Amsterdam UMC
University Medical Centers

Amsterdam Gastroenterology Endocrinology Metabolism

AGEM Annual report 2022

Colophon

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Contents

Directors looking back

Reflecting on the events of 2022, the directors of the Amsterdam Gastroenterology Endocrinology Metabolism (AGEM) research institute agree that it was a year marked by both turbulence and excitement. After seven years of dedicated service, Professor Dr. Gerd Bouma stepped down as the director of the AGEM institute. In October, he was succeeded by Professor Dr. Anita Boelen from the Endocrine Laboratory. With this transition, the representation of endocrinology extends beyond the research board, as Professor Dr. Boelen assumes the role of AGEM director. Boelen enthusiastically embraced her new role, stating, "The first three months as director of AGEM have been truly exciting, and I look forward to the years to come."

In addition to the appointment of a new director, the AGEM institute expanded its team by welcoming Dr. Ric van Tol as a Business Developer and Maartje Schots as a second policy officer. With this strengthened team of five, the directors are invigorated by the renewed positive energy within the institute. "I am delighted that, after facing some challenges, we can now forge ahead with the AGEM institute," expresses Van de Graaf. The directors highlight that this progress has facilitated enhanced communication and engagement with AGEM researchers, as they seek input on the institute's current standing and areas for improvement. To this end, the AGEM institute initiated a project in collaboration with the consultancy firm Catalyze in 2022. This project involved a series of interviews and working sessions with AGEM Principal Investigators (PIs), focusing on the institute's mission, vision, and strategic plans for the upcoming years. "We are confident that this has fostered a stronger sense of involvement among our PIs," states Van de Graaf, "but it has also revealed that there is still much work to be done in the coming years."

Despite the challenges, the directors take great pride in the AGEM institute's accomplishments in 2022. One notable event was the Responsible Research Dinner Debate, where AGEM researchers from different departments and career stages came together to discuss ways to promote scientific integrity in their workplace. "This is an important theme, and we will certainly explore how we can integrate it into AGEM's policies," asserts Boelen.

Van de Graaf recalls the successful AGEM PhD retreat, held in March 2022, which took place in person after two years of online meetings due to the COVID-19 pandemic. "It was truly exciting," explains Van de Graaf, "as it was evident that everyone was eagerly looking forward to reconnecting face-to-face." The institute's concerns about the retreat becoming a potential super spreader event turned out to be unfounded. Van de Graaf chuckles, saying, "Fortunately, it seems we were spared by the annual skiing holiday outbreaks that occurred just before the AGEM retreat."

In addition to these events, the directors are pleased with the institute's ability to sponsor a Leadership course in Heidelberg for newly appointed AGEM group leaders. The participants in this year's course expressed great enthusiasm, as noted by Boelen, who affirms, "We will certainly continue offering this course in the future." Van de Graaf also highlights the successful symposium on Laboratory(free) animal research, which AGEM contributed to organizing. "This event resulted in the development of an informative website and an accompanying film," he adds.

In 2022, AGEM researchers received several significant grants, highlighting the institute's valuable research. Prof. Dr. De Jonge and Prof. Dr. Van Limbergen were awarded a TKI-PP grant, while Prof. Dr. D'Haens, Prof. Dr. De Jonge, and 17 partners secured a substantial €10.4 million grant for their "methylomic" study. "Successful applications for these competitive grants underscore the quality of our research and will even further boost our multidisciplinary IBD research," states Van de Graaf. Apart from these grants, the directors are also proud of other notable achievements by AGEM researchers. Prof. Dr. Van Karnebeek, for instance, was honored with royal recognition for her co-founding of the Jeroen Pit Huis, which opened in the summer of 2022. Additionally, Dr. Kemp completed a successful pilot study on sex-specific newborn screening for X-linked adrenoleukodystrophy – which has now been submitted at the Dutch Ministry of Health further implementation in the national screening program.

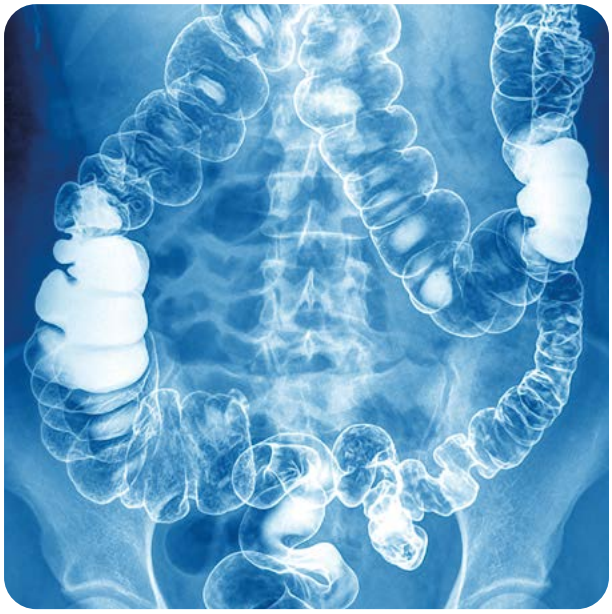
Considering all of these achievements, the directors are confident that 2022 was a fruitful year for the AGEM institute. "And as a testament to our progress, we have produced a beautiful annual report once again," concludes Boelen, "we hope everyone enjoys reading it!"

Prof. dr. Anita Boelen and Prof. dr. Stan van de Graaf

Research Programs

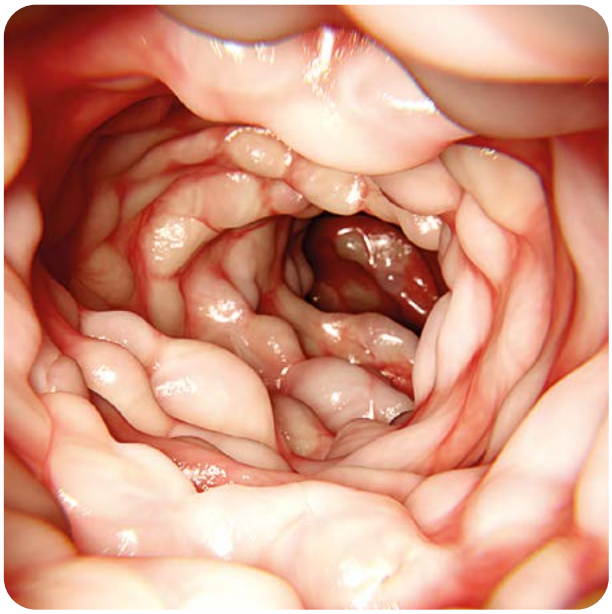
Based on an inventory of the strengths of the research in gastroenterology, endocrinology and metabolism conducted at the Amsterdam UMC, the following four research programs have been specified. Our aim is to stimulate research in these 4 themes, and also multidisciplinary research that bridges them.

1. Re-generation and neoplasms of the digestive system



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

2. Digestive function and pathology



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

3. Endocrinology, metabolism and nutrition

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

4. Inborn errors of metabolism

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

Research Board 2022

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

The AGEM research board 2022

New to the AGEM Research Board

Maartje Schots

Since June 2022, Maartje Schots joined the AGEM research board as AGEM policy officer. Maartje has always had a clear interest in healthcare, which led her to obtain a bachelor degree in Biomedical Sciences and a master's degree in Global Health. Her interest in policy making was sparked when she studied the impact of COVID-19 on healthcare access and utilization in South Sudan at KIT Royal Tropical Institute. The challenging nature of conducting health systems research in such a fragile and politically unstable country helped grow her interest in complex political systems and strategic innovation.

What I want to achieve with the AGEM research institute…

My ambition is to help improve human health, by supporting health research and, subsequently, better healthcare provision. I believe AGEM can play a pivotal role in this, by best supporting her researchers to bring their research to the next level. The coming years, I will convey my interest in strategic development into AGEM's six-year evaluation according to the Strategy Evaluation Protocol (SEP). Through this, I hope to be able to help the institute grow to an (inter)nationally renowned institute, that contributes to improving gastroenterological, endocrine and metabolic health across the world.

Noam Zelcer

Since September 2022, Noam Zelcer joined the AGEM research board as research board member. Noam is a molecular biologist working at the Department of Medical Biochemistry, location AMC. He studies the (post) transcriptional regulation of lipid metabolism in the context of NAFLD and CVD.

What I want to achieve with the AGEM research institute…

As a basic science researcher there are two main goals that I would like to achieve within the AGEM. First, to ensure that basic science in the realm of AGEM is supported and valued, in face of a growing pressure to shift research towards clinical translation. Second, to further strengthen collaborative efforts between research groups that belong to the AGEM as together we can increase the institute's impact.

Joep Derikx

Since September 2022, Joep Derikx joined the AGEM research board as research board member. Joep is pediatric surgeon in Emma children's hospital of Amsterdam UMC. He earned his PhD on '(Patho)physiology of gut wall integrity in health and disease in man' in 2009 at the University of Maastricht. He was trained as general and pediatric surgeon in Sittard and Maastricht from 2008 to 2014 and as pediatric surgeon in Amsterdam from 2015 to 2016. Since then he is clinical staff member at the Department of Pediatric Surgery of Emma children's hospital in Amsterdam with a focus on neonatal abdominal surgery and pediatric thyroid gland surgery. His research is aimed at unraveling mechanisms underlying necrotizing enterocolitis, intestinal ischemia and intestinal anastomotic healing and leakage. This partly takes place at the Tytgat Institute Amsterdam, together with Prof. W.J. de Jonge. Furthermore he studies potential new markers for early diagnosis of intestinal damage.

What I want to achieve with the AGEM research institute…

I would like to connect clinical work and resulting research questions with fundamental research work: taking care of the translational side of AGEM. I also think it is important to give young (medical) researchers a good start to their career.

Anita Boelen

Since October 2022, Anita Boelen joined the AGEM research board as director. She is a Professor of Thyroid Hormone Metabolism, in particular molecular and diagnostic aspects, at the Endocrine laboratory, department of Clinical Chemistry at location AMC (University of Amsterdam). Her research focusses on thyroid hormone metabolism in innate immune cells and on mechanisms involved in congenital central hypothyroidism. In addition, she leads the regional Dutch Neonatal Screening program at the Endocrine Laboratory and is thereby responsible for the measurements in heel prick blood of newborns.

What I want to achieve with the AGEM research institute…

I'm excited to be part of the management of AGEM and look forward to collaborating with leaders of other research institutes within Amsterdam UMC. I believe that for AGEM to continue making valuable contributions it is essential to ensure that researchers from the different research programs are equally involved and represented. As co-director, this will be one of my main focus points. In addition, I want to continue the ongoing work of keeping our young researchers enthusiastic about their scientific jobs by facilitating growth and career prospects.

Stephan Kemp

Since December 2022, Stephan Kemp joined the AGEM research board as research board member. Stephan was trained as a translational researcher at Johns Hopkins University and he specializes in inherited neurometabolic diseases and newborn screening with a particular focus on X-linked adrenoleukodystrophy (ALD). One of his main aims of the last decade was to realize implementation of ALD newborn screening in the Netherlands. Following the successful pilot, it is expected the nationwide screening will start in 2023. He is the founder and editor of the ABCD1 Variant Database (www.adrenoleukodystrophy.info) and member of the medical and scientific boards of 4 patient organizations in Europe and the USA.

What I want to achieve with the AGEM research institute…

With patient care, diagnostic and research labs close together, the Amsterdam UMC offers a unique environment for translational research. This enables the translation of new scientific findings to the clinic and vice-versa translate clinical questions into their scientific components. I will use my expertise with ALD to stimulate and further intensify the collaboration between the clinic and research.

Ric van Tol

Since December 2022, Ric van Tol joined the AGEM research board as dedicated business developer for AGEM. His role is to identify valuable synergies within our institute, and craft new propositions for external partnerships. He can assist in setting up collaborations with various stakeholders and clients; e.g. academic/technology institutes and food/pharma industries. From target/compound identification to non-invasive disease monitoring, from early life to healthy ageing, and from nutrition to pharma. Translating science into innovative clinical and technological applications, with societal and commercial impact in mind.

What I want to achieve with the AGEM research institute…

That AGEM will be (inter)nationally visible and recognized as a prominent institute, where fundamental and preclinical research is translated into innovative healthcare and treatment practices. Where the three domains in our acronym collaborate on today's major health challenges. That we not only thrive on our solid (clinical) science base, but distinguish ourselves in cross-functional excellence. And where such fertilization will result in impactful innovations that drive a healthier society. Obviously supported by external funding opportunities.

AGEM directors

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. Stan van de Graaf

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

Professor of Experimental Hepatology and Metabolism
Specialization: Biochemistry/Physiology
Research subject: Targeting metabolite dynamics to treat metabolic and liver diseases

Prof. dr. Gerd Bouma

Department of Gastroenterology and Hepatology

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

AGEM office

Dr. Eva Dirkx-Beuling

Amsterdam Gastroenterology Endocrinology Metabolism (AGEM)

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

Dr. Ric van Tol

Amsterdam Gastroenterology Endocrinology Metabolism (AGEM)

Business Development & Innovation Strategy
Specialization: Nutrition and GI Health, Industrial Research Management

MSc. Maartje Schots

Amsterdam Gastroenterology Endocrinology Metabolism (AGEM)

Policy officer AGEM
Msc. International Development / Global Health

Linda van den Noord

Amsterdam Gastroenterology Endocrinology Metabolism (AGEM)

Secretary
October 2020 – May 2022

AGEM Research Board members

Dr. Anje te Velde

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

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

Prof. dr. Annemieke Heijboer

Endocrine Laboratory & Department of Clinical Chemistry

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

Prof. dr. 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

Assistant 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.

Dr. Frédéric Vaz

Department of Clinical Chemistry

Clinical Biochemist
Specialization: Metabolic disease and metabolomics
Research subject: Complex lipids and their role in genetic disease, acquired disorders and aging.

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.

Dr. Joep Derikx

Department of pediatric surgery

Function: pediatric surgeon
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.

Dr. Stephan Kemp

Department of Clinical Chemistry

Function: Associated professor
Specialization: inherited neurometabolic diseases
Research subject: lipid metabolism and neurotoxicity with a focus on X-linked adrenoleukodystrophy

Science Impressions 2022

To give an impression of the research conducted at the AGEM research institute, seven couples of young investigators and their supervisors were invited to present the research projects they worked on in 2022.

Digital Healthcare

Marlies Schijven and Sebastiaan van der Storm

Research digital healthcare

In times of limited resources, healthcare is on the lookout of the smart use of digital solutions to support healthcare and to limit costs. Prof. dr. Schijven and her research group have a broad interest in digital innovations in patient care, medical research, and education. Professor Schijven is a gastrointestinal surgeon at the Amsterdam UMC and Program Leader eHealth of the Netherlands Federation of University Medical Centers. Her research group has conducted research on digital healthcare, such as video consultation during follow-up care as an alternative to face-to-face consultation, serious games for medical education for surgical residents, medical data recorders in the operating room to improve interprofessional cooperation and surgical safety, and mobile health as remote care.

Mobile apps improving gastrointestinal surgical care

Sebastiaan van der Storm started his PhD "Mobile applications in gastrointestinal surgical care" in 2019. The ultimate goal of his PhD is to improve care for patients undergoing gastrointestinal surgery. Mobile applications (apps) may offer the potential to facilitate or improve gastrointestinal surgical care, benefiting patients, healthcare providers, or both. He started his PhD to assess already available apps in a systematic review, which showed that the apps generally have several flaws in their development and evaluation. In collaboration with patients and involved healthcare providers, he developed several patient-centred apps and won the Medical Inspirator Award 2020/2021 for the app "StoMakker" (for children with a stoma). As an important part of this PhD, all apps are being investigated in terms of their effectiveness.

The multicentre randomised controlled trial "ERAS APPtimize" was completed. Perioperative care in colorectal surgery is systematically established using the Enhanced Recovery After Surgery (ERAS) protocol. The ERAS protocol improved perioperative colorectal care in a multidisciplinary and multimodal manner, simulating early and safe hospital discharge. In general, compliance with the ERAS protocol is adequate; however, there is still room for improvement in compliance by actively involving patients in their recovery. The main objective of this study was to investigate whether compliance with selected items in the ERAS protocol could be improved by actively involving patients in the ERAS colorectal care pathway using a patient-centred mobile application. Adult patients who underwent elective colorectal surgery were included in this study. Patients in the intervention group used a mobile application combined with an activity tracker to be guided and simulated through the ERAS pathway. The patients in the control group received standard care and wore an activity tracker to monitor their daily activities. Although the data analysis has not been fully completed, we can conclude that the ERAS APPtimize app significantly increased patient compliance. We intended to further improve the app based on insights from the trial and to implement the app in clinical practice.

Marlies Schijven and Sebastiaan van der Storm

Strategies to improve the clinical management of inflammatory bowel disease

Mark Lowenberg and Adriaan Volkers

Inflammatory bowel diseases - background

Inflammatory bowel diseases (IBD) is a term describing two chronic inflammatory diseases of the gastrointestinal tract (Crohn's disease and ulcerative colitis), that are characterized by relapsing and remitting phases. Symptoms of a disease flare can vary from abdominal pain, diarrhoea, rectal blood loss and extra-intestinal manifestations. Although these diseases are extensively studied, the pathogenesis remains largely unclear and no curative treatment is available yet. An important treatment goal is to induce and maintain clinical and endoscopic remission. The clinical management is composed of regular monitoring of intestinal inflammation and adequate medical and surgical treatment. Although various new treatment options have been developed in recent years, IBD is associated with impaired quality of life. The IBD centre Amsterdam (ICA) of the department of Gastroenterology and Hepatology of Amsterdam UMC is a well-known (inter)national expertise centre. The care that we deliver to our patients is performed in a multidisciplinary way, in close collaboration with gastroenterologists, IBD nurses, surgeons, dietitians, pathologists and radiologists.

Dr. Mark Löwenberg is a gastroenterologist and is specialized in IBD. As a clinician, he is involved in patient care and (pharma and investigator-initiated) trials. His main research focus is on optimizing treatment strategies in IBD, imaging studies (endoscopy and capsule endoscopy) and translational research on intestinal fibrosis.

Adriaan Volkers started his PhD at the gastroenterology department in 2019. The main goal of his research is to improve IBD management through a variety of projects.

Dalia Lartey started her PhD at the gastroenterology department in 2021 and is currently setting-up a research line to investigate intestinal fibrosis. She will be focussing on the pathophysiology of intestinal fibrosis and on new ways how to visualize this phenomenon in IBD.

Capsule endoscopy for Crohn's disease

Mucosal healing is associated with improved clinical outcomes and is predominantly assessed with ileocolonoscopy, but this is expensive, unpleasant for patients and it visualizes only the last 10-20 cm of the terminal ileum. Capsule endoscopy is a simple, relative safe and non-invasive imaging modality that involves swallowing a capsule with two cameras, located at the front and rear side. With technological innovations, pan-enteric capsule endoscopy became possible, visualizing the entire gastrointestinal tract.

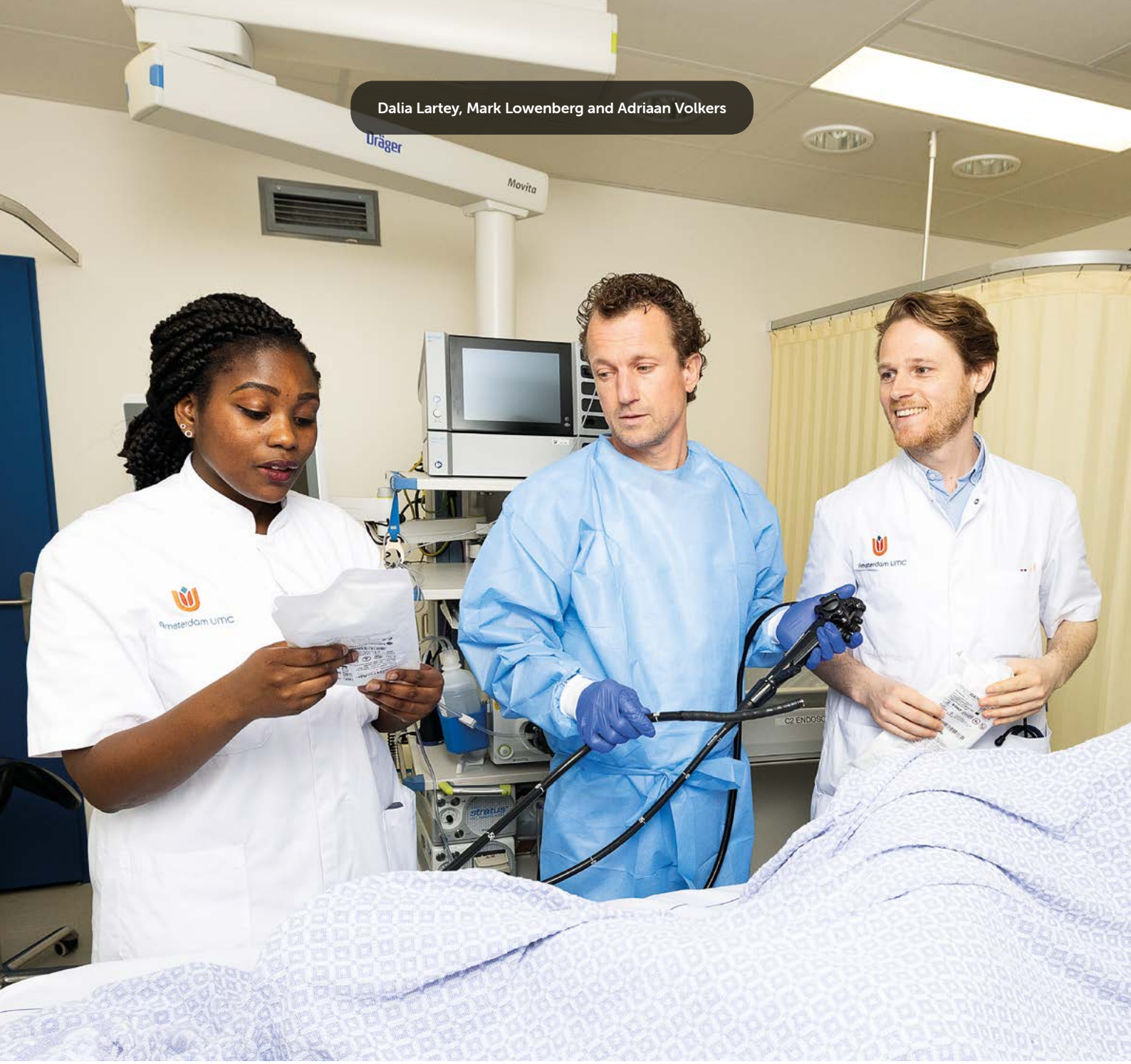
In the STOC (Sensitivity TO Change) study, we investigated changes in mucosal disease activity using pan-enteric capsule endoscopy before and after starting biologic treatment in Crohn's disease patients. We found that pan-enteric capsule endoscopy is a useful technique to assess changes in mucosal disease activity. Future studies should focus on the development and validation of a pan-enteric activity index and artificial intelligence algorithms to facilitate scoring and to improve the reading time.

Mercaptopurine treatment for ulcerative colitis: randomized controlled trial

Although thiopurines, such as mercaptopurine, are being used since many decades for ulcerative colitis, their use is not supported by solid evidence. As the treatment landscape in IBD is rapidly evolving, scepticism about the efficacy of thiopurines is rising. We performed a randomised placebo-controlled trial in the Netherlands (OPTIC, that stands for OPtimised Thiopurines In ulcerative Colitis). The study, that was sponsored by ZonMW and was set-up by PhD candidate and gastroenterologist in training Sara van Gennep, investigated mercaptopurine treatment using therapeutic drug monitoring (i.e. mercaptopurine metabolites were measured in the blood and doses were adjusted accordingly). We found that mercaptopurine was superior to placebo in achieving clinical, endoscopic and histological outcomes after one year of treatment. However, more adverse events occurred with mercaptopurine treatment compared to placebo, which was mainly observed in the first few months after treatment initiation. We concluded that thiopurines are a valuable treatment option for ulcerative colitis patients who tolerate it. We are now planning to investigate if thiopurines are cost effective in a health economic analysis.

Imaging and unravelling intestinal fibrosis in IBD

Although intestinal fibrosis is commonly seen in IBD, representing an unmet medical need, the underlying pathophysiological mechanisms remain to be elucidated. There are no approved anti-fibrotic drugs on the market to treat intestinal fibrosis. One of the main challenges is the lack of imaging techniques that can be used to visualize and quantify intestinal fibrosis.



Dalia Lartey, Mark Lowenberg and Adriaan Volkers

We are currently setting-up the infrastructure that is required to investigate intestinal fibrosis using a novel promising imaging technique (68Ga–Fibroblast Activation Protein inhibitor (FAPi) PET imaging) to visualize in vivo fibrosis (Imaging center, AUMC) in IBD patients receiving anti-inflammatory treatments with different modes of action. For this technique, a quinoline-based PET tracer will be used that targets fibroblast activation protein (FAP), a candidate fibrosis biomarker. In parallel, translational research will be performed (Tytgat institute, AUMC) to unravel fibrosis in IBD, which will be done at the cellular level in colonic resection specimens, obtained from stricturing Crohn's disease and therapy-refractory ulcerative colitis patients, using different laboratory techniques, including immunohistochemistry, mass cytometry and ex vivo stimulation assays with primary fibroblasts.

Hormone action in health and disease

Peter Bisschop and Esther Speksnijder

Hormones are chemical messengers that are produced and released by various glands and tissues in the body. They travel through the bloodstream and act on target cells or organs. Hormones are of utmost importance because they act as chemical messengers that help coordinate and regulate the functions of various organs and systems in the body. Even small imbalances in hormone levels can have significant effects on health and well-being. Hormonal disorders or dysregulation can lead to a wide range of conditions, such as osteoporosis, pregnancy loss, metabolic disorders, mood disorders, and more. Understanding hormones and their role in the body is essential for maintaining overall health and addressing any hormonal imbalances or related conditions.

Our group is especially interested in thyroid disorders and sex hormones, their interaction during pregnancy and their role in osteoporosis and diabetes.

Key questions related to thyroid disorders that we are trying to answer are: What is role of thyroid hormone during pregnancy? Can we improve prediction of recurrent Graves' hyperthyroidism and develop more effective non-surgical therapies for Graves' orbitopathy? Last year we presented the results of the T4LIFE study. In this randomised, double-blind, placebo-controlled trial we showed that levothyroxine administration does not improve live birth rate in euthyroid, thyroid peroxidase antibody positive women with recurrent pregnancy loss. We are currently developing an improved prediction model including genetic markers for recurrent Graves' hyperthyroidism, that will be validated in a prospective study. Patients with active moderate-to-severe Graves' orbitopathy are now being enrolled in a randomized, double-blind, placebo controlled trial on the efficacy of a novel drug targeting the orbital fibroblast.

Our key questions related to the role of sex hormones in osteoporosis and diabetes are: How does the loss of estradiol around menopause lead to accelerated bone loss? What is the role of bone marrow adipose tissue in postmenopausal osteoporosis and is bone marrow adipose tissue regulated by sex hormones? Does estradiol regulate glucose metabolism in humans and does menopause increase the risk of diabetes?

Esther's PhD project focusses on the effects of estrogen deficiency after menopause on bone metabolism and glycemic regulation in patients with diabetes. Bone is a highly dynamic organ, that is constantly being renewed by specialised bone cells to maintain its integrity through a process called bone remodelling. Osteoclasts resorb damaged bone, followed by production of new bone in the resorption pit by osteoblasts, while osteocytes coordinate this tightly coupled process. We previously showed that biomarkers of bone resorption and formation fluctuate in sync with the menstrual cycle, suggesting a physiological role of fluctuating estradiol concentrations in bone metabolism. We also showed that short term administration of estradiol increases bone formation in postmenopausal women, while long term, continuous administration decreases bone formation. We hypothesize that, by mimicking the rhythmic concentrations during the menstrual cycle in postmenopausal women, a rhythmic rise in bone formation can be induced, resulting in a higher bone mass. In a randomised study, we will compare the effect of rhythmic 17-β-estradiol treatment to continuous treatment on bone turnover in postmenopausal women. In view of our previous studies on the effect of estradiol on glucose metabolism in rats, we will also determine the effect of fluctuating estradiol administration on glucose tolerance in the same study. In addition, Esther has recently completed a systematic review on the effect of menopausal hormone therapy on glycemic regulation in patients with diabetes mellitus suggesting that hormone therapy can be beneficial. Clinical observations suggest that glycemic control changes around menopause in patients with type 1 diabetes, but a structural evaluation has never been performed. As part of her PhD project Esther will carry out this evaluation using questionnaires in a large cohort of patients with diabetes.

Through our research we aim to increase our understanding of hormone action in normal physiology and during disease with the ultimate goal to improve the health and well-being of patients with hormone related conditions.

Peter Bisschop and Esther Speksnijder

Fatigue in inflammatory bowel disease

Anje te Velde and Paula Metselaar

Inflammatory bowel disease (IBD)

IBD, comprising Crohn's disease and ulcerative colitis, are chronic, non-infectious inflammatory disorders of the gastrointestinal tract. The diseases are affecting more people every year, with significant loss of quality of life and a high societal and economic burden due to incapacitating symptoms and the cost of biologic medicines. IBD is characterized by alternating periods of inflammation and remission, and it is presently unclear why many patients cannot maintain remission, why some respond to certain therapies and others do not, and what triggers the disease in the first place. These questions present some of the current challenges in the field, as well as how to improve the therapeutic ceiling and how to treat complex symptoms such as fatigue.

IBD researchers

Amsterdam University Medical Centers (Amsterdam UMC) has a large team of professionals working on IBD, both in patient care and in clinical, translational and fundamental research. Part of the team at Amsterdam UMC's Tytgat Institute for Liver and Intestinal Research focusses on the different aspects of fundamental and translational IBD research, in close collaboration with the clinical experts working at the hospital. Anje te Velde is an immunologist by training, interested in intestinal health and the pathophysiology of IBD among other topics in the past 30 years as a researcher at the Amsterdam UMC and Tytgat Institute. The damage in the intestine because of an over reactive immune response and the role of the environment are a current focus of the research. One of the main triggers in IBD is the "Western lifestyle". Food components of ultra-processed food can result in microbiota changes and immune dysregulation (1). One of the main environmental signalling molecules is the NLRP3 inflammasome. In 2019, Paula Metselaar started her PhD with Anje to investigate fatigue in IBD, focussing on the role of a derailed immune system in chronic intestinal inflammation.

Fatigue

Fatigue is one of the most frequently reported concerns of patients with IBD, impacting quality of life, work productivity, and normal activities such as exercise, child care, social functions or household tasks. It is beyond a passing feeling of 'being tired', but an overwhelming sense of tiredness, lack of energy and feeling of exhaustion that is not relieved by rest or sleep. Fatigue in IBD is thought to be multifactorial, with contributions from active inflammation, nutritional deficiency, altered metabolism and immunological factors. Strikingly, fatigue is a symptom that does not always abates when IBD goes in remission, showing little effect of current treatments. There is a substantial lack of understanding of the biological mechanism of fatigue other than that it is part of normal, transient, sickness behaviour. Little research has focussed on biomarkers, objective measures of fatigue, and causes other than active inflammation, depression or anaemia. That is why fatigue is of interest to the team of fundamental and clinical researchers, as well as caretakers at the hospital, to understand the symptom and to be able to help patients prevent or overcome it.

Fatigue study

In collaboration with gastroenterologist Mark Löwenberg and researchers at TNO, an observational study was set up at the AMC to characterize fatigue in patients with IBD, both in patients with active disease and in remission. Patients give blood and fill in questionnaires about fatigue and wear a heart rhythm-, respiration- and activity monitor for three days. Validated questionnaires are currently the only way to diagnose fatigue, albeit subjectively. In combination with vital sign monitoring, the goal is to correlate the clinical outcomes with biochemical determinants. Several proteins and signals are measured in the blood, as well as changes to DNA methylation and RNA expression of immunologically relevant genes.

Danger theory

In the laboratory, the immune response in blood of IBD patients is put to a 'stress test' to evaluate the hypothesis of an overactive or conversely a desensitized immune system. The danger theory suggests that the immune system is constantly on the lookout for danger signals that indicate tissue injury or damage and, when detected, an inflammatory response is activated by innate immune cells to try to eliminate the source. Chronic inflammation and autoimmune diseases may occur when the immune system becomes overactive to these danger signals, leading to prolonged inflammation and tissue damage. This theory has led to the development of new treatments for autoimmune diseases that focus on dampening the immune system's response to these danger signals. In the context of the danger theory, fatigue could be a symptom of an overactive immune system causing sustained sickness behaviour.

In 2022, inclusion of patients into the study has begun and initial results confirm a high prevalence of fatigue in IBD patients. Preliminary data shows a higher expression of an immune complex involved in sensing danger signals in IBD patients, the larger picture will emerge in the final year of Paula's PhD.

1. Sandys O, Te Velde A. Raising the Alarm: Environmental Factors in the Onset and Maintenance of Chronic (Low-Grade) Inflammation in the Gastrointestinal Tract. Dig Dis Sci. 2022;67(9):4355-68.

Hypothalamic Integration Mechanisms

Andries Kalsbeek and Delaram Pour Moghadam

In my group at the Endocrinology Lab we study the role of the hypothalamus in the control of energy metabolism, with a focus on glucose metabolism, hormonal rhythms, the central biological clock and the autonomic nervous system. We take a multidisciplinary approach combining neuro-anatomy, systems biology, molecular biology and behavioral physiology, to understand the mechanisms involved in the circadian control of energy metabolism, and how its perturbation may lead to pathologies like type 2 diabetes and obesity.

Together the autonomic nervous and endocrine system constitute the brain output that is responsible for maintaining homeostasis. The hypothalamus is the core brain structure controlling the activity of the endocrine axes and the autonomic nervous system (ANS). An important scientific question throughout these years has been how either circadian information generated in the hypothalamic biological clock or metabolic feedback information received by the arcuate nucleus in the hypothalamus is integrated by the different hypothalamic nuclei and "translated" into an appropriate and balanced output via the ANS and endocrine axes. Thus far our physiological experiments in experimental animals, using targeted brain infusions in combination with denervation of the sympathetic and/or parasympathetic input to the liver, have provided clear evidence for the involvement of the hypothalamic pre-autonomic neurons in the control of glucose metabolism, nevertheless many details are still unknown.

The organization of the neuro-endocrine system is well understood: hypophysiotropic neurons control the release of the pituitary hormones and ultimately that of peripheral hormones such as cortisol, thyroid hormone, estrogen and testosterone via secretion of "releasing factors" such as CRH, TRH and GnRH. These releasing factors also functioned as a kind of "markers" for the neuro-endocrine neurons and allowed to reveal the wide diversity of modulators of these neurons, such as gender, time-of-day, stress and food deprivation. In contrast, no such clear "markers" are available to recognize the hypothalamic pre-autonomic neurons that control the activity of the sympathetic ('fight-flight') and parasympathetic ('rest-digest') branches of the ANS. Consequently, virtually nothing is known about these neurons, except for the mere fact that they exist. Yet, a deeper understanding of autonomic regulation and dysfunction associated with metabolic and cardiovascular disease to improve current treatment options for pathological conditions such as obesity, hypertension and type 2 diabetes can only be obtained if these pre-autonomic neurons can be recognized more easily. Good news is that 2 years ago we obtained a grant from ZonMw to find markers for these pre-autonomic neurons in order to get a deeper insight in their regulatory mechanisms, entitled "Benchmarking the hypothalamic pre-autonomic neurons". We hypothesized that by combining retrograde tracing to label the pre-autonomic neurons and subsequent single-cell RNA sequencing (scRNAseq) of these labelled neurons we can identify a set of unique molecular markers that characterize the pre-autonomic neurons.

To benchmark the hypothalamic pre-autonomic neurons we formed a new Amsterdam – Leiden consortium with combined interest and expertise in the neuro-anatomy of the hypothalamus. In Leiden, Prof. Onno Meijer and Dr. Ahmed Mahfouz will focus on the single-cell RNA sequencing and in Amsterdam Profs. Andries Kalsbeek and Eric Fliers together with Dr. Chun-Xia Yi will supervise the tracing experiments necessary to obtain the brain tissue with labelled neurons for the scRNAseq experiments. Two PhD's have started last year to work on this project. In Leiden Jari Berkhout will do the scRNAseq experiments and in Amsterdam Delaram Pour Moghadam will perform the tracing experiments.

To visualize the sympathetic and parasympathetic pre-autonomic neurons in the hypothalamus, we will inject a retrograde neuronal tracer into respectively the thoracic spinal cord, containing the sympathetic pre-ganglionic neurons, or dorsal complex of the brainstem, containing the para-sympathetic pre-ganglionic neurons. To identify the neuro-endocrine neurons, animals will be injected intravenously with a fluorescent retrograde tracer. When injected systemically, this tracer does not cross the blood-brain barrier, rather it is taken up by neurons that project to the median eminence and posterior pituitary. The subsequent scRNAseq on the labelled hypothalamic neurons should provide markers to differentiate pre-autonomic from neuro-endocrine neurons, and sympathetic from parasympathetic pre-autonomic neurons.

The pre-autonomic neuron markers identified with the current project will also be very useful when working with human brain tissue. We have collected hypothalamic tissue from >100 post-mortem human brains donated to the Netherlands Brain Bank. With the help of this

Delaram Pour Moghadam and Andries Kalsbeek

unique collection of brain tissue, we have found that neuronal populations in the hypothalamus are differently affected by obesity and diabetic pathogenesis, as well as anti-obesity and anti-diabetic treatments. Recognizing pre-autonomic neurons in the human hypothalamus, which is not possible at present, will allow for the identification of a potential role for these neurons in the prevalent pathologies mentioned. For instance, it is not clear, whether the increased CRH-expression in the hypothalamus observed with hypertension is in neuro-endocrine or pre-autonomic neurons. Significant changes in pre-autonomic neurons would not only increase insight in the pathogenesis of these conditions, but also open up new strategies to intervene in the long term.

New ways, better outcomes: N-of-1 for All

Clara van Karnebeek and Bibiche den Hollander

With increasing insights into disease mechanisms, treatment opportunities emerge regularly for inherited metabolic disorders (IMDs). Often these are affordable, e.g. medical diets, vitamins and repurposed medications (PMID: 35332073). Systematically generating evidence for the effect of such targeted treatments requires a customized protocol for evaluation to realize market authorization and reimbursement. This can be a challenging task. Classical randomized controlled trials (RCTs) are hard to carry out because of low prevalence and heterogeneity of IMDs which cause that lengthy trials are needed to include sufficient patients and to achieve acceptable power. Moreover, these designs don't measure individual response to therapy.

Hence, patients miss out on disease-modifying and potentially life-changing interventions, just because of methodological and/or practical reasons. This situation is unacceptable! Our national consortium United for Metabolic Diseases addresses this unmet medical need via the N-of-1-forall platform. Professor Clara van Karnebeek, Dr Marion Brands, prof Martina Cornel and Dr Agnies van Eeghen supervise dr Bibiche den Hollander in her PhD trajectory. Together with an interdisciplinary group of clinicians researchers and patients, we have created a sustainable infrastructure to perform investigator-initiated intervention studies (nutritional and drug(repurposing)), to generate evidence for emerging therapies for all IMDs. Innovative methodologies and relevant outcome measures with patient and family participation are key elements in our N-of-1-for-all success. We work according to the P4-medicine model: personalized, preventive predictive and participatory (figure 1) and contribute to the Treatabolome (PMID: 33845862).

In her PhD, Bibiche focusses on the development and implementation of alternative trial designs for IMDs with small patient numbers, foremost the n-of-1 study design (figure 2).

N-of-1 designs are double blind, multiple crossover randomized controlled trials in a single patient. The n-of-1 designs consider an individual patient as the sole unit of observation in a study investigating the efficacy or side-effect profiles of different interventions. The patient undergoes multiple cycles of experimental and control/placebo treatment, and thus serves as their own control group against which to measure the effect of the experimental treatment (see figure) on personalized and relevant outcome measures (PMID: 33504638). N-of-1 studies can be modified according to the characteristics of the specific patient group and treatment. Meta-analysis of n-of-1 studies generates highest level of evidence similar to large randomized placebo-controlled double-blinded clinical trials.

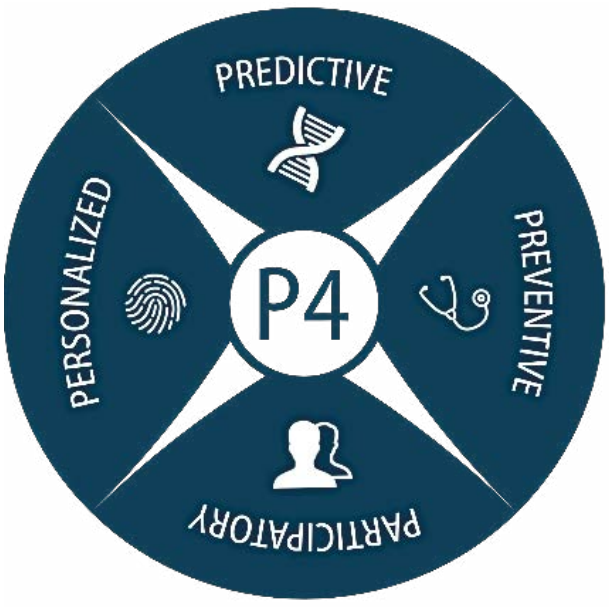


Figure 1. P4-medicine model

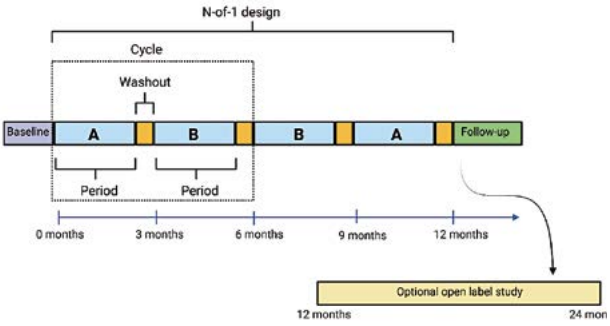


Figure 2: Schematic of a single n-of-1 trial


Bibiche den Hollander and Clara van Karnebeek
N-of-1 Trials for Innovative Treatments
Randomized trial period
Washout
Base-line
Placebo
Placebo
Follow up
Blinded
Relevant & Personalized Outcome Measures
umd·nl
united for metabolic diseases

The ultimate goal of an n-of-1 trial is to determine the safe and optimal intervention for an individual patient using objective data-driven criteria. A n-of-1 expert board with members of 3 participating UMCs represents the required multidisciplinary expertise. The board consists of IMDs clinicians, statisticians, epidemiologists, methodologists, pharmacists, nurses, PhD students, and patient organizations members. This board is the core of the project and gather monthly to evaluate the theoretical aspects as well as the practical execution of the intervention trials. We also provide advice and expertise to colleagues in the Netherlands regarding the trials in rare metabolic and genetic diseases.

In Bibiche's PhD project, we selected three IMDs and interventions for three n-of-1 trials.

Additionally, we performed three open label experimental trials. A n-of-1 trial is not always feasible, especially due to the lack of appropriate and measurable outcomes measures or because the drug or other intervention may linger in the system or influence the behavioral patterns and psyche of the patient once their administration is stopped, thereby influencing the future intervention and results. Such effects may confound the interpretation of the effectiveness of subsequent interventions. A third challenge is related to the use of washout periods which can be used to combat carryover effect, but their use may compromise patient safety since they may result in taking a patient off all treatment during the course of the trial. At last, sometimes blinding is not possible, due to the lack of an identical placebo.

N-of-1 trial: Ambroxol in patients with type 3 Gaucher Disease (PI Dr Marion Brands)
Gaucher is disease is caused by a deficiency of the lysosomal enzyme glucocerebrosidase. Patients represents with multisystemic disease manifestations such as enlarged liver and spleen, anemia, thrombocytopenia, and bone manifestations. Specific for type 3 Gaucher is the neurological involvement of the disease ranging from eye movement disorders to profound neurological involvement, such as epilepsy and cognitive impairment. Ambroxol is a chaperone that has been shown to increase glucocerebrosidase activity and is able to cross the blood-brain-barrier (BBB). This latter is of most importance since the current treatment of enzyme replacement therapy is not able to cross the BBB and hence does not affect these neurological symptoms. We will perform a placebo-controlled n-of-1 trial in 4 patients with type 3 Gaucher and neurological symptoms. Solid biomarkers in the liquor and plasma are available and are the primary outcome measure. Currently, the study is approved by the METC and we expect to start in the first quarter of 2023.

Open label and n-of-1 trial: L-serine supplementation in patient with GRIN2B loss-of-function (LoF) mutation (PI prof C van Karnebeek)
LoF mutations in GRIN2B result in neurologic abnormalities due to N-methyl-D-aspartate receptor (NMDAR) dysfunction. In vitro experiments showed that the naturally occurring coagonist D-serine restores function to GluN2B (mutation)-containing NMDARs. In previous case studies possible improvements in motor and cognitive performance and communication were observed after L-serine, the precursor of D-serine, dietary supplementation. This motivated us to perform and publish an open label trial with L-serine supplementation in two patients with GRIN2B LoF (PMID: 36758276). In one patient improvement in psychomotor development and cognitive function was observed. To generate stronger evidence for effect of L-serine in GRIN2B-neurodevelopmental disorder (NDD), we are currently performing a placebo-controlled n-of-1 trial in 4 patients with GRIN2B LoF. The main outcome measure is the PRPP (perceive-recall-plan-perform), which is a standardized, client-centered and criterion-referenced procedural task analysis, which allows occupational therapists to assess the application of information processing strategies in the context of meaningful everyday activities. The PRPP-Assessment has been used to measure performance in a range of different population including children with learning difficulties, children with autism and IDD, adults with disabilities, traumatic brain injury, and schizophrenia. The trial has started in January 2023 and we expect the first results in one year.

N-of-1 trial: Cannabidiol (CBD) in patients with Sanfilippo syndrome, Tuberous Sclerosis Complex (TSC), and Fragile X syndrome (FXS) (PI: Dr van Eeghen)
Rare genetic neurodevelopmental disorders are often characterized by intellectual disability (ID) and severe psychiatric comorbidity including behavioural problems such as irritability, aggression and self-injurious behaviour. These bbehavioral problems are often refractory to regular psychological or pharmacological treatment, posing a great burden for patients as well as their caregivers and often necessitating intensive intramural care. Prompted by reports from families describing an improvement in behavioral problems by using CBD for TSC, Sanfilippo syndrome, and FXS, we will perform a placebo-controlled trial in pediatric and adult patients, suffering from severe behavioral manifestations. Currently, the study is under review of the METC.

Open label trial: Sialic acid in NANS-CDG (PI Prof C van Karnebeek)

NANS-CDG is a congenital disorder of glycosylation (CDG) presenting clinically with intellectual developmental disorder (IDD), skeletal dysplasia, neurologic impairment, gastrointestinal dysfunction and dysmorphic features. NANS-CDG is caused by genetic variants in the gene encoding an enzyme in de sialic acid synthesis, which plays a key role in biological processes such as brain and skeletal development. We were the first to report this CDG in 2016, delineated the clinical spectrum (PMID: 34163424) and recently investigated the effect of sialic acid treatment pre- and postnatally in humans in an open-label pilot study in NANS-CDG. The effect of oral sialic acid treatment depended on the timing of initiation: Postnatal treatment with horal sialic acid neither led to a biochemical nor a measureable clinical response. Prenatal treatment has possible beneficial effects on neurodevelopmental outcomes (manuscript under review). At the moment, other targets and strategies for treatment of NANS-CDG are under investigation in patient-derived stemcell models.

Open label trial: Volanesorsen in LPL deficiency (PI: prof C van Karnebeek)

Lipoprotein lipase (LPL) deficiency is a rare inherited metabolic disorder, presenting with lipid abnormalities and medical complications, including high triglyceride (TG) levels, recurrent episodes of abdominal pain, pancreatitis, and hepatomegaly. A lifelong severe fat restricted diet, that is very hard to comply with, is the only therapeutic option to lower TG levels. Volanesorsen is approved as an adjunct to diet in adults patients but not in pediatric patients. In this study we explored the effect of volanesorsen in a pediatric patient with very good results. Our included patient was a 13-year old female patient and her medical history included 53 hospital admissions, including 4 IC admissions. Volanesorsen decreased TG levels, there were no episodes of pancreatitis, abdominal pain, and hospital admissions; the dietary restrictions could be loosened. Both patient and parents reports the treatment as a “life-changing“ therapy. We strongly support the availability and reimbursement of this treatment to other children and adolescents with severe LPL deficiency.

Clinical evaluation remains challenging in trials for rare disorders, especially in very heterogeneous groups like IMDs, and when a solid biomarker, responsive to therapy, is missing. Selection of meaningful and relevant endpoints is fundamental to rare disease clinical trial designs and requires an understanding of the natural history of the disease. N-of-1 trial have the potential to radically change the way in which evidence-based and individualized medicine is pursued. Not only are the results of n-of-1 trial of immediate benefit to the patient and the treating physician, but if enough of these are pursued, patient characteristics that ultimately differentiate those that benefit from a particular intervention from those that do not can be explored, allowing for stratification of future patient group in a way that would further benefit patient care.

Currently, in the Emma Center for Personalized Medicine we are expanding the platform into a Trial Hub for rare genetic diseases, expanding the scope to include nutritional, drugs, RNA and gene therapies. We will harmonize our efforts with the stem cell facility for preclinical therapy evaluation (site) and our EU funded drug repurposing study SIMPATHIC , the expertise centers for rare diseases (ECZA) and Metab-ERN European reference network. Our Hub empowers colleagues to catalyze the bench to bedside process, and enable patients and families in the Amsterdam UMC and beyond to access innovative therapy trials faster and safer. Stronger together!

Inflammation in Crohn's Disease

Jeroen den Dunnen and Chiara Geyer

Acute and Chronic Inflammation Team

Dr. Jeroen den Dunnen is an immunologist at the Center for Experimental and Molecular Medicine (CEMM) at the Amsterdam UMC. The central theme of his research team is 'antibody-dependent inflammation'. In 2012 the team discovered a new function of human antibodies: the induction of vigorous inflammation. This feature of human antibodies serves an important physiological function, by inducing an inflammatory response that counteracts bacterial infections.

Yet, soon thereafter they discovered that antibody-dependent inflammation also has a 'dark side' by strongly promoting inflammation in the context of inflammatory disorders. For example, during the COVID-19 pandemic, in a large international collaboration the team identified that this dark side of antibodies is one of the key events that drives pathology in severe ill COVID-19 patients. In addition, antibodies also induce pathological inflammation in in the context of autoimmune diseases such as rheumatoid arthritis and lupus, which is caused by auto-antibodies that (instead of a pathogen) recognize antibodies of the host.

Because of its relevance for both infectious diseases and autoimmunity, subsequent research was performed to assess the potential relevance of antibodies in the human intestine. In collaboration with dr. Manon Wildenberg (Amsterdam UMC), the team discovered that antibodies can also induce inflammation in the intestine. This inflammatory response is induced by immune cells in the intestine, which express so-called Fc Receptors that can directly recognize bound antibodies. Again, this mechanism serves an important physiological function by counteracting invading bacteria. Yet, because the inflammatory response by these otherwise immunosuppressive intestinal immune cells was extremely pronounced, PhD student Chiara Geyer started a new study to determine whether this inflammatory pathway could also be involved in pathological intestinal inflammation, particularly in Crohn's Disease.

Intestinal Inflammation in Crohn's Disease

Crohn's Disease is a chronic relapsing inflammatory diseases of the gastrointestinal tract that has devastating effects on the quality of life. Although the precise etiology remains elusive, Crohn's Disease patients seem to display a dysregulation of their immune responses against their luminal flora, resulting in chronic intestinal inflammation.

Since antibodies and their receptors on immune cells are known to be important for controlling the balance between immune tolerance and inflammation, the project led by Chiara Geyer set out to determine whether this mechanism is dysregulated in Crohn's Disease patients. The key hypothesis for this project is that Fc Receptors on intestinal immune cells are activated undesirably, in this case not by antibodies, but by something else: C-reactive protein (CRP).

CRP is a prototypical acute-phase protein in humans, which is rapidly up-regulated (>1000 fold) in response to inflammation. High serum concentrations of CRP in Crohn's Disease are associated with poor prognosis and increased risk of relapse following withdrawal of therapies. Normally, CRP is only produced in the liver. However, Crohn's Disease patients also produce large amounts of CRP in the intestine, particularly by mesenteric fat cells. Since CRP can bind to and activate Fc Receptors, this could provide a signal of continuous activation leading to chronic inflammatory responses by intestinal immune cells.

Indeed, Chiara Geyer's research has shown that CRP, when bound to bacteria or dead cells, strongly activates human macrophages. While several involved cell signal transduction molecules have been identified, the key driver between CRP-induced inflammation appears to be specific metabolic changes within the immune cells. Through collaboration with Riekelt Houtkooper and Marjolein van Egmond (both Amsterdam UMC), a novel metabolic pathway in human macrophages was identified that is responsible for excessive inflammation induced by CRP. As part of a Marie Curie secondment, Chiara is currently studying the underlying metabolic pathways in greater detail at the LUMC in Leiden, under the supervision of dr. Bart Everts.

Chiara Geyer and Jeroen den Dunnen

Upon identification of the underlying molecular pathways, the ultimate goal of this project will be to identify a therapeutic approach to counteract this inflammatory pathway in Crohn's Disease. Since the metabolic pathway appears to be quite unique, targeting this pathway may provide the intriguing opportunity of a new class of therapeutics, i.e. metabolic inhibition, which specifically counteracts excessive inflammation without affecting other immunological responses. Since CRP is elevated in various chronic inflammatory disorders, inhibition of this metabolic pathway may also be of therapeutic use in other CRP-associated disorders, including atherosclerosis (where elevated CRP is a main risk factor) and rheumatoid arthritis (which is characterized by high CRP levels in the inflamed joints).

Best Publication 2022

In 2022, AGEM again 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 post doc, that published as first author in a top journal in 2022. Out of these nominees members of the AGEM Research Board selected a top 4. These selected candidates were offered a pitch workshop and, with the skills learned, Gerlinde Haverkamp and Charlotte van Veldhuisen (Lotte de Boer and Remco Kersten were not available unfortunately) pitched their publication during the AGEM Retreat of 2023. After this so-called "battle for the AGEM Best Publication 2022 award", the attendants of the retreat voted for their ultimate favorite. The author of the publication with the most votes was named winner of the AGEM Best Publication 2022.

Please meet the nominees for the AGEM Best Publication 2022...

Remco Kersten

Remco Kersten was nominated by Ulrich Beuers and Stan van de Graaf for his article published in the Journal of Hepatology: "*Role of the IgG4-related cholangitis autoantigen annexin A11 in cholangiocyte protection".* Journal of Hepatology 2022 vol. 76 j 319–331.

Prof. Beuers' motivation for the nomination was: "I fully support the nomination of Remco Kersten for the "AGEM best publication 2022" award. His highly remarkable experimental skills, his self-developed innovative methodological approach as crucial part of this study and his intrinsic high motivation and commitment to excellence made it possible that this paper published in a highly ranking journal (IF>30) is seen by experts on our field of immune-mediated hepatobiliary diseases as a potential landmark paper for better understanding of the pathogenesis of IgG4-related cholangitis. The paper was chosen as most remarkable publication 2022 on the field of immune-mediated liver diseases for presentation at the bimonthly EASL Journal Club in 2022.

Remco Kersten is a highly talented and driven, efficiently co-operating, broadly interested, socially active, highly reliable young researcher and an empathically caring physician."

Lotte de Boer

Lotte de Boer was nominated by Albert Wiegman for her article published in the European Heart Journal: "*Lipoprotein(a) levels in children with suspected familial hypercholesterolaemia: a cross-sectional study".*
Eur Heart J. 2022 Nov 16;ehac660

Dr. Wiegmans motivation for the nomination was: "For long, it was thought that familial hypercholesterolemia is one cardiovascular-disease-creating entity, whereas Lotte and our group beautifully showed that high lp(a) is a separate CVD-creating entity, which can be easily diagnosed in childhood if one thinks of this rather unknown disorder, especially if there is elevated LDL-cholesterol without a known pathogenic mutation for FH. The consequences will be really important: not only will high lp(a) leads later in life to CVD, the moment a child bears both FH ánd high lp(a), the risks of these entities multiply, and presumably these children need earlier and more intensive treatment."

Gerlinde Haverkamp

Gerlinde Haverkamp was nominated by Richard IJzerman for her article published in the New England Journal of Medicine: "*The After-Dinner Dip".*
N Engl J Med 2022;386:2130-6.

Dr. IJzemans motivation for the nomination was: "After seeing a patient with hypoglycaemia (which is often a diagnostic challenge), Gerlinde performed a complex diagnostic trajectory, reviewed the scientific literature, and diagnosed the patient with insulin autoimmune syndrome. Then she wrote a clinical problem-solving paper (NEJM) indicating the importance of a structured diagnostic approach to spontaneous hypoglycemia, and of considering insulin autoimmune syndrome among the potential causes."

Charlotte van Veldhuisen

Charlotte van Veldhuisen was nominated by Hans de Vries for her article published in the JAMA Surgery: "*Bihormonal Artificial Pancreas With Closed-Loop Glucose Control vs Current Diabetes Care After Total Pancreatectomy A Randomized Clinical Trial".*
JAMA Surg 2022.3702.

Prof. de Vries' motivation for the nomination was: "Charlotte is first author of a paper in JAMA Surgery. JAMA Surgery is ranked 1st out of 211 surgery journals (JCI) with an IF of 16.7. The paper reports on the first use of a bihormonal artificial pancreas in patients who underwent a total pancreatectomy. It is a nice example of a true AGEM collaboration between gastrointestinal surgery (Marc Besselink) and endocrinology (myself). We convinced the company to develop their product not only for patients with type 1 diabetes, but also for the rare group of patients after total pancreatectomy. It is expected that the availability of a bihormonal pancreas may increase the acceptability of this potentially life-saving surgical procedure. The work received an AGEM grant, which is acknowledged in the paper. Charlotte's contribution was crucial. She contributed to the design, was the central investigator, made a very successful bridge between surgery and endocrinology, did the statistical analyses and wrote the first draft of the paper. She successfully defended her thesis in 2022 as well, and is now in training at our institution to become a surgeon."

And the winner of the AGEM Best Publication 2022 is...

Charlotte van Veldhuisen

My name is Charlotte van Veldhuisen, MD-PhD student in the group of Prof. Marc G. Besselink within the Dutch Pancreatitis Study Group (DPSG) and I just started my surgical residency in the Amsterdam UMC. The DPSG, together with the Dutch Pancreatic Cancer Group (DPCG), aims to enhance diagnostic tools, to obtain better knowledge of the pathophysiology and to improve treatment and clinical outcomes in patients suffering from pancreatic diseases. During my PhD, one of the most interesting and innovative research projects was the study in which the artificial pancreas in patients after a total pancreatectomy was investigated.

Besselink Group

Bihormonal Artificial Pancreas With Closed-Loop Glucose Control vs Current Diabetes Care After Total Pancreatectomy - A Randomized Clinical Trial

Total pancreatectomy is increasingly performed in highly selected patients with main duct intraductal papillary mucinous neoplasm (IPMN), pancreatic cancer, or therapy refractory painful chronic pancreatitis. All these patients develop diabetes and glucose control in these patients is problematic because of the complete absence of α- and β-cells, leading to impaired quality of life. A novel, bihormonal artificial pancreas (BIHAP), using both insulin and glucagon, was assessed in terms of safety and efficacy in patients after total pancreatectomy in a randomized crossover clinical trial. In 12 adult outpatients after total pancreatectomy, the fully closed-loop BIHAP was compared with current diabetes care (ie, insulin pump or pen therapy). This first-in-patient study began with a feasibility phase in 2 patients. Subsequently, 12 patients were randomly assigned to 7-day treatment with the BIHAP (preceded by a 5-day training period) followed by 7-day treatment with current diabetes care, or the same treatments in reverse order. The primary outcome was the percentage of time spent in euglycemia (70-180mg/dL [3.9-10 mmol/L]) as assessed by continuous glucose monitoring.

In total, 12 patients (7 men and 3 women; median [IQR] age, 62.5 [43.1-74.0] years) were randomly assigned, of whom 3 did not complete the BIHAP phase and 1 was replaced. The time spent in euglycemia was significantly higher during treatment with the BIHAP (median, 78.30%; IQR, 71.05%-82.61%) than current diabetes care (median, 57.38%; IQR, 52.38%-81.35%; P = .03). In addition, the time spent in hypoglycemia (<70mg/dL [3.9 mmol/L]) was lower with the BIHAP (median, 0.00% [IQR, 0.00%-0.07%] vs 1.61% [IQR, 0.80%-3.81%]; P = .004). No serious adverse events occurred.

In conclusion, patients using the BIHAP after total pancreatectomy experienced an increased percentage of time in euglycemia and a reduced percentage of time in hypoglycemia compared with current diabetes care, without apparent safety risks.

After completing this study, we received a research grant from Koningin Wilhelmina Fonds for the follow-up trial, the PANORAMA trial, which will start next month. The PANORAMA will be a larger randomized trial, including a longer period of treatment and more patients. We are very excited about this trial!

Grants 2022

In 2022, AGEM awarded three types of grants. Like previous years AGEM awarded the *AGEM talent development* grant for exceptionally talented researchers who are in the first 5 years after obtaining a PhD-degree and want to start their own research line (VENI-profile) or who want to further develop their own research line (VIDI-profile, max 8 years after PhD graduation), the *AGEM innovation grant* for innovative ideas beneficial to the AGEM research institute as a whole, and the *AGEM contribution printing costs of theses* of AGEM PhD-students.

The AGEM talent development grant 2022 (€65.000)

Patrick de Jonge (VENI-like-profile)

Viruses as contributors to short-chain fatty acid metabolism in the human gut

Patrick de Jonge

My background lies in fundamental microbiological research, with a focus on bacteriophages. These are viruses that can only infect bacteria, and their interactions with bacteria across ecosystems was the focus of my PhD thesis 'On uncovering and understanding interactions between bacteriophages and bacteria'. During the research for my thesis, I combined classical 'wet-lab' and data-driven computational analyses. After defending my thesis in 2020, I joined the department of experimental vascular medicine at the Amsterdam UMC as a post-doc. Here, my research is centered on bacteriophages as modulators of bacteria in the human gut microbiome, and my role within the research is that of computational researcher and supervisor. Since joining the Amsterdam UMC, I have participated in bacteriophage research based on three main topics. Firstly, the dynamics of gut bacteriophage population in large human cohorts, secondly the interactions between bacteriophages with the human immune system, and thirdly clinical trials where bacteriophage populations are used to modulate the gut microbiome.

The AGEM talent development grant allows me…

… to start up my own research line. This will focus on the effect of singular bacteriophage species on the metabolism of gut bacteria, and through them on the human host. As a first stage, my research will focus on short-chain fatty acid-producing bacteria in the human gut. These bacteria convert dietary fiber into metabolites such as butyrate, which in turn are associated with a healthy gut microbiome. It is known that the majority of bacteriophages in the gut have the capability to incorporate themselves into bacterial genomes, and when they do this, they sometimes alter the bacterial metabolism with so-called auxiliary metabolic genes. I aim to identify gut bacteriophages that infect butyrate-producing bacteria and carry auxiliary metabolic genes with which they can alter bacterial butyrate production. Once identified, such phages will be isolated and used to study the effects on bacterial metabolism upon infection at a molecular level. The data from this study will then enable future in vivo studies and to apply for a ZonMW veni grant.

Patrick de Jonge

Felicia Bloemendaal (VENI-like-profile)

Mapping the circulating immune cell signature at a single cell level to predict response to anti-TNF treatment in Crohn's disease.

Felicia Bloemendaal

I am a resident in Gastroenterology and Hepatology with special interest in inflammatory bowel disease (IBD). I have previously completed a PhD in experimental Gastroenterology focused on the effector mechanism of anti-TNF in IBD through Fc-receptor mediated macrophage polarization. My research now aims to find a solution for the lack of determinants to select the right patient group for the right therapeutic class, as currently such therapeutic algorithms are lacking.

The AGEM talent development grant allows me…

… to search for the signature of response in peripheral blood of Crohn's disease patients treated with anti-TNF via single cell sequencing. Monoclonal antibodies against TNF are the first line treatment for moderate to severe Crohn's disease, but only a proportion of patients reach sustained remission and there is an unmet clinical need for biomarkers. We hypothesize that patients responding to anti-TNF possess a monocyte subtype capable of resolving intestinal inflammation through anti-TNF engagement. For this purpose we will use samples from IBD patients that we collect in a large biobank at the Gastroenterology department of the Amsterdam UMC. The unbiased approach of single cell sequencing will allow the opportunity to test a multitude of known potential biomarkers and identify novel pathways at once. With this project we hope to contribute to strategies of personalized medicine.


Felicia Bloemendaal

The AGEM innovation grant 2022 (€50.000)

Jan Verhoeff, Febe van Maldegem and Wouter de Jonge

Spatial biology at the single cell level from formalin-fixed paraffin-embedded intestinal biopsies

Jan Verhoeff

Jan Verhoeff is a postdoctoral research fellow specialized in advanced cellular phenotyping through single cell technologies s. He is working at the Tytgat Institute, part of the Gut Research group. He did his PhD in tumor immunology at the MCBI department in close collaboration with the MCCF core facility there, making use of the Helios mass cytometer, Aurora spectral flow cytometer and novel data analysis methods.

Febe van Maldegem

Febe van Maldegem is an immunologist focusing on the tissue microenvironment of non-small cell lung cancer. She started her group at the MCBI after postdoctoral research fellowships at the Francis Crick Institute in 2021. An expert in imaging mass cytometry, she has applied to mouse models of immunotherapy targeting NSCLC. Her rapidly growing research group is expanding the research topics to new areas, with a core focus on imaging mass cytometry.

Wouter de Jonge

Wouter de Jonge is leading the Gut Research group at the Tytgat Institute. Research topics include the pathogenesis and treatments of inflammatory and functional bowel disorders and related complications such as fibrosis and fistulae formation, interactions between the gut and the brain, and the epigenetics of mucosal immune cells .

The AGEM innovation grant allows us…

The department of Gastroenterology at the Amsterdam UMC has been able to set up a world-class research environment. Nearly every patient that is diagnosed with an IBD-related illness is included in ongoing studies. This goes back many years, leading to a large amount of samples, biopsies, or resection material that have been stored in paraffin blocks. For many patients this includes samples before start of treatments and after, or samples before later complications or recurrence of symptoms.

A premier method of investigating these FFPE biopsies is through imaging mass cytometry (IMC). A highly multiplexed imaging technique, it allows for the simultaneous measurement of 35+ protein targets at a resolution of 1 µm. Subsequent data analysis results in single cell segmentation, which quantifies protein expression and morphology, plus the spatial information. The AGEM innovation grant allows us to create a backbone panel of 20 antibodies, in itself sufficient to widely phenotype intestinal immune cells, epithelial cells and surrounding stromal cells. This ready-to-use panel would be applicable to any FFPE human sections. AGEM researchers interested to use IMC would not require to invest the (considerable) start-up cost of purchasing an entire panel, instead working with us from a central stock. Project specific antibodies can be easily added, expanding on the backbone.

Data from the IMC will quantify the number, phenotype, and activation status of (infiltrating) immune cells in the intestine. Through the spatial information, interactions with epithelial and stromal surroundings can be quantified and compared between experimental groups. Our own research line will investigate what role stromal cell activation plays in fistulae formation in Crohn’s disease.

Jan Verhoeff, Febe Maldegem and Wouter de Jonge

Miriam van der Werf, Mireille Serlie and Peter Bisschop

The effect of nutritional desynchronization on bone turnover and circadian rhythm in intestinal failure patients

Miriam van der Werf

Miriam van der Werf, is a registered dietician, clinical epidemiologist and PhD candidate at the Parenteral Nutrition and Intestinal Failure Clinic of the Amsterdam UMC, University of Amsterdam, Department of Endocrinology & Metabolism. She combines her clinical work with teaching at The Hague University of Applied Sciences, Faculty of Health, Nutrition and Sports, department Nutrition and Dietetics, the Netherlands.
Her research interest focusses on micronutrient status of patients with malabsorption due to intestinal failure or intestinal insufficiency. She is a specialist in enteral and parenteral nutrition, with more than 14 years of clinical experience in this field. In 2022 she was awarded with a Doctoral Grant for Teachers by the Dutch Research Council (NWO) and with an AGEM innovation grant.

Mireille Serlie

Mireille Serlie is an endocrinologist at the department of Endocrinology and Metabolism at the Amsterdam University Medical Centers (location AMC) and professor of Medicine at the University of Amsterdam as well as Yale University in the USA. She is the medical director of the Parenteral Nutrition and Intestinal Failure Clinic at the AUMC. Her research focusses on the nutrition, the neuroscience of obesity and on mechanisms of insulin sensitivity.

Peter Bisschop

Peter Bisschop is a consultant endocrinologist and professor of Endocrinology at the University of Amsterdam. As a PhD student he worked on the role of macronutrients in the regulation of insulin sensitivity. After he obtained his PhD in 2004 the primary focus of his research is on thyroid and bone disease.

The AGEM innovation grant allows us…

Intestinal failure is defined as “the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, requiring parenteral nutrition and/or fluids and electrolytes”. Intestinal failure can be caused by primary gastrointestinal diseases, complicated major abdominal surgery, radiation enteritis or motility disorders. Many chronic intestinal failure patients are on cyclic infusion of parenteral nutrition during the nighttime for practical reasons, but this pattern of feeding is not concordant with their biological clock. Nocturnal parenteral nutrition may negatively affect bone turnover, nitrogen balance, sleep/wake rhythms and glucose metabolism. Diurnal administration of parenteral nutrition is expected to be more in line with the biological clock and can possibly lead to fewer complications due to circadian resynchronization. The AGEM innovation grant allows us to study the effect of nocturnal versus daytime cyclic infusion of parenteral nutrition in adult chronic intestinal failure patients on bone turnover, glucose metabolism, nitrogen balance, sleep and wake rhythm and clock genes expression. The results of this study could have direct implications for patients with chronic intestinal failure. Beyond the scope of patients with chronic intestinal failure, our study also provides a unique human model to study the effects of nutritional desynchronization.

Miriam van der Werf and Peter Bisschop

The AGEM contribution printing costs of theses 2022 (€250)

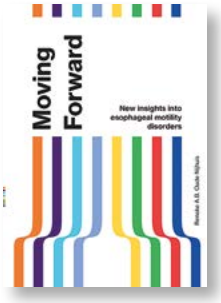
Kyra van Rijn

Date of defense: January 20th,2022

MRI for Gastrointestinal Diseases: Advances in assessment of small bowel motility and perianal Crohn's disease

Magnetic Resonance Imaging (MRI) is a frequently used imaging technique for several diseases of the gastrointestinal tract. The research in the first part of this thesis investigates the use of cine-MRI, a technique that can capture a movie of the bowel, to gain insight in small bowel motility disorders. In the second part of this thesis, advances in the use of MRI to evaluate treatment responses in perianal Crohn's disease patients are investigated.

Renske Oude Nijhuis

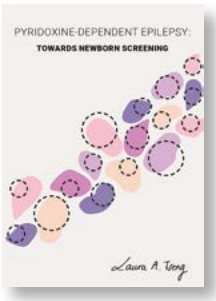


Date of defense: February 3rd, 2022

Moving forward: new insights into esophageal motility disorders

Clinical care involving patients with esophageal dysfunction has changed significantly in the past decade under influence of new developments including high-resolution manometry, impedance planimetry, endoscopic treatment modalities such as per-oral endoscopic myotomy and studies providing new perspectives on diagnostic algorithms and therapeutics. The studies described in this address some of the current knowledge gaps and specifically focus on three esophageal motility disorders. Namely, gastroesophageal reflux disease, achalasia and the inability to belch syndrome.

Laura Tseng

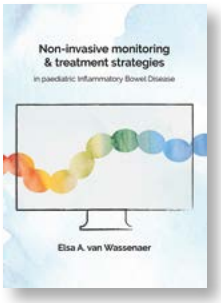


Date of defense: January 26th, 2022

Pyridoxine-dependent epilepsy: Towards newborn screening

The aim of this thesis is to provide and discuss evidence that enables informed decision making on inclusion of pyridoxine-dependent epilepsy (PDE-ALDH7A1) in newborn screening programs. Studies included aim to improve knowledge about phenotype & disease course, pathophysiology, and treatment outcomes, with a focus on the effect of lysine-reduction therapies and timing of therapy on neurodevelopmental outcomes. Additionally, an international guideline and national care pathway are provided to optimize standardized management of PDE-ALDH7A1.

Elsa van Wassenaer

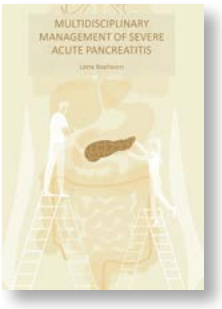


Date of defense: March 18th, 2022

Non-invasive monitoring & treatment strategies in paediatric Inflammatory Bowel Disease

Inflammatory Bowel Disease (IBD) is a debilitating chronic relapsing and remitting condition. This thesis focused on non-invasive monitoring strategies for IBD in children, with a focus on the use of intestinal ultrasound (IUS). We analysed the patient perspectives on IUS and assessed diagnostic accuracy of IUS. Furthermore, we assessed whether a physician can be trained to perform a point-of-care IUS with equal accuracy as a paediatric radiologist and lastly, we demonstrated the clinical added value of IUS as point-of-care monitoring tool.

Lotte Boxhoorn

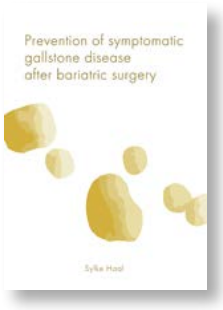


Date of defense: March 25th, 2022

Multidisciplinary management of severe acute pancreatitis

The aim of the studies described in this thesis is to improve treatment of patients with severe acute pancreatitis. The central studies in this thesis investigate the timing of treatment and the use of different stents for endoscopic treatment. Also the long-term clinical outcomes of patients with severe acute pancreatitis are described in a follow-up study.

Sylke Haal



Date of defense: April 8th, 2022

Prevention of symptomatic gallstone disease after bariatric surgery

Obese patients undergoing bariatric surgery are at high risk for cholesterol gallstone disease and form gallstones extremely rapid after surgery. This thesis contributes to the knowledge of the pathogenesis of cholesterol gallstone formation after bariatric surgery and whether UDCA prophylaxis should be prescribed after bariatric surgery to prevent symptomatic gallstone disease, and to whom.

Esther Klaver

Date of defense: March 30th, 2022

Towards improved risk stratification in Barrett's esophagus

Barrett's esophagus (BE) is a premalignant condition, increasing the risk to develop esophageal adenocarcinoma (EAC). The majority of patients with BE, however, will never progress to EAC. This generates the need for better risk stratification. The first part of this thesis focuses on expert pathology in BE and the development of an expert review panel. The second part of this thesis focuses on identification and validation of biomarkers and risk factors for malignant progression.

Manon de Krijger

Date of defense: May 13th, 2022

Gut-liver interactions in primary sclerosing cholangitis and inflammatory bowel disease

Primary sclerosing cholangitis (PSC) is a rare, chronic inflammatory liver disease, with an unknown aetiology, and frequent co-occurrence with inflammatory bowel disease (IBD). This thesis contains three parts. The first part investigates the presence of gut-specific T-cells in long-term PSC and pouchitis. The second part shows that quantification of fibrosis in liver biopsies of patients with PSC is strongly correlated with long-term clinical outcome in PSC. The last part describes an extensive molecular screen on PSC-IBD-associated colorectal cancers, which could not explain the excess risk of colorectal cancer in PSC.

Abraham Hulst

Date of defense: May 25th, 2022

Glucose control therapies in the perioperative period

This thesis focusses on the treatment of glucose in patients in the perioperative period. In part I current treatment of of patients with diabetes in the perioperative period in Dutch hospitals is discussed. Futhermore, we describe the difference in perioperative glucose control between patients with type 1 and type 2 diabetes mellitus. Finally we report the ineffectiveness of metformin continuation to improve perioperative glucose control. Part II revolves around the use of incretin mimetics.

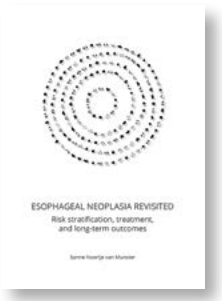
Paul Vollebregt

Date of defense: June 24th, 2022

Disorders of continence and defaecation - Insights into risk factors, underlying pathophysiology and treatment

Faecal incontinence (uncontrolled loss of stool) and constipation are common symptoms which can have a negative impact on quality of life. In this thesis we evaluated potential underlying pathophysiological mechanisms, some of which require further investigation to evaluate clinical importance (anal motor dysfunction), while others were shown to impact on symptom profile and severity (rectal sensorimotor dysfunction). Conservative (transanal irrigation) and surgical (sacral neuromodulation) treatment were studied, aiming to improve future management in these patients.

Sanne van Munster

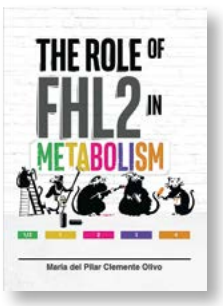


Date of defense: June 17th, 2022

Esophageal neoplasia revisited: risk stratification, treatment, and long-term outcomes

Barrett's esophagus is a condition characterized by damage to the distal part of the esophagus by reflux disease and is associated with development of esophageal adenocarcinoma (EAC). Patients with Barrett's esophagus undergo surveillance aiming to detect cancer at early stages and allow for low-risk endoscopic therapy. In this thesis, we evaluated indications for endoscopic treatment, outcomes of the current treatment strategy, personalization of care and we evaluated new techniques for endoscopic treatment.

Maria Pilar Clemente Olivo

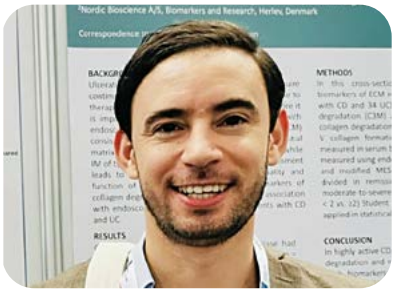


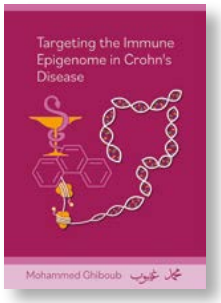
Date of defense: June 30th, 2022

The role of FHL2 in metabolism

This thesis describes the role of the protein 'FHL2' in metabolism. In the adipose tissue and in the pancreas, the presence of FHL2 increases with the aging of an individual. We show for the first time that FHL2 has an effect on obesity and type 2 diabetes, where a low level of FHL2 is beneficial to prevent these diseases. This makes FHL2 a potential target for future treatments to combat obesity and type 2 diabetes.

Mohammed Ghiboub





Date of defense: September 14th, 2022

Targeting the Immune Epigenome in Crohn's Disease

Epigenetic processes play a critical role in the regulation of myeloid cell differentiation and gene expression, mediated for instance by DNA methylation and histone post-translational modifications. In this thesis, we investigated the therapeutic potential of targeting the immune-epigenome, focusing on myeloid cells and inflammatory bowel disease, as well as exploring the possible existence of differential DNA methylome as a putative biomarker associated with different clinical activity in Crohn's disease patients.

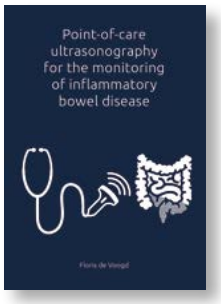
Lotje van Ruiten

Date of defense: September 27th, 2022

Effects of SGLT2 inhibition and GLP-1 receptor agonism on the regulation of food intake and body weight: illuminating the role of the brain

We investigated if SGLT2-inhibitors induce changes in brain responses to food-cues, possibly inducing hyperphagia, and thereby inducing less weight loss than expected. We found that SGLT2-inhibitors cause ~3kg weight loss, but also an unfavorable effect on brain responses, and an increase in carbohydrate intake, which contributes to the difference between observed and expected weight loss. In combination therapy, GLP-1RA can overcome the unfavorable effects of SGLT2-inhibitors on brain responses, which contributes to more weight loss.

Floris de Voogd



Date of defense: September 21st, 2022

Point-of-care ultrasonography for the monitoring of inflammatory bowel disease

In this thesis we investigated the role of intestinal ultrasound (IUS) for the monitoring of inflammatory bowel disease. Predominantly bowel wall thickness (BWT) and hypervascularity of the bowel wall correlate perfectly with endoscopic disease activity scores in Crohn's disease and ulcerative colitis. Furthermore, IUS accurately determined endoscopic treatment response, already two to eight weeks into treatment. Thereby IUS allows tight monitoring and could function as a surrogate marker for endoscopic disease activity in most patients.

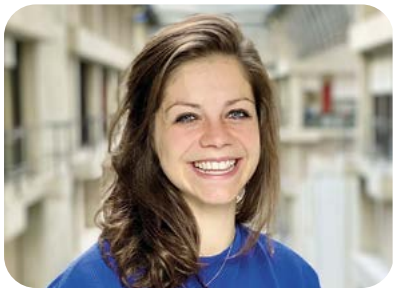
Sanne van Neerven

Date of defense: September 30th, 2022

On the origin of Colorectal Cancer: Cell competition in the intestine

Every week, the entire epithelial monolayer is being replaced by intestinal stem cells (ISCs) that reside in crypt bottoms, where they continuously divide and generate all cell types necessary for intestinal homeostasis. Within a crypt bottom, small numbers of ISCs are engaged in an ongoing neutral competition with each other, a process that can dramatically be disturbed whenever an ISC acquires a mutation that can initiate cancer development.

Britt Houwen

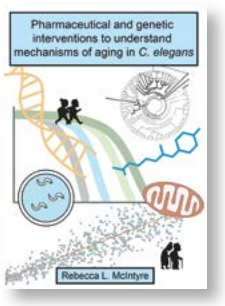


Date of defense: September 30th, 2022

Human-machine collaboration: Improving endoscopic detection and characterization of colorectal neoplasia

One of the most prominent clinical challenges in colorectal cancer (CRC) prevention is to further optimize the endoscopic detection and characterization (optical diagnosis) of colorectal polyps. Three approaches to improve this are investigated in this thesis: improving endoscopic detection and characterization of polyps by use of advanced endoscopic techniques, improving endoscopic characterization of polyps by development of dedicated training programs and competence standards, and improving endoscopic characterization with reduced inter-observer variability by assistance of machine learning.

Rebecca McIntyre

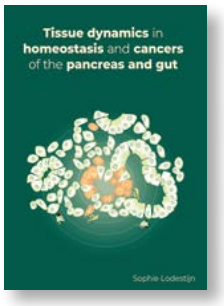


Date of defense: October 14th, 2022

Pharmaceutical and genetic interventions to understand mechanisms of aging in C. elegans

As aging is the major risk factor for many chronic diseases, understanding how to slow these pathways is critical to human well-being. In this thesis, we aimed to contribute to the understanding of aging mechanisms and treatment of age-related diseases by (1) investigating mitochondrial dysfunction as a hallmark of aging, (2) identifying and validating pharmaceuticals to promote healthy aging, and (3) utilizing these pharmaceuticals to deepen understanding of aging mechanisms in the model organism, C. elegans.

Sophie Lodestijn

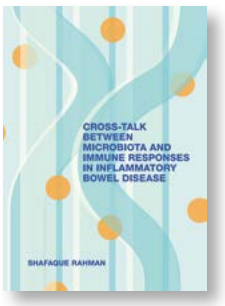


Date of defense: October 7th, 2022

Tissue dynamics in homeostasis and cancers of the pancreas and gut

In this thesis, we have employed proliferation-dependent, marker-agnostic lineage tracing systems in combination with quantitative models to provide insights in the fundamental characteristics of tissue homeostasis, repair and cancer growth, in the intestine and the pancreas. We found that all acinar cells have an equal ability to contribute to pancreatic tissue homeostasis and regeneration after pancreatitis induction. In colon and pancreas cancer, we found that tumor expansion is defined by the tumor microenvironment.

Shafaque Rahman

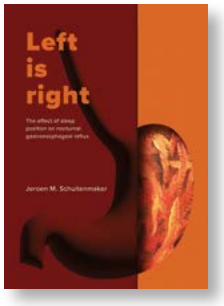


Date of defense: October 28th, 2022

Cross-talk between microbiota and immune responses in inflammatory bowel disease

The dissertation investigates the role of the microbiome and immune responses contributing to the pathophysiology of inflammatory bowel disease. At first, the various tools developed to study intestinal physiology and functions are described. Next, the effects of curdlan on the microbiome and intestinal inflammation in mice and the role of fungi in human FMT are studied, respectively. Furthermore, we explored the immune responses elicited through microRNA-511 in different colitis models in mice.

Jeroen Schuitenmaker

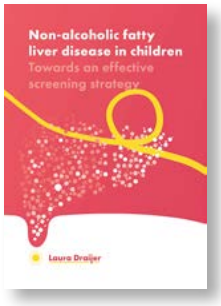


Date of defense: November 2nd, 2022

Left is right: the effect of sleep position on nocturnal gastroesophageal reflux

Gastroesophageal reflux, the movement of gastric content into the esophagus, is a physiological phenomenon that occurs multiple times a day. When it leads to esophageal mucosal damage and/or symptoms such as heartburn and regurgitation, it is referred to as gastroesophageal reflux disease. This thesis covers studies on gastroesophageal reflux disease, mainly focusing on nocturnal gastroesophageal reflux. We evaluated current available treatment options, investigated the effect of sleep position on nocturnal reflux and explored sleep positional therapy as novel treatment strategy for nocturnal gastroesophageal reflux.

Laura Draijer

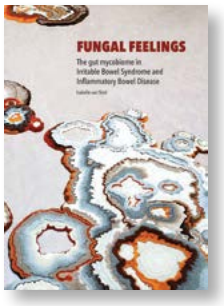


Date of defense: November 17th, 2022

Non-alcoholic fatty liver disease in children: Towards an effective screening strategy

Non-alcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver disorder in children and adults worldwide. It is highly associated with obesity and can lead to serious complications such as fibrosis or liver failure. This thesis is aimed to improve screening for NAFLD in children. Therefore we evaluated the usefulness of several diagnostic tests, identified barriers for screening in clinical practice, determined the long-term outcomes of pediatric NAFLD and explored risk factors for progression.

Isabelle van Thiel

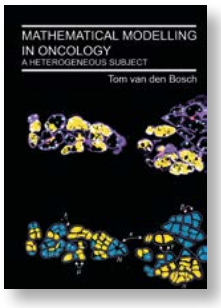


Date of defense: November 4th, 2022

Fungal Feelings: the gut mycobiome in Irritable Bowel Syndrome and Inflammatory Bowel Disease

Irritable Bowel Syndrome (IBS) is a functional bowel disorder characterized by frequent abdominal pain. Recent evidence indicated that fungi in the intestine may contribute to abdominal pain. In this thesis, we investigate how the fecal fungi may contribute to (severity of) abdominal pain or inflammatory bowel disease (IBD). We show that changes in the fungal composition and partially associate with abdominal pain in IBS, and that genetic and phenotypic changes occur among yeasts isolated from feces.

Tom van den Bosch

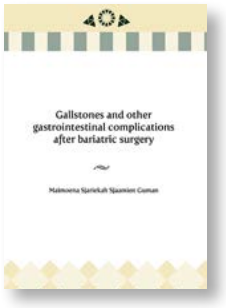


Date of defense: November 21st, 2022

Mathematical modelling in oncology: A heterogeneous subject

Mathematics can be applied in many different fields, oncology being no exception. Mathematical models require data to be constructed, tested and validated, which makes their applications largely driven by opportunity. Furthermore, different hypotheses require different mathematical models. As such, many different kinds of mathematical models can be used depending on the available data and proposed research question. In this work, three distinct aspects of mathematical oncology are studied as a result.

Maimoena Sjariekah Sjaamien Guman



Date of defense: December 2nd, 2022

Gallstones and other gastrointestinal complications after bariatric surgery

Gallstone development after bariatric surgery seems to be caused by different pathways compared to gallstones in the general population. Moreover, metabolic active adipose tissue and certain bacteria might protect against gallstone development after bariatric surgery. Prophylactic use of ursodeoxycholic acid reduces the occurrence of symptomatic gallstone disease, but the effect relies on the adherence. Other causes for abdominal complaints after bariatric surgery, such as altered bowel habits and exocrine pancreas insufficiency, should also be considered.

Events 2022

AGEM PhD-student course

January 17th – 28th 2022

AGEM PhD-student course 2022

Amsterdam UMC, locations AMC and VUmc and online via ZOOM

In January of 2022, AGEM offered for the third time a course specifically developed for PhD-students that perform research in the field of gastroenterology, endocrinology and/or metabolism. This course aimed to inform (starting) PhD-candidates about gastroenterology, endocrinology and metabolism, including those topics that are not necessarily within the scope of the PhD-candidates own research. The course was coordinated by five AGEM members, Anje te Velde, Dries Kalsbeek, Sarah Siegelaar, Riekelt Houtkooper and Maarten Soeters, and more than 40 teachers gave lectures during the course.

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

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

At the beginning of the course the PhD-students were given an assignment in small groups of three or four students. During the course the PhD students wrote a multidisciplinary grant proposal that was, well-prepared by the pitch workshop given in the first week, pitched to all participants on the last day of the course.

Presentation by Dirk Jan Stenvers

Presentation by Paul van Trotsenburg

AGEM annual retreat

March 31st & April 1st 2022 AGEM retreat 2022

Bilderberg Hotel 't Speulderbos, Garderen

The goal of the AGEM retreat is to discuss, share and learn from each other's research. Mixing AGEM retreat customs with new ideas, definitely resulted in successfully obtaining this AGEM vision. After two years of COVID, we were able to organize a live retreat again. It was absolutely fantastic to see all the PhD-students, postdocs and PIs together and enjoying this event!

For a lot of PhD-students this was the first live conference, which resulted in a record number of participants – more than 120 – this year. It was wonderful to be able to have this meeting in a non-hybrid/no-Teams format, but with real colleagues in the same room.

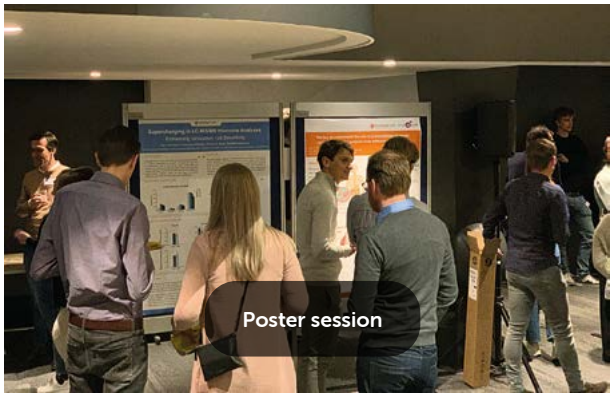
Plenary session

We had a full and diverse program. Due to the large number of participants, which we all wanted to give the opportunity to present their work, we had three plenary sessions as well as three parallel sessions (consisting of three sessions each). Many interesting classical presentations and elevator pitches within the fields of gastroenterology, endocrinology & metabolism were given by our colleagues. New this year were the poster presentations, enabling participants to share their findings in a different way and resulting in various interesting discussions between the presenter and other attendees.


Parallel session

Next to these lectures, the attendees could choose a workshop to attend from an array of relevant topics. The options offered this year were: "Presenting with Humor", "Rapid Reading", "Business Drawing/House of Imagination" and "Wim Hof/Iceman Challenge", where participants enjoyed a real ice bath in the snow.

To get to know each other better, we organized a fun and interactive evening program. We started with some drinks. After dinner, laughing and relaxing was stimulated by a hilarious and phenomenal performance by an illusionist. The first day ended with a good party themed 'Alter ego'. Everybody excelled in their outfits and dance moves; it was incredible to see the great effort participants had made to match their outfits to the retreat's theme.


Poster session

As in previous years, Friday morning started with an energetic bootcamp, with a special touch: snow! This year's keynote speaker was Prof. Max Nieuwdorp, who gave an very inspiring lecture on microbial metabolites to treat autoimmune diabetes.

Last but not least we would like to congratulate those who won an award: Koen Wortelboer for best presentation, Vera de Kleijne for best poster presentation, Ömrüm Aydin for most contributing participant and Sanne Jolien van der Veen for best party outfit.

Thank you all for making this a great AGEM retreat in 2022. We look forward to see you again, and to welcome new participants in 2023!

On behalf of the Organizing Committee,
Claire van Helsdingen & Elsa van Liere

Workshop
1 t/m 4

Illusionist

Bootcamp

AGEM meetings 2022

May 11th 2022

Symposium: "ImmunoMetNet" supported by AGEM

VU NU building, Amsterdam

Finally! After a virtual ImmunoMetNet symposium last year and many Online Immunometabolism Seminars during the first lockdown in 2020, we could finally meet and discuss science in person again!

Apparently people were eager to do so, resulting in more than 100 registrations and a very interactive symposium. ImmunoMetNet was set up by Jan Van den Bossche in 2019 to build a network between immunology and metabolism research and medicine across different disciplines and institutes. ImmunoMetNet 2022 clearly achieved this goal by attracting both fundamental and clinical Amsterdam UMC researchers from AGEM, ACS, AII and CCA, as well as immunometabolism enthusiasts from all over the Netherlands and even abroad.

With the support of the different Amsterdam UMC research institutes and sponsors, some renown international speakers were invited and together with the presentations of national and local specialists and pitches of young reseachers, they made ImmunoMetNet 2022 a big success.

The day was kicked off by Keynote speaker David Sancho (CNIC, Madrid, Spain) who presented unpublished work on the role of oxidative phosphorylation in maintaining tissue macrophage homeostasis. Next, Ron Heeren (Maastricht University) presented applications of imaging mass spec to define (immune)metabolic profiles at single-cell resolution. The following short pitches by PhD's highlighted that immunometabolism research is booming in and around Amsterdam UMC and that there is a need for more regular local ImmunoMetNet symposia allowing young researchers to present their ongoing immunometabolism-related work across the borders of the different research institutes.

After a well-deserved coffee break, Eric Eldering, Arnon Kater (both Amsterdam UMC, CCA & AII) and Sander de Kivit (LUMC) presented their new work in a session dedicated to immune-metabolic crosstalk in cancer. The first afternoon session was more atherosclerosis-focused with local (Karl Harber), national (Marit Westerterp, UMCG) and international (Florian Kahles, Aachen and Mandy van Leent, Mount Sinai, NY) presenting on immunometabolic changes regulate inflammation in cardiovascular disease. The last session included talks about macrophage metabolism in cancer therapy (Cesar Oyarce Diaz, CCA) and O-GlcNAcylation in macrophages (Graham Heieis, LUMC), and the scientific part of this fruitful meeting was closed by a keynote lecture by Peter Murray (Max Planck Institute of Biochemistry, Martinsried) on Immunologic anti-ferroptosis.

Beer, wine and bitterballen (bitter balls?) fueled the networking part of ImmunoMetNet and we ended the day with a tasteful and fun dinner at PizzaLab.

The post-event survey confirmed our feeling during the day; ImmunoMetNet 2022 was a big success! It also became clear that there is a need for more regular local ImmunoMetNet symposia where young Amsterdam UMC will present their ongoing immunometabolism work. This idea is currently being developed but it is clear that in addition to the annual (inter)national ImmunoMetNet symposium, there will be regular ImmunoMetNet AMS meetings and that AGEM will play an import role in this. Keep an eye on www.immunometnet.com, follow @immunometnet on Twitter or reach out to immunometnet@amsterdamumc.nl for more information on future ImmunoMetNet symposia.

Presentation by David Sancho

Presentation by Ron Heeren


ImmunoMet-Networking
Agilent Technologies

May 18th 2022

AGEM Symposium: "Treating NASH: Translating new molecular insight into targeted therapy"

Amsterdam UMC, location AMC

On May 18th 2022, the second edition of the AGEM NAFLD symposium took place. Since the first edition in November 2020 consisted of an online seminar series, we were thrilled to be able to invite our speakers live in the AMC this time around.

Introduction by Eveline Bruinstroop and Onno Holleboom

We started at 13:00 with a Meet-the-Expert lunch, where young investigators got the chance to speak with our speakers: prof. Stefano Romeo from the University of Gothenburg, prof. Paul Yen from Duke-NUS Medical School, Singapore and "our own" prof. Stan van de Graaf, from the Tytgat Institute at the AMC. In small groups, topics surrounding research, a career in academia, and much more was discussed.

The symposium started at 15:30 in Collegezaal 5, which could also be followed through an online stream. After an introduction from moderators Eveline Bruinstroop and Onno Holleboom, prof. Stefano Romeo told us about his research journey in human genetics to identify therapeutic targets for fatty liver disease. Though known for his identification of the PNPLA3 risk variant for NAFLD, he now told us about his more recent research on PSD3, a novel NASH gene.

Presentation by Stefano Romeo

The second speaker of the day was prof. Stan van de Graaf. He explained the potential of targeting hepatic bile salt uptake to treat NAFLD. After introducing bile acids as a sort of hormones, with a peaking rhythm during the day after each meal, he explained the therapeutic potential of inhibiting NTCP, the main hepatic bile salt uptake transporter in humans. NTCP inhibition reduces obesity, steatosis, atherosclerosis and inflammation, and its inhibition may provide a novel therapy for NAFLD/NASH.

After a coffee break, it was time for the second session of the symposium, where 4 young investigators presented their research in short talks. First up was Milena Schönke from Leiden UMC, who spoke about her mouse work into circadian exercise – could it be more beneficial to do sports in the evening than in the morning? Interestingly, she showed that early exercise could even induce an inflammatory response whereas late exercise did not. The second short talk was by Willemien van Zwol from the UMC Groningen. She explained her research on Smlr1, a small protein that may play an important role in the trafficking of ApoB/VLDL in hepatocytes. Thirdly, Mark Davids (Amsterdam UMC) took the stage to tell us about the production of endogenous alcohol by gut

bacteria. He and his colleagues measured plasma alcohol concentrations in patients with NAFLD, which increased greatly after a meal when alcohol dehydrogenase (ADH, the enzyme that breaks down alcohol in the liver) was blocked. This alcohol spike diminished after treatment with antibiotics. Perhaps NAFLD isn't so 'Non-Alcoholic' after all? Lastly, the short talk round was finished up by Dyonne Vos from the UMC Groningen, who talked about her work on hepatic retromer (VPS35) as an important player in cholesterol homeostasis, through its function in lysosomal trafficking.

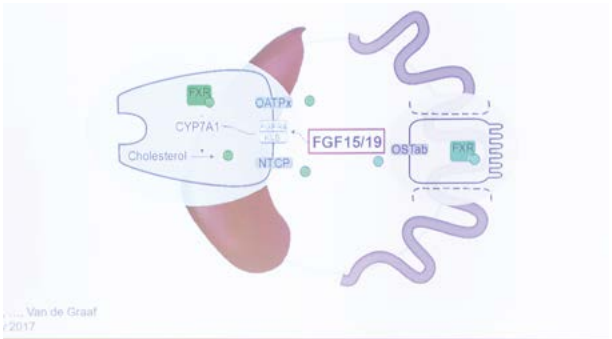
The evening continued with a dinner in the Box. Participants and speakers mingled while enjoying some food and drinks, before continuing to the last session.

The first speaker of the evening was prof. Paul Yen, who explained the importance of vitamin B12 and folate. In the metabolism folic acid, homocysteine is formed. Prof. Yen showed us that hyperhomocysteinemia can be a risk factor for hepatic steatosis and NASH. Perhaps vitamin B12/folate supplementation could be a safe and inexpensive first-line method to prevent NASH progression? As our final speaker, we were excited to introduce prof. Patrick Rensen from the Leiden UMC. He spoke about three potential therapeutic targets to treat NAFLD/NASH that his lab has tested in the APOE*3 Leiden.CETP mouse model: firstly, the FGF21 receptor; secondly, the gut hormones GLP1 and GIP; and thirdly, a novel strategy of inhibiting DHCR24 to increase the endogenous LXR agonist desmosterol he is currently working on. The evening ended with some drinks in the box.

We look back on a very successful event and thank all of the participants (live and online) for your attendance and great interactions!

The organizers of the AGEM NAFLD symposium,

Anne Linde Mak, Anne-Marieke van Dijk, Maarten Tushuizen, Saskia van Mil, Onno Holleboom and Eveline Bruinstroop




Presentation by Stan van de Graaf

Presentation by Paul Yen

June 8th, 2022

Symposium "Laboratory animal (free) research in Amsterdam UMC – Where are we now?" supported by AGEM

Amsterdam UMC, location VUmc and online

On Wednesday June 8th 2022, seven of the eight research institutes of Amsterdam UMC jointly organized a symposium on 'Animal (free) research in Amsterdam UMC – Where are we now?'. This symposium was the start to be more transparent about the fact that we, within Amsterdam UMC, in some cases still use laboratory animals to address specific research questions.

From each research institute, one researcher presented their research and clearly indicated for which part no laboratory animals are necessary and for which part they still are used.

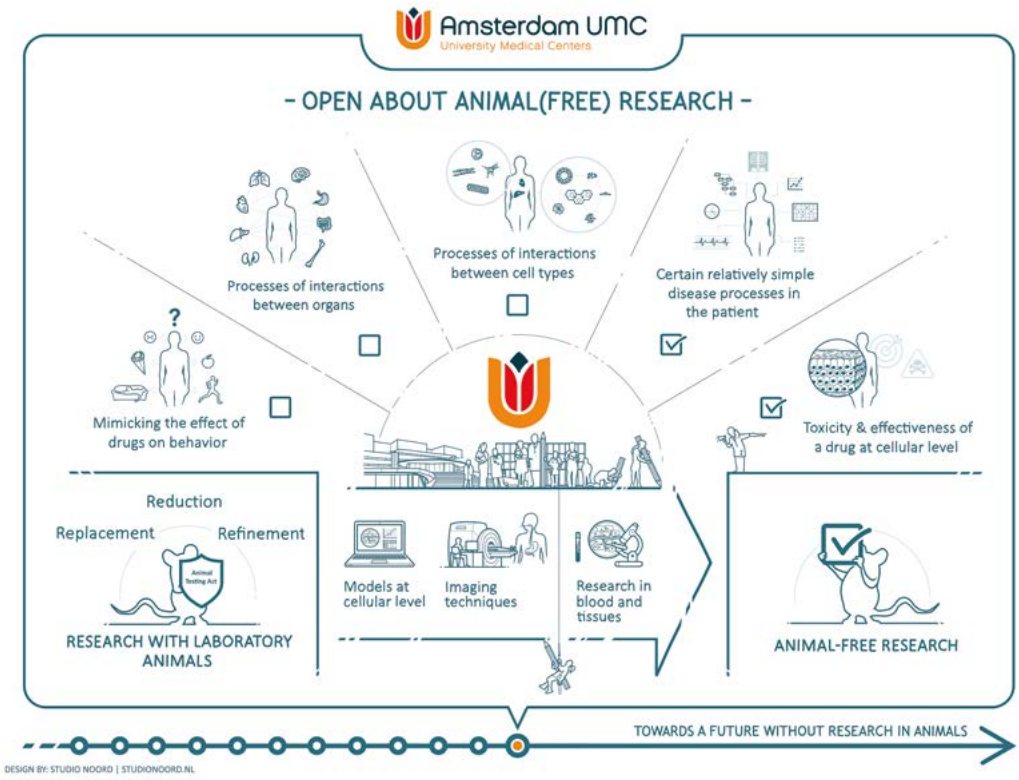
At the end of the symposium there were two panel discussions, each with its own main question:

1. Is animal testing still necessary?
2. What is needed from Amsterdam UMC to be more transparent/open about the use of laboratory animals?

In addition to the two portfolio holders of laboratory animal policy of the Amsterdam Research Board and the chairman of the Animal Welfare Body of location AMC, the following people were attending the panel discussions: a researcher Ethics and Animal Agency of Wageningen University & Research, senior program manager 'More Knowledge with Fewer Animals' of ZonMw, director of Proefdiervrij and a science advisor of 'People for the Ethical Treatment of Animals' (PETA).

The symposium was very successful and received well by the audience. There was an interesting discussion and points were raised for us as Amsterdam UMC to improve. This meeting will be an annual event to show society and politics what we are doing, and to discuss with them the challenges that exist to replace research in laboratory animals with animal-free models. In addition, it is a moment of reflection for us. To conclude in the words of PETA's science advisor: 'You choose to use laboratory animals in some cases. It's a choice.' This is absolutely correct: it is a choice we make as we believe that, for some cases, it is the only way to gain a better understanding of a specific disease or to test whether a certain strategy can lead to treatment or even prevention of a specific disease. More information can be found here:

- Amsterdam UMC | Animal free research
- Transition Animal-free Innovations - More about - Vrije Universiteit Amsterdam



Photography: Marieke de Lorijn

Animal facility

November 7th, 2022 AGEM – AII 2nd meet and greet

Volkshotel, Amsterdam

Twenty PIs and researchers from several departments (Rheumatology and Clinical Immunology, Tytgat Institute, Experimental Immunology, Molecular Cell Biology and Immunology, Clinical Chemistry, Medical Biochemistry, Dermatology, Gastroenterology and Genetic Metabolic Diseases) were present for lively discussions and exchange of ideas. Six PI's (most of whom were not at the first meeting) presented in a short pitch their research. A mix of diseases with immunological, metabolic and malignant basis and how our collaborative efforts can contribute to further understanding pathogenesis as well as improve diagnosis and treatment of these diseases was discussed.

Dr Lisa van Baarsen presented results on altered lipid metabolism in synovial fibroblasts of individuals at risk of developing rheumatoid arthritis and metabolic alterations in lymph node stromal cells from RA patients; a collaborative study that was initiated at the first meeting. A fine example of the success of our joint efforts.

We are confident that from this second meeting more new fruitful collaborations between AGEM and AII members will commence. We are looking forward to the next joint meeting.

Organization:
PIs from AII: Sander Tas and Conny van der Laken
PIs from AGEM: Anje te Velde
PI form AII and AGEM: Hetty Bontkes

December 7th, 2022 AGEM – RPO Responsible Research Dinner Debate

Vrijzaal, Amsterdam UMC, location AMC

In order to work on a research environment that promotes and guarantees responsible research practices, AGEM and Amsterdam UMC Research Policy Office (RPO) launched a new event in December 2022: the Responsible Research Dinner Debate (Diner Pensant). We invited three experts, who pioneered with specific responsible research practices, to share their experiences in the scientific integrity field with 30 AGEM researchers, from PhD students to Principal Investigators.

After a short introduction by AGEM director Stan van de Graaf, the 30 participants found their way to either of the three tables for the first course. Each of these tables was hosted by an expert, who first shared insights about best practices in creating a responsible research environment, drawing from their own experience and using tangible use cases. Subsequently, there was plenty of time for open debate between the experts and participants.

After the first course, during which fruitful discussions were held, participants switched tables and groups for the next course. This way, during the three-course dinner, participants were able to broaden their horizon on three different themes of responsible research practices, and join in knowledge and experience sharing with varying peers. The atmosphere was relaxed, allowing for open and honest discussions. The diverse group of participants, from different fields of expertise and different career stages, helped create interesting conversations.

Participants mentioned the event got them inspired and ready to bring ideas to foster responsible research practices to your own research group. Ever since, the first initiatives on responsible research practices have already been implemented at different departments. Thus, the first edition of this Responsible Research Dinner Debate was a great success!

December 9th, 2022

AGEM – CCA symposium: "HPBetter Symposium 2022 / Together we can make HPB treatments better"

O|2 building, Amsterdam UMC and online

On Friday December 9th, the second edition of the HPBeter symposium took place in the O2 building at De Boelelaan. HPB refers to disorders that affect the hepato-(liver)-pancreato-biliary organs. The symposium aims to gather medical professionals to improve treatment strategies and the quality of life for patients suffering from HPB disorders.

A diverse group of medical professionals and researchers from across the Amsterdam region gathered to learn about the latest developments and current state of practice in the field of HPB medicine, including both benign and malignant disorders. To achieve this, various speakers stepped up to the challenging task of presenting their work and insights gained from their many years of research and clinical experience in concise presentations. Researchers presented the latest results of their ongoing studies as well as their pending studies, and medical specialists and experts shared their insights on the use of new techniques and treatment strategies in daily practice.

Topics included:

- Progress in (robotic) minimally invasive partial liver resections
- Long-term outcomes following different strategies in the treatment of pancreatitis
- Optimal work-up prior to resection or ablation of colorectal liver metastases
- Alternative approaches of bile duct drainage
- Quality of life in different stages of pancreatic cancer
- A potential breakthrough in the treatment of Crigler Najar disease.

Collaborations are imperative

A recurring theme was the importance of cooperation between hospitals, research institutes, and sponsors. It was frequently mentioned that without this cooperation, much of the research discussed at the symposium would not have been possible.

Liver-perspectives in history

To conclude the day, the audience was treated to an engaging lecture by Thomas van Gulik, who shared the rich history of liver medicine and its influence on art and science throughout the ages, from the myth of Prometheus to 16th-century anatomical drawings.

Inspired to look forward

Overall, the HPBeter Symposium 2022 was a highly successful and engaging event, providing attendees with a wealth of interesting and motivating information and insights. The symposium was made possible by Cancer Center Amsterdam and the Amsterdam Gastroenterology Endocrinology Metabolism Research institute. Planning for the next edition of the HPBeter symposium is already underway, with a focus on expanding the audience and organization both regionally and hospital-wide, among other topics. We hope to see all who are affiliated with HPB clinics and/or research in the Amsterdam region in 2023!

HPBeter symposium organizing committee:
Rutger-Jan Swijnenburg, Michiel Zeeuw, Charlotte van Veldhuisen, Deesje Doppenberg, Boris Janssen, Jeska Fritzsche, Remco Kersten, Marjolein Lansbergen, Anne Gehrels and Britte ten Haaft.

AGEM seminar series 2022

AGEM Tager Lectures

The AGEM research institute has a seminar series in the Amsterdam UMC, location AMC, focused on metabolism; the Tager Lecture, called after Professor Joseph Tager. Joseph Tager made important contributions to Fabry, Pompe and Gaucher disease and had a major impact on our understanding of peroxisomal diseases. He was chairman of the Biochemistry Department at the University of Amsterdam (1980-1991). The Tager Lecture series is organized by AGEM PI's Riekelt Houtkooper, Susanne La Fleur, Stan van de Graaf and Noam Zelcer. Suggestions for future speakers for the Tager lecture are always welcome.

Thursday October 13th, 2022 **Amsterdam UMC, location AMC**

Dr. Sabine Fuchs

Associate professor, pediatrician (PhD, MD), pharmacist
Dpt. of Metabolic Diseases, UMC Utrecht

"Prime Time": Adult stem cell (organoid) technology and precise gene (prime) editing to develop innovative therapies for patients with metabolic diseases

ImmunoMetNet AMS meetings

Tuesday November 29th, 2022 **Amsterdam UMC, location VUmc, O|2 building**

The ImmunoMetNet AUMC series are started! Instead of the keynote talk that was initially considered, the series was kicked off by ImmunoMetNet initiator Jan Van den Bossche. Next to the scientific talk about the newfound immunometabolism D-2-hydroxyglutarate in macrophages and the plans his lab with this wonderful molecule, the past and future of ImmunoMetNet was discussed. A short poll at the end of the presentation provided useful insight into what AUMC researchers expect from this series. Looks like we are well on track and aligning with the expectations, we will probably schedule the meetings every 3 months (instead of 2 months) and invite an external speaker every once in a while. Drinks and snacks were kindly provided by AGEM and certainly fueled ImmunoMet-networking, which is an important goal of these meetings.

Tuesday December 20th, 2022 **Amsterdam UMC, location VUmc, O|2 building**

After the successful kick-off for the ImmunoMetNet AUMC series by Jan Van den Bossche (Welcome to the wonderful world of immunometabolism) on November 29th, the first “real” local ImmunoMetNet meeting was organized on December 20. With between 20 and 25 participants and some very good discussions during the low-key presentations, this afternoon was certainly a success. We scheduled 4 talks by junior and senior PhD’s, and one postdoc. The different institutes were well represented:

- Esmée Hoen (AGEM/AII) from the lab of Anita Boelen presented her ongoing work and plans on Thyroid hormone transporters and their role in macrophage activation
- Felipe Correa-da-Silva (AGEM/Neuro) from Chun-Xia Yi’s group presented on microglia dysfunction in Prader-Willi-Syndrome;
- Beatriz Marton Freire (ACS/AII) shared here work on how beta-2 adrenergic receptor affects metabolic rewiring in macrophages;
- Helga Simon-Molas (CCA/AII, postdoc on the lab of Eric Eldering and member of the ImmunoMetNet organizing committee) presented ongoing work on how T cells are metabolically fueled in chronic lymphocytic leukemia.

Grand Rounds in Digestive Diseases

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 a new series of lectures organized by the Department of Gastroenterology & Hepatology, entitled 'Grand Rounds in Digestive Diseases'.

In bi-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, four times a year more general topics are covered. For example, we had the pleasure to host Marcel Levi discussing the differences in health care systems in the Netherlands and the UK. In addition, we hosted the Dutch minister of Health Care, Prof. Ernst Kuipers, in a special 'College Tour' edition of the Grand Rounds which enabled the audience to ask specific questions to our Health Care minister.

These series of lectures have been initiated by Prof. Geert D'Haens and Dr. Joep Grootjans from the department of Gastroenterology & Hepatology, together with the research institute AGEM (Amsterdam Gastroenterology Endocrinology Metabolism). 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 the location AMC (bi-monthly, Thursday morning from 8.00AM to 8.45AM) and online via zoom.

January 13th, 2022	Prof. Marcel Levi ***Is there any impact of differences in health care systems on outcome?***
January 27th, 2022	Prof. Evelien Dekker ***Population screening for colorectal cancer: strengths, weaknesses, opportunities and threats***
February 10th, 2022	Prof. Jaap Stoker ***Novel MR imaging techniques for inflammatory and motility disorders of the small bowel***
March 10th, 2022	Prof. Wouter de Jonge ***The gut-brain axis-how the nervous system controls inflammation***
March 24th, 2022	Dr. Charlotte Scott ***DeLIVERing an atlas of hepatic macrophage populations across species and disease***
April 7th, 2022	Prof. Geert d'Haens ***Breaking the therapeutic ceiling in Crohn's disease***
April 21st, 2022	Dr. Rutger-Jan Swijnenburg ***Image-Guided Precision Robotic Liver Surgery***
May 12th, 2022	Prof. Jaap Bonjer ***Going DUTCH; Digital United Training Centres for Healthcare***
June 2nd, 2022	Prof. Joanne Verheij ***Clinical relevance of the molecular subclassification of liver tumors***
June 16th, 2022	Dr. Nanne de Boer & Dr. Tim de Meij ***Volatile biomarkers in gastroenterology***

June 30th, 2022	Prof. Paul Fockens ***Treating acute pancreatitis is teamwork!***
September 8th, 2022	Prof. Willem Bemelman ***More than 25 years of IBD Surgery: lessons learned***
September 22nd, 2022	Prof. Ronald Oude Elferink ***'The seven year Itch'***
October 6th 2022	Prof. Marc Besselink ***Thrilling progress in surgical management of pancreatic cancer***
November 3rd, 2022	Prof. Guy Boeckxstaens ***Mast cells as new target for the treatment of abdominal pain***
November 10th, 2022	Prof. Arjan Bredenoord ***Epidemic of a new disease: eosinophilic esophagitis***
December 1st, 2022	Prof. Ernst Kuipers, Dutch Health Care Minister ***College Tour Edition***
December 15th, 2022	Prof. Marlies Schijven ***The black Box in operation room: a treat or blessing?***

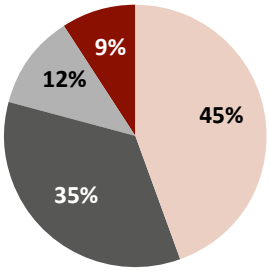
Numbers and Facts 2022

AGEM finances 2022

For 2022, the AGEM research institute was provided with €556.666 (€251.251 from board of directors VUmc and €305.415 from board of directors AMC). In the table below is shown how this money spend. Most of the 2022 budget was used for the AGEM grants. More money than previous years was spend on personnel costs. AGEM hired a second policy officer, which was necessary due to the increasing workload for the institute. Furthermore, AGEM hired a dedicated business developer and a strategic consultancy company to help formulate and promote the achievement of the institute's strategic goals.

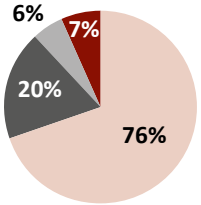
Income 2022	
AMC	€ 305,415,00
Vumc	€251,251,00
Total	**€ 556,666,00**

Expenditure 2022



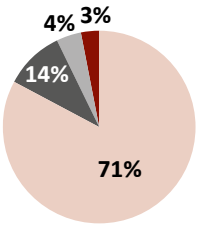
Income 2021	
AMC	€ 308,500,00
Vumc	€235,789,00
Total	**€ 562.289,00**

Expenditure 2021



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

Expenditure 2020



AGEM grants *Personnel* *Meetings* *Miscellaneous*

AGEM numbers 2022

AGEM Researchers

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

	2020	2021	2022
Principal Investigators	93	99	101
PhD-students	416	432	415
Other researchers	293	221	214
Total AGEM researchers	**802**	**752**	**730**

AGEM Publications

The reported data include all published research output as registered in the Research Information Systems Pure VUmc and Pure AMC in July, 2022. Research output of all researchers affiliated with AGEM are included. Publications are ascribed to AGEM based on the affiliations of the authors. A publication can be ascribed to one or more research institutes depending on the affiliations of the authors. Publications registered in the VUmc and AMC Pure instances have been combined and deduplicated. PhD-theses are ascribed to AGEM based on the affiliations of the (co-)supervisors. A thesis can be ascribed to one or more research institutes depending on the affiliations of the (co-)supervisors.

	2020	2021	2022
Refereed articles	1513	1619	1429
PhD-theses	74	77	90
Other publications	146	188	88
Total AGEM publications	**1733**	**1884**	**1607**

Appointed professors 2022

Prof. dr. Clara van Karnebeek

Personalized Medicine for Genetic Metabolic Diseases

On January 18th 2022, Clara van Karnebeek was appointed professor of Personalized Medicine for Genetic Metabolic Diseases. She delivered her inaugural lecture “Verbinding, versnelling, verandering” on April 8th, 2023.

Clara van Karnebeek is a pediatrician for Metabolic Diseases, principal investigator at the department of Pediatrics and Humane Genetics and director of the Emma Center for Personalized Medicine at Amsterdam UMC. She is director of United for Metabolic Diseases and founder of the Jeroen Pit House. Furthermore, she is affiliate professor at the department of Pediatrics at the University of British Columbia in Vancouver in Canada.

Clara’s chair focuses on the smart integration of all possibilities to bridge the gap between the lab and the patient. This enables not only to identify hereditary metabolic disorders faster but also to provide truly personalized care. Connecting a diagnosis to an individualized treatment. Based on this concept, the Emma Center for Personalized Medicine was recently established: an expertise center in the Emma Children’s Hospital where pediatricians, clinical geneticists, and various departments and laboratories collaborate. Clara van Karnebeek is one of the initiators.

Due to the acceleration in diagnostics and treatment, children with severe chronic conditions can live longer. Sometimes, this entails a life requiring intensive care and periods of hospitalization. Recognizing the profound impact this has on parents and families, Clara, along with others, established the Jeroen Pit House, providing a new form of care for chronically and severely ill children and their families. Clara has been appointed a Knight in the Order of Orange-Nassau for the establishment and opening of the Jeroen Pit House in May 2022.

Prof. dr. Alberto Pereira Arias

Internal medicine, Endocrinology

On January 25th 2022, Alberto Pereira Arias (Uruguay, 23 nov 1966) was appointed professor of internal medicine, in specific endocrinology. He delivered his inaugural lecture ‘2034’ on Jan 26, 2023.

Alberto is an internist-endocrinologist and head of the Department of Endocrinology and Metabolism of the Amsterdam UMC since march 2022. In 2012 he was appointed professor of Medicine and chair of Endocrinology at the Leiden University Medical Center, and founded the Center for Endocrine Tumors, an (inter)national multidisciplinary reference center for patient with endocrine tumors, based on patient-centered care pathways and VBHC, linking care and research.

He was president of the European Neuroendocrine Association (2016-2018), and since 2017 is the coordinator of the European Reference Network on Rare Endocrine Conditions (Endo-ERN). He is also PI of the Horizon2020 ERICA project, that aims to strengthen the ERN’s research and innovation capacity. His clinical and translational research focusses on the long-term effects of hypothalamic and pituitary diseases, and in specific on the effects of stress hormones on the brain. He is the recipient of the prestigious 2022 ESE Clinical Endocrinology Trust Award.

Did you know that...

... the careers of two AGEM internist-endocrinologists at Amsterdam UMC ended in January 2022. Prof. **Hans Romijn**, Chairman of the Board of Directors and Dean of the Faculty of Medicine at the UvA, and Prof. **Eric Fliers**, Head of the Section of Endocrinology of Internal Medicine and Professor at the UvA, said goodbye at the same time.

... on Wednesday May 11th 2022, the Jeroen Pit Huis was officially opened by queen Máxima. Founders AGEM PI **Clara van Karnebeek** and Job van Woensel, and co-founder Emilie van Karnebeek, received royal honours ("Ridder in de Orde van Oranje-Nassau") for their work on the Jeroen Pit Huis.

... AGEM PI Prof. **Geert D'Haens**, professor of Gastroenterology has published the results of three studies on therapies for inflammatory bowel diseases in the Lancet.

... **Anita Boelen** has started as co-director of Amsterdam Gastroenterology Endocrinology Metabolism (AGEM) research institute. Together with co-director **Stan van de Graaf**, she will be responsible for coordination and management of the institute's ventures, and for ensuring these align with its mission and vision. Anita Boelen is the successor of **Gerd Bouma**, who has been an inspirational co-director of AGEM for many years.

... together with 17 partners, the epigenetic biomarkers study "methylomic" of AGEM PIs **Wouter de Jonge**, **Geert D'Haens** and others was awarded a €10.4 million grant in the category of 'Personalized Medicine for non-malignant diseases'.

... AGEM Professor **Riekelt Houtkooper** (Genetic Metabolic Diseases) received EU funding to coordinate a MSCA Doctoral Networks consortium; the NAD International Scientist training network (NADIS).

... two AGEM Principal Investigators, Prof. dr. **Wouter de Jonge** and dr. **Johan van Limbergen**, have been awarded a TKI-PPP grant between € 300.000 and € 750.000, to perform a research project in the AGEM field in collaboration with an industrial party.

... **Clara van Karnebeek** (AGEM PI), was selected as one of the six finalists for the 2022 Huibregtsenprize. She was nominated for her work on United for Metabolic Diseases (UMD), which she founded with prof. dr. Hans Waterham (AGEM PI), and the Jeroen Pit Huis (JPH).

... Dr. **Martijn Finken**, Dr. **Georges Janssens** and Dr. **Mark Lowenberg** were appointed as (AGEM) PI in 2022.

... AGEM PI **Marlies Schijven** received the Societal Impact Award 2022 of the Amsterdam UMC for her work on how technology can better support hospitals, healthcare professionals and patients.

Future perspectives for the AGEM research institute

As we look ahead to 2023, AGEM directors Professor Dr. Van de Graaf and Professor Dr. Boelen are optimistic about the exciting plans and developments on the horizon. “In particular, we have the forthcoming external evaluation of the institute,” Boelen emphasizes, “which holds great significance for AGEM’s future.”

This evaluation is a mandatory assessment that occurs every six years and is conducted using the Strategy Evaluation Protocol (SEP). The evaluation thoroughly examines the research quality, societal relevance, and viability of the institute. By reflecting on the accomplishments of the past six years (2017-2022) and considering how the institute’s strategy aligns with its mission and vision, the evaluation will play a pivotal role in shaping research policies at Amsterdam UMC. Van de Graaf explains, “Consequently, this evaluation holds immense importance for all of our researchers, as its outcomes will likely influence strategic and policy decisions made by Amsterdam UMC and the AGEM institute.”

To ensure transparency and inclusivity, the directors emphasize their commitment to involving as many AGEM researchers as possible in the evaluation process. “AGEM researchers are the heart of the institute,” Boelen affirms, “and we are delighted to witness their active participation and valuable input.” Throughout 2023, the directors aim to engage AGEM Principal Investigators in separate conversations about the institute’s future. Furthermore, they encourage all AGEM researchers who wish to have a greater role to reach out to AGEM and express their interest.

In addition to the evaluation, the directors are preparing for a change within the AGEM directorate in 2023. After serving approximately eight years, Van de Graaf will step down as AGEM director. “I have thoroughly enjoyed my time as one of AGEM’s directors,” Van de Graaf shares, “but after eight years, I believe it is time for a fresh new leader to work alongside Anita Boelen.” Identifying a suitable successor for Van de Graaf will be one of the directors’ primary focuses in the coming year.

“With the imminent evaluation and the change in directorate, we anticipate a busy year ahead,” Boelen remarks. Nonetheless, the directors remain committed to strengthening previous initiatives, such as increasing the involvement of AGEM researchers, fostering talent management, and advancing business development. Van de Graaf adds, “We particularly invite AGEM researchers interested in public-private partnerships, especially those considering applying for a TKI grant, to contact our Business Developer, Ric van Tol.”

Overall, the directors eagerly anticipate another eventful year for the AGEM institute. They extend their gratitude to readers for engaging with the annual report of 2022 and express their hope to see many participants at the institute’s upcoming events in 2023.

Stan van de Graaf, AGEM director
Anita Boelen, AGEM director
Eva Dirkx-Beuling, AGEM policy officer
Maartje Schots, AGEM policy officer

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