially the presence of the researchers, staff physicians and physician assistants at the Emma Children's Hospital is highly anticipated.

The EKZ Science Committee also organizes Inspirational Speaker Sessions on Pediatric Research. These sessions are for EKZ researchers, young and older, and all interested parties in Amsterdam UMC are welcome!

Organized by the EKZ Research Committee: ekzwetenschapscommissie@amsterdamumc.nl

Thursday January 11th, 2024

Grand Rounds: Charles Agyemang

Cardiometabolic disease burden in migrants in Europe – Lessons from the RODAM study

Thursday February 15th, 2024

Inspirational speaker: Joep Derikx

My career as pediatric surgeon

Thursday March 14th, 2024

Grand Rounds: BrainStormzy

Brainstorming session about the pilars of the EKZ Research Committee

Thursday April 18th, 2024

Inspirational speaker: Ruud van Leuteren

Technical physician with a focus on respiratory support and cardiorespiratory monitoring

Thursday April 25th, 2024

Grand Rounds: Arne Popma

Mental health life course: from the street corner to the Emma Children's Hospital

Thursday May 16th, 2024	**Grand Rounds: Rianne Teeuw** The 'Amsterdam' Social Pediatrics
Thursday June 20th, 2024	**Grand Rounds: Simone Sanna-Cherchi** Genetic dissection of pediatric kidney diseases
Thursday June 27th, 2024	**Inspirational speaker: Mariken Gruppen** Lifelong learning!
Thursday September 12th, 2024	**Grand Rounds: PhD Spotlight**
Thursday September 26th, 2024	**Inspirational speaker: Haunted house**
Thursday October 10th, 2024	**Grand Rounds: Karen Kruijthof & Willem de Vries** Opportunities and challenges – perspectives on tomorrow's care. Future of healthcare, Future of pediatrics
Thursday November 14th, 2024	**Grand Rounds: Lidewij Henneman** Patient perspective in screening around pregnancy and childbirth.
Thursday December 12th, 2024	**Grand Rounds: Wieger Voskuijl** Global Child Health

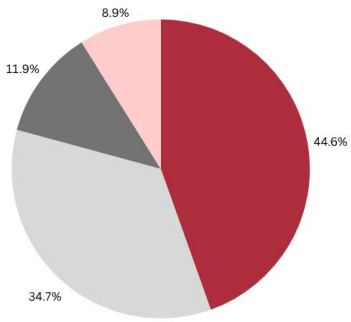
Numbers and Facts 2024

AGEM finances 2024

For 2024, the AGEM research institute was provided with €564.948 (€256.513 from VUmc and €308.435 from AMC). In the table below is shown how this money was spent. Most of the 2024 budget was used for the AGEM grants.

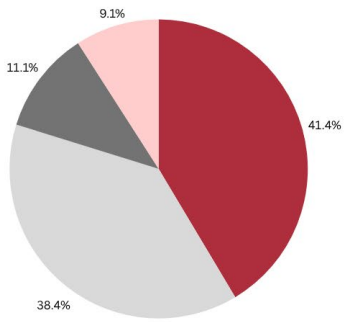
2022

Income	
AMC	€ 305.415
VUmc	€ 251.251
Total	€ 556.666



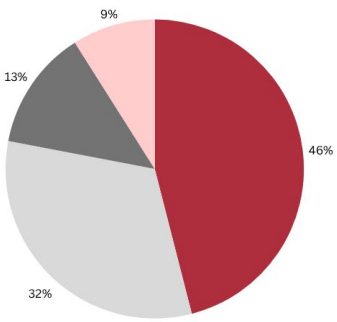
2023

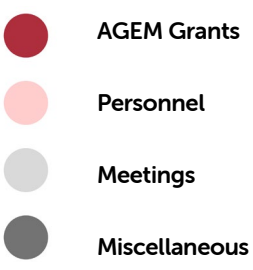
Income	
AMC	€ 305.415
VUmc	€ 253.838
Total	€ 559.253



2024

Income	
AMC	€ 308.435
VUmc	€ 256.513
Total	€ 564.948





AGEM numbers 2024

AGEM Reserachers

Information about the number of researchers affiliated with AGEM was collected using the Research Information Systems Pure Amsterdam UMC in May, 2025 and the AGEM administration. 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.

	2022	2023	2024
Principal Investigators	101	87	91
PhD Candidates	415	484	357
Other researchers	214	215	195
Total AGEM Researchers	**730**	**786**	**643**

AGEM Publications

The reported data include all published research output as registered in the Research Information Systems Pure Amsterdam UMC in May, 2025. 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. PhD-theses are ascribed to AGEM based on the affiliations of the supervisors. A thesis can be ascribed to one or more research institutes depending on the affiliations of the supervisors.

	2022	2023	2024
Refereed articles	1288	1182	1153
PhD-theses	92	120	103
Other publications	121	138	115
Total AGEM publications	**1501**	**1400**	**1371**

Appointed professors 2024

Prof. dr. Andreas van Kuilenburg

Enzymology of Metabolic and Oncological diseases

On May 1st, André van Kuilenburg was appointed as a full professor of Enzymology of Metabolic and Oncological diseases at the faculty of Medicine at the Vrije Universiteit (VU) Amsterdam. He delivered his inaugural lecture "The pivotal role of Enzymology in Inherited Metabolic Diseases" on September 20, 2024.

The pivotal role of Enzymology in Inherited Metabolic Diseases

There are currently more than 1,500 known inherited metabolic diseases, and as a group, they represent the leading cause of child mortality in the Netherlands. One in four children with a metabolic disorder does not reach the age of 18. More than 10,000 families are affected by the profound consequences of these diseases. In these conditions, the chemical factory of the cell and therefore the production and breakdown of building blocks and energy supply, is disrupted.

In metabolic diseases, a particular enzyme does not function properly, which can have serious consequences for metabolism. Enzymology allows us to determine which enzyme is malfunctioning and where precisely metabolism is failing. Being able to predict whether a patient will develop a mild or severe phenotype is important for the treating physician, and enzymology can help assist whether or not the patient should be treated and, if so, how.

Mucopolysaccharidose type 1

This is particularly the case for patients with mucopolysaccharidosis type 1 (MPS1). MPS1 is a lysosomal storage disorder which is included in the newborn screening program in the Netherlands, where newborn babies are tested for a number of inherited conditions that require treatment or intervention in the earliest stages of life to prevent serious complications or premature death.

MPS1, also known as Hurler-Scheie syndrome, is caused by a defect in the enzyme α-iduronidase. The severity of MPS1 can vary, depending on the degree of enzyme deficiency, from mild - called Scheie syndrome - to severe, known as Hurler syndrome. Patients with Scheie syndrome usually exhibit mild symptoms, such as joint stiffness, slight facial abnormalities, and reduced mobility. In patients with Hurler syndrome, brain function deteriorates at a certain point due to the accumulation of waste in the brain. Without treatment, these Hurler patients have a limited life expectancy and usually die in childhood.

Establish disease severity
For a newborn with a MPS1 deficiency, it is important for the physician to know whether the patient has the mild or severe form of MPS1, as this can have significant consequences for the patient and treatment. In the majority of cases, DNA analysis of the α-iduronidase gene, in conjunction with observed clinical abnormalities, can establish the severity of the disease, but not always. In those cases, sensitive enzyme diagnostics could help to determine whether the patient can be treated with enzyme replacement therapy, where a recombinant α-iduronidase is administered to the patient, or whether the more intensive and higher-risk stem cell transplantation is necessary.

Enzymology and new metabolic diseases
Enzymology is not only important for diagnosing known metabolic defects but can also help identify new metabolic diseases. When a metabolic disorder is suspected, genetic diagnostics, especially exome sequencing, are often used first. This technique enables the identification of alterations in more than 22,000 genes that could be responsible for the disease, allowing for an accurate diagnosis. This approach is successful in about 50 percent of patients with a suspected metabolic disorder, but not in the other half.

Glutaminase deficiency?
This was also the case with three young children, all of whom had delayed speech and language development and problems with balance and coordination. The only abnormality found in these three patients was a significantly elevated amount of the amino acid glutamine in their blood, which could suggest a deficiency in the enzyme glutaminase. This enzyme converts glutamine into glutamate, and if it is not functioning properly, glutamine can accumulate. However, a glutaminase deficiency had not been previously identified, and exome sequencing provided no indications for a glutaminase deficiency.

Genomic analysis
Therefore, we developed a method in our laboratory to measure glutaminase activity, which showed that this enzyme indeed does not function well in these three children. Subsequently, we studied the chemical processes in the patients' cells and analyzed the entire genome. In this way, we discovered that a piece of DNA, just before the so-called glutaminase gene, had multiplied, causing the gene to be switched off. With the multiplication, the DNA fragment had extended eight hundred to twelve hundred times its normal length. Such an extension is a unique finding, as diseases usually caused by deletions or loss of function variants in DNA.

To detect such extensions, you need to search among billions of DNA fragments—the proverbial needle in the haystack. Thanks to enzymology we knew where to look for the needle in this haystack, and it is the first time this type of DNA abnormality has been identified as the cause of a metabolic disease. In 2019, we published our study in the prestigious scientific journal The New England Journal of Medicine.

Conclusion
With the increasing use of DNA screening strategies, where large portions of the genome are analyzed, the likelihood of finding new or unclear variants also increases. The availability of enzymology is crucial as it provides direction for genome research: it allows for definitive conclusions whether or not a DNA change results in reduced enzyme function. Thus, the availability of enzymology enables us to provide personalized and improved care for each individual patient.

Prof. dr. Stephan Kemp

Inherited Neurometabolic Disorders and Newborn Screening

On July 1, 2024, Stephan Kemp was appointed full professor of Inherited Neurometabolic Disorders and Newborn Screening. He delivered his inaugural lecture "Boundless (Grenzeloos)" in the beautiful "Oude Lutherse Kerk" of the University of Amsterdam on January 29, 2025.

Newborn screening and the "grey zone"

Newborn screening is one of the most successful public health programs in the Western world. Newborn screening identifies individuals with conditions for which early diagnosis and effective treatment can have a significant impact on infant morbidity and mortality.

With medical tests such as genetic screening or blood work, we often expect a clear yes or no answer. But the reality is more complex. Genetic screening can also identify mild variants, non-disease variants, and variants of uncertain significance (VUS). Biochemical tests can produce results that fall into a "grey zone": higher than normal, but not high enough to be certain of the diagnosis. Identifying a VUS or grey zone value is challenging in terms of diagnostic uncertainty and confusion.

The fine balance between accuracy and reliability

In recent years, it has become clear that population screening, including newborn screening, is identifying genetic variants that were not previously identified, either because they were not associated with disease or because they are associated with mild symptoms at the extreme end of a clinical spectrum and went unnoticed.

Newborn screening uses dried blood spots to determine the levels of selected metabolites that may indicate the presence of a particular disorder. These tests typically have a predetermined cut-off level that is used to determine whether a result is considered screen positive or negative for a particular disorder. The cut-off for a newborn screening test determines the sensitivity and specificity of the test. Overall, for disorders in which an elevated metabolite is indicative of disease (such as elevated phenylalanine for babies with phenylketonuria), a lower cut-off may increase the sensitivity of the test and decrease the likelihood of missing a true positive result. However, it will also increase the number of false positives, including VUS and non-disease-causing variants. On the other hand, a higher cut-off may decrease the number of false-positive results but may also increase the likelihood of missing true positive results. Thus, there is a fine balance between the accuracy and reliability of the screening process.

While the goal of "not missing a patient" is understandable, the consequences of false positive results should not be underestimated. False positive results can lead to several negative outcomes, such as significant stress and anxiety for parents who may have to wait for additional testing to confirm the

diagnosis, increased health care costs, financial burden for families who may have to pay for additional testing, medical harm, and high false-positive rates can reduce public confidence in newborn screening programs; potentially leading to decreased participation and reduced effectiveness of the program.

Unbinding the boundaries of sick and healthy
Indeed, Stephan Kemp's research on newborn screening for adrenoleukodystrophy (ALD) illustrates the complexity of medical diagnosis and reminds us that the boundaries between 'sick' and 'healthy' are often more boundless (Grenzeloos) than we might think.

As newborn screening programs expand to include more treatable conditions, a shift to genetic screening becomes increasingly feasible as technology costs decrease. However, careful implementation is essential. The American experience demonstrates the risks of disrupting diagnostic pathways by outsourcing screening to commercial entities, potentially compromising the involvement of academic centers and metabolic experts.

A two-step approach - combining genetic testing with diagnostic biomarker determination – can distinguish between harmless and disease-causing DNA variants, avoiding unnecessary patient labeling while maintaining diagnostic accuracy.

This challenge underscores the importance of collaborative and innovative research. In this boundless quest for knowledge and improved care, we are reaching across national borders, sharing diagnostics and knowledge to improve patient care and minimize the impact of inconclusive results.

Did you know that...

... as of January 1st, 2024, **Nanne de Boer** has taken on the role of co-director of the AGEM research institute! Together with co-director **Anita Boelen**, he will build on the foundation that was laid by the previous directors **Stan van de Graaf** and **Gerd Bouma**.

... AGEM researcher and Young AGEM committee member **Anne van der Spek** was awarded a 25,000-euro Starting Grant from the Spinoza Fund of the Amsterdam University Fund (AUF) to investigate the changes in the gut microbiome and their impact on Graves' disease.

Picture made by: Van Harte Gefotografeerd

... AGEM co-director **Nanne de Boer** featured in the Janus magazine.

... the Dutch cabinet allocates €200 million for Holomicrobiome Institute. 'This unique initiative is an important impulse for the realization of a large, integrated national cohort and for the acceleration of new treatment methods from the microbiome', say AGEM researcher **Hilde Herrema** and endocrinologist Max Nieuwdorp (both Amsterdam UMC), initiators of the proposal for a Holomicrobiome Institute.

... AGEM PI **Joost Drenth** was appointed vice president of the UEG.

... gut bacteria mediate metabolism of dietary phytate in the human gut as explained by the article of AGEM researcher **Nam Bui**.

... the Young AGEM committee organized their first event: The Young AGEM Career Lunch.

... cofactors are the missing link between rare disorder phenotypes and a genetic diagnosis as described by the article of AGEM researchers **Clara van Karnebeek, Riekelt Houtkooper, Fred Vaz** and **André van Kuilenburg**.

... AGEM PI **Carla Hollak** was chosen as member of the KNAW.

...the AGEM Grant Award Ceremony was organized for the first time. With this, AGEM started a tradition we hope to continue for a long time. It is such a fun and festive event that celebrates our researchers in the way they deserve!

... **Chun-Xia Yi**, Associate Professor of Endocrinology and AGEM Principal Investigator, has been awarded a NWO Vici grant for her project "Unravelling microglial obesogenic memory underlying body weight rebound to combat obesity"?

... this year's 3FM Serious Request focused on metabolic diseases.

... Dr. Ir. **Hinke Kruizenga**, Dr. **Sabine Hannema**, Dr. **Joep Grootjans**, Dr. **Eveline Bruinstroop**, Dr. **Arwen Gao**, Dr. **Wendy den Elzen**, Dr. **Tineke Buffart**, Dr. **Joris Erdmann**, Dr. **Angelique de Man** were appointed as (AGEM) PI in 2024?

... fewer good gut bacteria increase the risk of serious infection as published in the article of AGEM researcher **Bob Kullberg**.

... AGEM researchers, **Fons van den Berg** and **Abraham Stijn Meijnikman**, have been awarded a NWO Veni grant for their projects "Darmflora bij acute alvleesklierontsteking; een potentieel nieuw medicijn?" and "Endogeen ethanol in leverziekte", respectively?

... hormone therapy reshapes the skeleton in transgender individuals who previously blocked puberty as AGEM researchers **Lidewij Boogers, Martin den Heijer, Paul van Trotsenburg**, and **Chantal Wiepjes** discuss in their paper.

Future perspectives

Spirits are high. The directors have just reflected on 2024 and seen that many good things happened within the institute. Riding this positive energy, they take a moment to look ahead at what's to come in 2025.

They begin with a personal note, musing on what they'd like to develop in their roles as directors. A new curriculum set up by central Amsterdam UMC will support this process, with all institute directors participating. de Boer sees it as a chance to tackle some specific growth points: "I'd like to improve how I give feedback in conversations, without it becoming unpleasant." Boelen approaches it more broadly: "Whichever aspects arise from the course, I think it will be good for us to improve on them."

Then it's on to AGEM's main priorities. de Boer opens with a grin: "World domination," he quips, as the room bursts into laughter. On a more serious note, Boelen reflects on AGEM's steady goals: "Organising strong symposia and good PI meetings. Basically, just putting together high-quality events." de Boer agrees, adding that it's important AGEM plays a role in identifying and supporting talent, particularly when it comes to HR policy. "We need to have a seat at the table, even if it's just an advisory role." Boelen says she finds it especially fulfilling to contribute to appointments within Amsterdam UMC, such as for PIs.

Another shared priority is strengthening internal collaboration. "What I also foresee for 2025 is more interaction between the different OZIs," Boelen says. de Boer adds, "That's also a result of the curriculum. Everyone sees its value. As OZIs, we'll start working together more, which will help us build momentum." He also believes it will lead to more research collaboration: "You'll find each other more easily."

The directors also acknowledge a few challenges. Financial shifts at central Amsterdam UMC mean institutes must find new ways to fund their business developers. "We looked at how other OZIs approached it and added our own personal twist," says de Boer. While AGEM has taken steps to address it, 2025 will be the year to evaluate outcomes. There's also the ongoing work on SEP recommendations. "We're gradually working through them, and we'll take more steps this year to ensure that continues."

If 2025 proves successful, the directors hope to look back on wise use of redistributed research institute funding. "I also find it very important that our research board would be satisfied," says de Boer. "And I'd like to reflect on the directors curriculum, and on any further developments in the Food for Life initiatives that AGEM set up."

Asked what they hope people will say about AGEM at the end of 2025, Boelen answers, "That it was another enjoyable AGEM year. And that the increased grants were helpful." de Boer adds, "That it was a year in which we were a reliable partner. That we helped people where it was needed."

That sentiment echoes what the directors said during their reflections on 2024: a research institute should offer researchers a sense of belonging and support.

de Boer closes the conversation with a final hope: "By the end of 2025, I hope people are proud to be part of AGEM. 'I belong to AGEM'—I've always liked that phrase."

Nanne de Boer, AGEM director
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