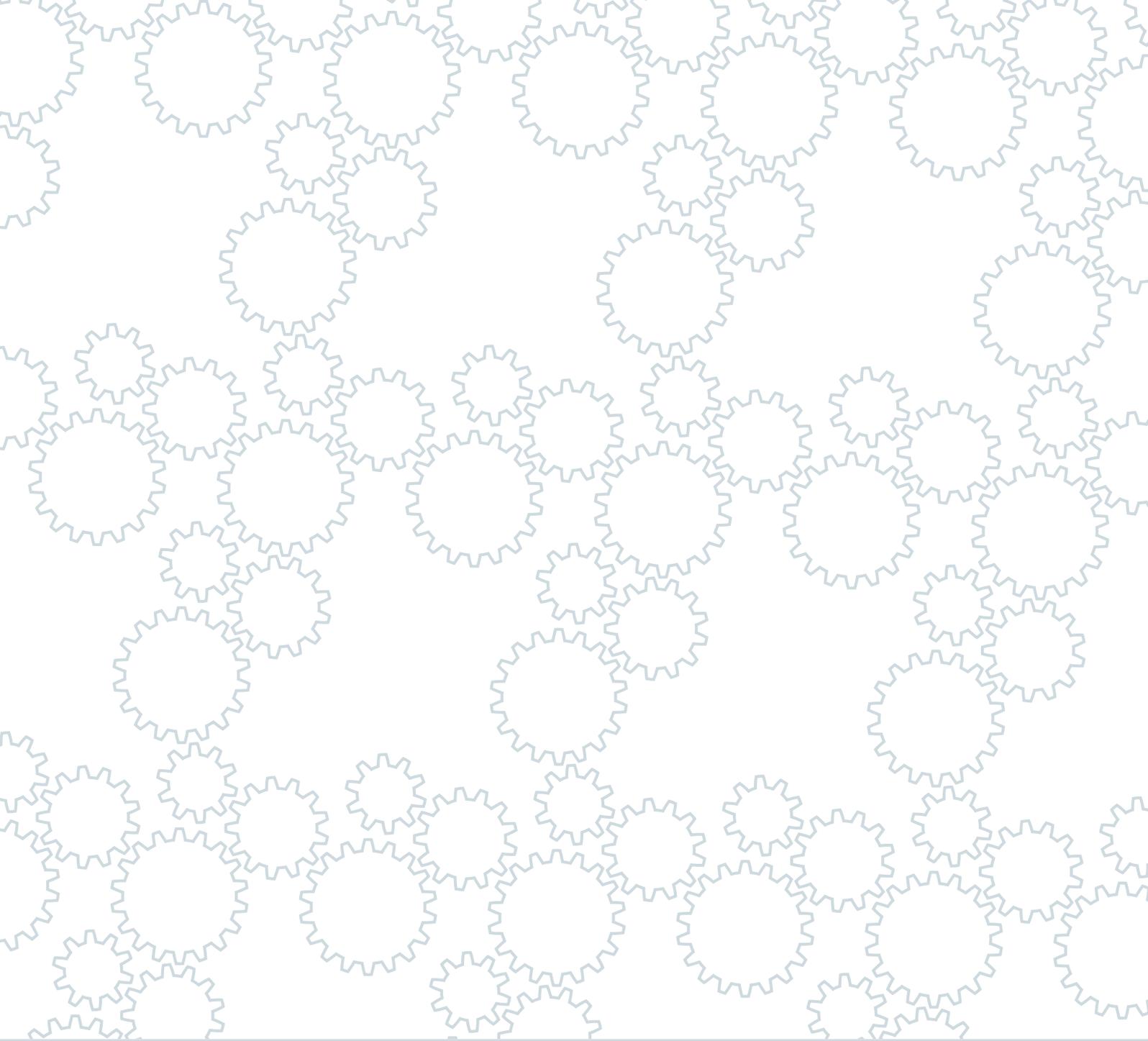


Amsterdam Gastroenterology and Metabolism

AG&M Annual report 2018





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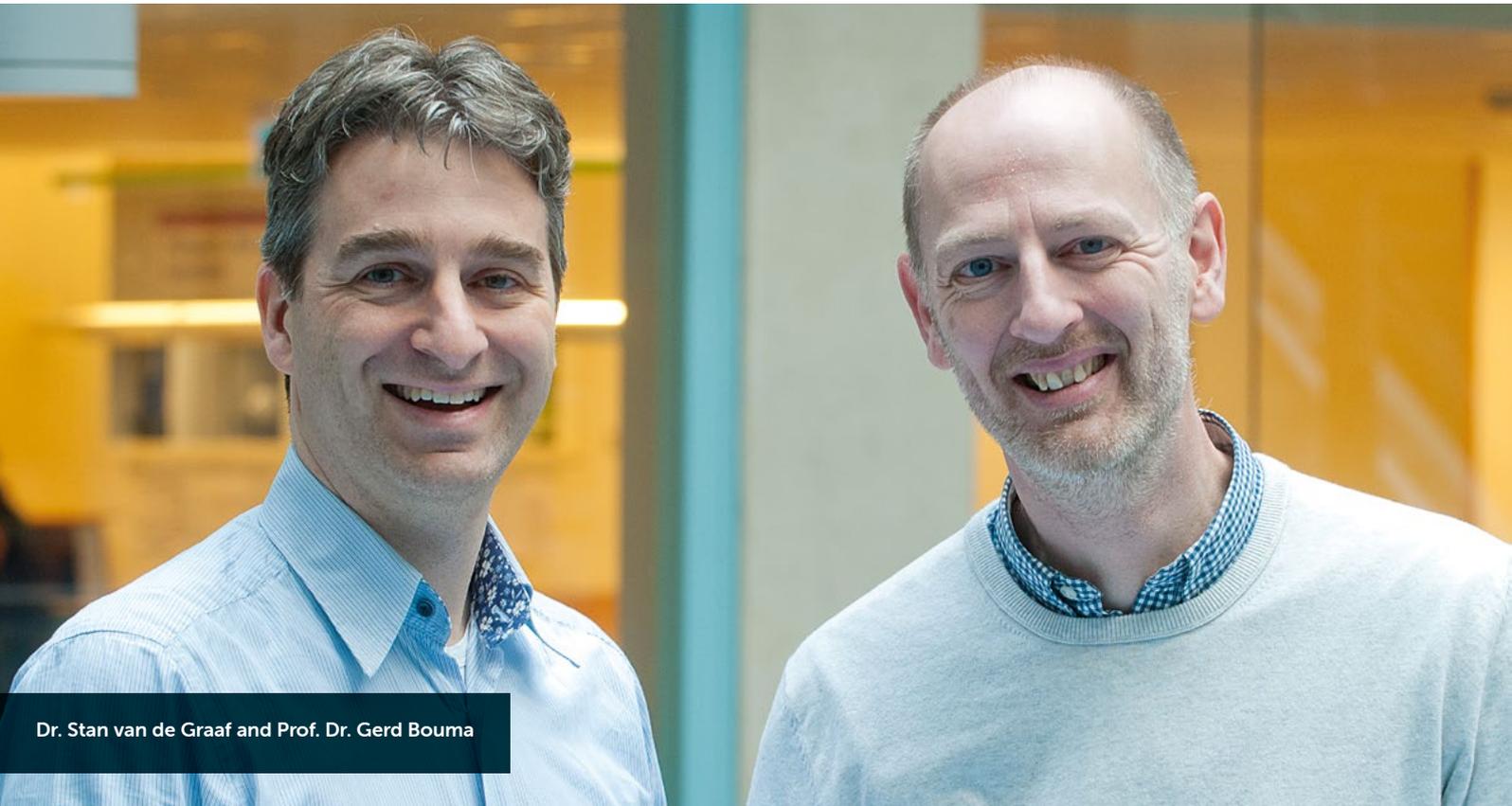
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The mission and vision of the AG&M directors



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

“It was tentative at first, trial and error, those guys across the Amstel were our competitors, now we had to collaborate, to trust them, we were told to just go for it.” Such were the birth pangs of the Amsterdam Gastroenterology & Metabolism (AG&M) research institute according to co-director Professor Gerd Bouma. Now, just two years on, Bouma sees it beginning to work “exquisitely well” with clinicians and scientists beginning to talk, work, and think together.

“It was tentative at first, trial and error, those guys across the Amstel were our competitors, now we had to collaborate, to trust them, we were told to just go for it.”

His co-director Dr. Stan van de Graaf - from across the river - shares his confidence. He sees the AG&M research institute as “unique” in the Netherlands, simply for its size, with well over 400 PhD students, serving an Amsterdam catchment population of approximately 1 million, and with its dedicated focus on gastroenterology, metabolism and endocrinology in one institute. Today, he sees a sense of unity, of being part of something bigger, of the promise of “special opportunities” for science, healthcare and patients.

There had been talk of Amsterdam’s University Medical Center (AMC) and Free University medical centre (VUmc) merging since 2011. At the beginning of 2017, it suddenly became real as the two major hospitals’ culture, politics and ways of organizing science had to begin to come together. Among many other things, the challenge was to take the VUmc’s popular research institutes and to merge this concept with the AMC’s principal investigator approach. Eight research institutes finally emerged of which AG&M was one, building on the former AMC’s research focus on Metabolic/Endocrine disorders and Gastrointestinal diseases.

With limited funding or, then, any obvious incentives, the first step was simply: “to promote a spirit of common purpose” of identity. Meetings were deliberately not held at either the AMC or VUmc sites, but at a third location. Then came the crucial first annual AG&M meeting or “retreat” the “mainstay of this Institute” where all scientists and PhD students present their work. Van de Graaf: “We needed to hear what everyone was doing, what was their line of research. We thought we already knew, but in fact we didn’t know at all.”

“We needed to hear what everyone was doing, what was their line of research. We thought we already knew, but in fact we didn’t know at all.”

This created knowledge, trust, and the belief that “we can work together”. The first retreat “was a bit intense”, with a huge number of pitches to introduce the vast amount of different research topics, but now, the third, “was really fabulous” says Van de Graaf.

In addition to the annual AG&M retreat, monthly seminars and symposia were organized while, in this spirit of collaboration, scientists were encouraged to attend clinical settings such as multidisciplinary team meetings to discuss real patients. Collaboration was also promoted through funding, grants for talented teams of researchers who could demonstrate a degree of synergy in their work.

For Professor Bouma, what began was no less than a change of attitude, of mindset, and from the bottom up. “Whatever your expertise, the discipline your working in, you are part of something bigger and we can benefit from each other.” And more often than not



this was achieved by simply meeting socially, talking and “realizing they have something in common and can profit from one another”.

“Whatever your expertise, the discipline your working in, you are part of something bigger and we can benefit from each other.”

Yet the challenges posed by 21st century medicine and society for a research institute standing at the junction of nutrition, microbiology, digestion, endocrinology and metabolism are immense. So too is the AG&M’s ambition. Its **mission** statement speaks of performing research that “promotes healthy nutrition and metabolism, prevents or cures gastrointestinal, endocrine and inherited and acquired metabolic disease, and improves the well-being of our patients.” While its **vision** for 2020 aims to forge its parent hospitals’ research in gastrointestinal, endocrine and metabolic health and disease into a single organization with four programs, namely: re-generation and cancer of the digestive system; digestive immunity; endocrinology, metabolism and nutrition; and, inborn errors of metabolism.”

<https://www.amsterdamresearch.org/web/gastroenterology-and-metabolism/home-5.htm>

While there are dozens of examples of where collaboration, economies of scale, and cross fertilization of specialist expertise can benefit research, perhaps three examples could be allowed to speak for the many. With Inflammatory Bowel Disease, the VUmc brings mucosal immunology expertise to join forces with the clinical and fundamental research on mucosal homeostasis in the AMC. And now with a combined patient cohort of approximately 4,000 patients, single center clinical trials are possible. Targeting colon cancer, the VUmc offers research into minimally invasive surgical techniques for resection to add to the expertise

into the cell and molecular biology of colorectal cancer at the AMC’s Center for Experimental Molecular Medicine (CEMM). The AMC is renowned too for its research into autoimmune diseases of the liver, such as Primary Sclerosing Cholangitis (PSC). This can now benefit from the recognized expertise from the VUmc research into autoimmune hepatitis - both research now benefitting too from the larger patient cohort.

...there are dozens of examples of where collaboration, economies of scale, and cross fertilization of specialist expertise can benefit research,...

Ideally Van de Graaf would like to see collaboration in research looking at a particular disease which covers the entire path from pre-clinical studies to translation research and clinical application. And, within this, for connections to be made between different areas of expertise.

...collaboration in research looking at a particular disease which covers the entire path from pre-clinical studies to translation research and clinical application.

He cites, as a current example, work being done on endoscopy which has discovered that by disrupting the outer lining of the duodenum by inserting a balloon with hot water, it improves the insulin sensitivity following regeneration. This has benefits for diabetes. “We are not yet sure how this works but other researchers are working on insulin regulation

and diabetes. So we have a gastroenterologist and an endocrinologist working in the same research institute who can start to work together. Those kinds of connections are logistically challenging, but it is developing.”

Today, the AG&M is directly promoting this kind of research, promoting collaboration and a pragmatic clinical application, through its innovation grants. Examples include, the work of PhD students Sofieke de Jonge and Kyra van Rijn measuring small bowel motility with dynamic MRI. This could, they hope have applications for clinical neurogastroenterology. Also Michel van Weeghel, analytical chemist who manages the UMC Amsterdam’s Core Facility (for) Metabolomics (CFM), is working with research technician Bauke Schomakers through an AG&M innovation grant developing tracer-based metabolomics (fluxomics). This should make it possible to measure dynamics in metabolism using stable labeled isotope tracers and, thus, help predict the severity of metabolic disease and so target treatment more to an individual patient’s needs.

These are described in more detail later in in this annual report. And there are many more examples.

Though this is still early days for the AG&M in terms of a research institute, this kind of grant funding demonstrates the fostering of collaboration is already underway. Van de Graaf: “Here we can show that we have already begun to help in bringing together expertise from imaging experts and

gastroenterologists.” Another example is research, in which he himself is involved, where a resected liver is attached to an advanced pumping device outside of the body in order to test different surgical strategies and the hepatic metabolism. “Here, in our case, there is collaboration between surgeons and basic scientists from both locations of the Amsterdam UMC.”

“Here we can show that we have already begun to help in bringing together expertise from imaging experts and gastroenterologists.”

And while Van de Graaf is hesitant to claim specific success in its short life for the AG&M, he believes it has consciously built upon the strong connections which already existed, for example between gastroenterology and hepatology on one side, and surgery and imaging, on the other. Meanwhile there are signs of better links between, for example, pediatric gastroenterology, such as research into necrotising enterocolitis, and basic science on gut research. “Those types of connections are getting stronger,” he says, adding that the potential of the AG&M as a center of excellence on a European level is already being demonstrated at the United European Gastroenterology (UEG) conference by “the impressive number of sessions chaired by our principal investigators”.





Research Programs

Based on an inventory of the strengths of the research in gastroenterology, endocrinology and metabolism conducted at the Amsterdam UMC, four research programs have been specified:



1. Re-generation and cancer of the digestive system

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

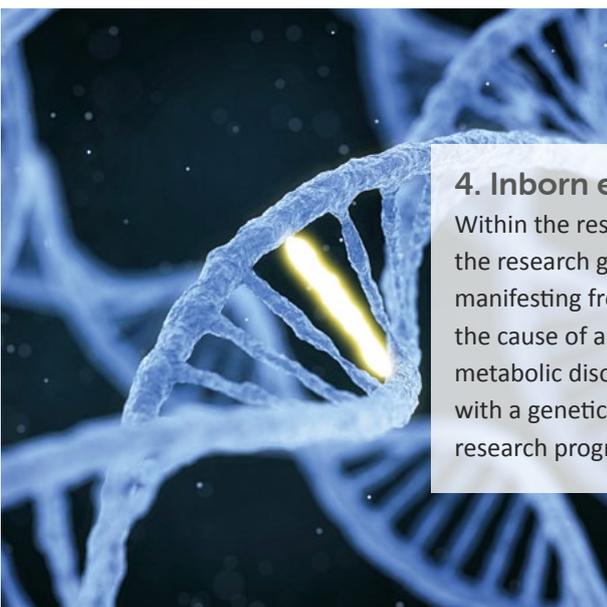


2. Digestive immunity

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

3. Endocrinology, metabolism and nutrition

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



4. Inborn errors of metabolism

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





The AG&M Research Board 2018

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



New to the AG&M Research Board



Annemieke Heijboer

Since September 2018, Annemieke Heijboer joined the AG&M research board. Annemieke is head of the Endocrine Laboratory. As principal investigator, she studies physiology and pathophysiology within the field of endocrinology and translates this into improved diagnostics of endocrine disorders.

What I want to achieve with the AG&M research institute...

As a clinical chemist and researcher with a special interest in endocrinology, I participate in the research board of AG&M to stimulate the interaction between the different fields within our institute. Networks between the researchers in AG&M can lead to even more excellent research. Moreover, I think it is important to have general topics on the agenda of the institute, such as quality, methodology and gender sensitivity.

AG&M directors



Prof. dr. Gerd Bouma

Department of Gastroenterology and Hepatology

Professor of Gastroenterology and Hepatology
Group leader & AG&M Co-Director VUmc

Specialization: Gastroenterology

Research subject: Mucosal immunology



Dr. Stan van de Graaf

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

Associate professor
Group leader & AG&M Co-Director AMC

Specialization: Biochemistry/Physiology

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

AG&M Research Board members



Prof. dr. Max Nieuwdorp

AMC and VUmc Internal Medicine

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

AG&M Research Board member

Specialization: Internal medicine: Endocrinology

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



Prof. dr. Riekelt Houtkooper

Laboratory Genetic Metabolic Diseases

Professor of Translational Metabolism

Principal investigator at Laboratory Genetic Metabolic Diseases

AG&M Research Board member

Specialization: Biochemistry/Physiology

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



Prof. dr. Louis Vermeulen

Center of Experimental and Molecular Medicine

Professor of Molecular Oncology

Principal investigator at Center of Experimental and Molecular Medicine

AG&M Research Board member

Specialization: Molecular oncology; colorectal cancer

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



Dr. Anje te Velde

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

Principal investigator at Tytgat Institute for Liver and Intestinal Research

AG&M Research Board member

Specialization: Immunology

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



Prof. dr. Gajja Salomons

Metabolic Laboratory & Department of Genetic Metabolic Diseases

Professor of Molecular Biology of Neurometabolic Disorders

Head of Department of Genetic Metabolic Diseases

AG&M Research Board member

Specialization: clinical laboratory geneticist,
(inborn errors of) metabolism

Research subject: inborn errors of metabolism with a focus on
neurometabolic disorders including white matter disorders



Dr. Annemieke Heijboer

Endocrine Laboratory & Department of Clinical Chemistry

Associate professor

Principal investigator at Endocrine Laboratory

AG&M Research Board member

Specialization: Endocrinology/Clinical Chemistry

Research subject: To study physiology and pathophysiology within the field
of endocrinology and to make the translation into endocrine diagnostics
including the use of biomarkers.

AG&M office



Dr. Eva Dirkx-Beuling

Amsterdam Gastroenterology & Metabolism (AG&M)

Policy officer AG&M

Secretary AG&M Research Board

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





AG&M Science Impressions 2018

To give an impression of the research conducted in the AG&M research institute, eight couples of young investigators and their supervisors were invited to present the research projects they worked on in 2018.

Development of diagnostic approaches for (complicated) celiac disease, and autoimmune-enteropathy.

Hetty Bontkes and Maxine Rouvroye

R&D at the Medical Immunology lab (dept. Clinical Chemistry) at the VUmc, headed by Dr Hetty Bontkes aims at identification, evaluation and optimization of diagnostic and prognostic *in vitro* parameters for patients with (complicated) celiac disease, neuro-celiac disease and other inflammatory small bowel enteropathies. We focus on minimal invasive markers in blood and on local cellular parameters, primarily in diagnostic duodenal biopsies of small bowel enteropathies.

The pathogenesis of celiac disease has been largely elucidated which has led to one very effective therapy: a gluten free diet. Very good diagnostic serological and histological tests are available that help to diagnose most patients which present with classic symptoms at childhood. However celiac disease can also present quite frequently at a later age, often without classical gastro-intestinal symptoms. Results from the available diagnostic test are in these atypical cases often not clear cut, particularly when individuals suspected of celiac disease have started a gluten free diet prior to diagnosis.

The intraepithelial lymphocyte fraction changes in celiac disease patients. There is a lymphocytosis and the proportion of gammadelta T-cells ($\gamma\delta$ T-cells)

increases. We have investigated whether the size of the $\gamma\delta$ T-cells can be used diagnosing celiac disease. We showed that the proportion of $\gamma\delta$ T-cells is increased in celiac disease patients on a gluten free diet and that this parameter may help to diagnose celiac disease in potential celiac disease patients who do not fulfil all diagnostic criteria.

Antibodies against the autoantigen tissue transglutaminase (Transglutaminase 2) and against gluten peptides (i.e. gliadin), which are deamidated by the tissue transglutaminase, are the cornerstones of diagnostic laboratory tests in the diagnosis of celiac disease. While these antibodies decline and in most cases disappear upon a gluten free diet, gliadin specific T-cells persist in the peripheral blood, while in non-celiac healthy donors with normal gluten intake these T-cells are absent from the peripheral blood. With support from the Dutch Digestive Foundation (MLDS) we will evaluate the diagnostic potential of gliadin specific T-cell detection in peripheral blood for diagnosis of celiac disease to apply in difficult cases where other diagnostic tests and clinical picture are inconclusive.

Active celiac disease, refractory celiac disease (proven celiac disease not responding to a strict gluten free



Hetty Bontkes and Maxine Rouvroye

diet) and autoimmune enteropathy have villous atrophy of the small intestine in common. However villous atrophy can only be determined by invasive endoscopic procedures. We have shown that in these cases the intestinal fatty acid binding protein (I-FABP) is increased. Although I-FABP levels in serum have no role in differential diagnosis of these three entities, the levels do correlate with intestinal damage and as such are a low invasive marker for intestinal damage.

In addition to the development of diagnostic tests, we are currently investigating the functional role of intraepithelial lymphocyte subsets and leucocyte subsets residing in the lamina propria in the development of these diseases in order to identify possible future targets for therapy. Of particular interest are the $\gamma\delta$ T-cells which increase in celiac disease and remain elevated upon remission on a gluten free diet, suggesting a protective role for these cells.

In 2017, Maxine Rouvroye started her PhD on diagnostic approaches of (refractory) celiac disease and on the epidemiology of gluten related neurological disorders.

The spectrum of gluten related disorders consists of a wide array of clinical manifestations triggered by dietary gluten. Whereas celiac disease is the

best known disorder, increasingly more reports on neurological manifestations of gluten sensitivity, such as gluten ataxia emerge. However, the underlying neuropathological mechanism is yet to be unraveled. A large part of Maxine's PhD focusses on the epidemiology of gluten related neurological disorders. In collaboration with the Radboudumc ataxia clinic, the Maastricht UMC small fibre neuropathy clinic and the Utrecht UMC neurology clinic we will study the incidence of gluten related antibodies in patients with ataxia and neuropathy of unknown aetiology. Transglutaminase 6 is a member of the transglutaminase enzyme family which has been shown to be predominantly expressed in the central nervous system. We hypothesize that not Transglutaminase 2, but Transglutaminase 6 is the main autoantigen in gluten related neurological disorders.

Atrophy of a particular class of neurons located in the cerebellum, the Purkinje cells, is associated with ataxia. In a study on post-mortem material of patients with neuro-celiac disease we observed a significant loss of these Purkinje cells and an influx of CD8+ lymphocytes in the cerebellum (unpublished data) indicating a T-cell mediated response in the brain. Further research on these cases will focus on the origin of these lymphocytes and their target antigens.

Neurogastroenterology and Motility

Arjan Bredenoord and Willemijn de Rooij

Prof. dr. Arjan Bredenoord has been appointed professor of Gastroenterology in February 2019, his main focus are Neurogastroenterology and Motility disorders of the upper gastrointestinal tract. This includes diseases such as achalasia, reflux disease and eosinophilic esophagitis (EoE).

Clinical care, teaching and training and research are closely integrated in this group. The members of the group are active in education in Epicurus, training of specialist trainees, and on national and international courses. The clinic has become the largest upper GI motility clinic in the Netherlands and the group executes several multiple research projects in the area of pathophysiology, diagnosis and treatment of Motility disorders.

The Amsterdam UMC location AMC is the only NFU (Netherlands Federation of University Medical Centers) accredited achalasia center of expertise for achalasia in the Netherlands and gastroenterologists work close together with pediatricians, esophageal physiologists and surgeons to treat this rare disorder.

EoE is a relative newly recognized disorder, probably caused by an esophageal allergic inflammatory response to food allergens. A huge rise in incidence of EoE has been seen in the past 15 years, the reason for this observed increase is unknown.

In 2018 several research grants in the field of EoE were acquired by Dr Bredenoord, of which a ZonMW Vidi Grant of € 800 000, A NWO TTW grant of € 579 004 and a NWO TKI grant of € 265 000. The projects supported by these grants focus on unraveling the pathophysiology of EoE by investigating the exact role of food allergens, mucosal immunology and epithelial permeability and on the role of dietary treatment in EoE.

Dietary treatment of eosinophilic esophagitis

Willemijn de Rooij graduated as medical doctor in 2017 and then started as PhD-student on research projects centered around eosinophilic esophagitis (EoE) in the AMC Neurogastroenterology and Motility research group. EoE leads to eosinophilic inflammation and

clinical symptoms of esophageal dysfunction such as dysphagia, chest pain and food impaction. Compelling evidence points toward food antigens as the principle allergic trigger, since elimination of causative foods and in particular elemental diets (by exclusive use of amino acids-based formulas) have proven to be highly effective. Chronic use of anti-inflammatory drugs (swallowed topical corticosteroids) is often undesired, therefore dietary antigen elimination seems a promising and drug free long-term solution. Current dietary approach includes elemental and empiric elimination diets. An elemental diet is most effective in achieving disease remission, but adherence to this restrictive diet is challenging and the use of an amino-acid based formula as sole source nutrition is not acceptable as long-term treatment. Empiric elimination diets show moderate response rates and are based on exclusion of four or six most common allergy triggering food groups (milk, gluten soy, egg, peanuts/tree nuts and shellfish/fish) with subsequent stepwise reintroduction to identify EoE-triggers.

The supplemental elemental trial (SET)

Data suggested that amino-acid based nutrition has independent anti-inflammatory effects itself and could therefore contribute to the effect of an empiric elimination diet, thus making this an ideal combination. In collaboration with Nutricia Research and a specialist dietician, we are finalizing a randomized controlled trial to evaluate whether the addition of an elemental (amino acid-based) formula to an empiric Four Food Elimination Diet (FFED; excluding milk, gluten soy and egg) is more effective in decreasing esophageal eosinophilic inflammation and improving diet adherence. All patients undergo an esophagogastroduodenoscopy (EGD) at baseline and after 6 weeks of dietary intervention (FFED or FFED + elemental formula) to assess histological disease activity and other parameters. A substudy focusses on specific anti-inflammatory effects of the elemental formula. The project is funded by both Nutricia Research and NWO TKI. A new collaboration is focused around measuring markers of fibrosis development in serum of EoE patients.



Willemijn de Rooij and Arjan Bredenoord

Psychological well-being among adult EoE patients

Moreover, we initiated another research project in collaboration with the department of medical psychology from the Amsterdam UMC. EoE is known to negatively impact the Health related Quality of life of patients and their families. In particular, invalidating symptoms such as dysphagia and food impaction, its unpredictable and chronic course, indicated lifetime long (medical or dietary) treatment and the need for multiple endoscopic interventions can considerably affect patients' daily life. Since current data is lacking on this pertinent topic, the extent to which an

EoE-patient currently receives sufficient mental care in clinical practice remains questionable. Therefore, we conducted a study to evaluate the psychological well-being, prevalence of psychological distress and coping strategies among adult EoE patients in the Netherlands.

The incidence of EoE has increased incredibly in the past decade and so did the scientific developments into this disease. The Neurogastroenterology and Motility research group in the Amsterdam UMC has contributed significantly and the grants acquired in 2018 will ensure this will continue in the next 5 years.

Fabry and the Brain – Connecting doctors' perspectives to patients' experiences

Carla Hollak, Mirjam Langeveld and Simon Körver

Carla Hollak's group focuses primarily on the natural history, pathophysiology and treatment of lysosomal storage disorders. Basic science on lysosomal storage disorders was already initiated at the Amsterdam University Medical Centers, location AMC in the seventies and eighties by Profs. Joseph Tager and Hans Aerts. Their research and network has paved the way for translational and clinical investigations, mainly focusing on sphingolipidoses. In the nineties, Carla initiated clinical studies on Gaucher disease with Hans Aerts' group, leading to successful discovery of biomarkers and tailor-made treatment approaches. With the launch in 2008 of Sphinx, the AMC has formally established its position as expert center, integrating research and care. Currently, Carla's group works closely together with the laboratory of genetic metabolic diseases for diagnostics and more basic research on for example the lipidome in LSD's, cholesterol trafficking, oxidative stress and mitochondrial dysfunction. Clinically, research focuses on clinical trials with innovative treatments as well as on the course of disease and its variations, both in treated and untreated patients. For this purpose, large and well maintained registries and biobanking are necessary: a huge investment, which has resulted in more than 350 deep phenotyped sphingolipidoses patients and hundreds of stored samples. In addition, a large Fabry disease international database was set up, which has formed the basis for more individualized treatment approach of patients. The clinical group was strengthened with the appointment of Dr. Mirjam Langeveld, metabolic internist, who broadened the research field to in inherited disorders of fatty acid oxidation and interpretation of function tests such as exercise testing. Because of the high costs and lack of knowledge on long term effects of therapies for lysosomal disorders, the necessity for independent research as well as appropriate use of therapies has grown. This notion has led to the development of a new branch of research, i.e. regulatory science for orphan drugs as well as development of programs to support access of affordable therapies to patient with rare diseases.

Fabry disease

Simon Körver is one of the PhD students in Carla Hollak's group. Under co-supervision of Dr. Mirjam Langeveld and Prof. Ivo van Schaik, he investigates the connection between objective involvement of the brain and clinical outcomes, such as cognition and depressive symptoms, in patients with Fabry disease (FD).

Patients with FD, a rare inherited lysosomal storage disorder, are at risk for complications of heart, kidney and brain. Complications include left ventricular hypertrophy, arrhythmias, renal failure and stroke. Sex is an important predictor of disease severity in FD, with a higher complication rate in men. Phenotypically, patients can be classified as having classical or non-classical disease, with a more attenuated disease course in non-classical patients. Enzyme replacement therapy (ERT), an intravenous supplementation of the missing enzyme in FD, is the oldest and most commonly used treatment option. Treatment with ERT has shown to postpone some complications, but the effect on cerebral disease manifestations remained unclear.

Routinely performed brain MRIs often reveal confluent white matter lesions (WMLs) and infarctions in FD patients. However, the relation between the brain involvement and clinical outcomes such as cognition and depressive symptoms is unclear.

Brain MRIs, cognition and depressive symptoms

Two main studies were performed: in the first study a total of 852 routine brain MRIs of 149 patients were assessed on WMLs and infarctions. In the second study, in a subset of 81 patients cognitive functioning and depressive symptoms were measured using a neuropsychological test battery and questionnaires.



Simon Körver and Mirjam Langeveld

Patients with FD have a high risk of developing confluent WMLs and infarctions. Even though these are also present in the aging population, the prevalence in our cohort at a median age of 40 years is observed at least 20-40 years later in the general population. Progression of WMLs and infarctions in FD was mainly related to sex, phenotype and age: older men with a classical disease phenotype had the highest progression risk. Treatment with ERT did not alter the risk of progression in our study.

Cognitive impairment was present in patients with FD (16%), again mainly in men with a classical disease phenotype (41%). Depressive symptoms were highly prevalent in all FD patients (38%). Cognitive impairment was independently related to a history of stroke and showed some relation to severe WMLs but not to depressive symptoms. Depressive symptoms were not related to WMLs or stroke but were independently related to coping styles, pain and health perception. Again, treatment with ERT had no relation with any of these outcomes.

These studies endorsed the hypothesis of our research group that ERT does not greatly influence the progression of the brain involvement in FD and show there is an unmet need for treatment options improving cerebral outcomes. Men with a classical phenotype have a high risk of disease progression and should be monitored with brain MRIs and neuropsychological assessments. All patients with FD have a high risk for depressive symptoms, especially if debilitating pains are present and if a patients' health perception and coping behavior is suboptimal. Future studies could focus on psychological interventions to alter coping behavior.

Using fecal scent patterns for non-invasive detection of gastrointestinal diseases

Nanne de Boer and Sofie Bosch

The electronic nose research program

Nanne de Boer is a consultant and associate professor at the Gastroenterology and Hepatology department of the Amsterdam UMC, location VUmc. In 2007, he obtained his PhD on the pharmacology and toxicity of thiopurine treatment for inflammatory bowel disease, which now has become one of his main research programs, covering topics as rediscovery of the drug 6-thioguanine and drug induced hepatotoxicity. Nanne also has investigational interests in sigmoid vaginoplasty and diversion vaginitis. His second research program was initiated in 2013. Together with Tim de Meij, a consultant pediatric gastroenterology, he aims to develop a so called electronic nose (eNose) for the detection and follow-up of various gastrointestinal diseases.

Electronic nose measurements

The potential of volatile organic compounds (VOC) for non-invasive disease detection has been of increasing interest over the past few decades. These gaseous chemicals are the end-products of metabolic pathways in the human body, and together form the so called 'volatolome'. VOCs are emitted from all bodily fluids, like sweat, urine, exhaled breath, feces, blood and vaginal secretions. The fecal volatolome is particularly known to be affected by alterations in the intestinal microbiota. Composition of the volatolome can be assessed by means of an electronic nose (eNose), which allows for non-invasive, high-throughput and low-cost diagnostics. Numerous studies have shown the potential of VOC analysis by electronic nose for the detection of a variety of diseases, including endocrine, infectious and inflammatory diseases.

Fecal scent for non-invasive CRC screening and surveillance

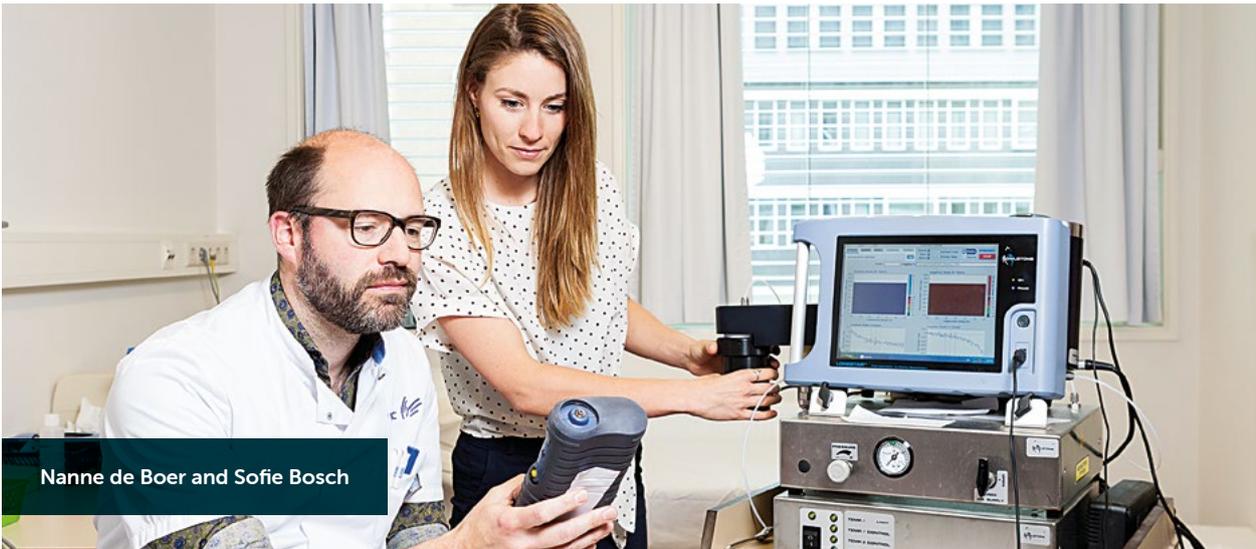
Sofie Bosch is one of the PhD-students researching topics embedded in the eNose program. Currently she is finishing her PhD on the development of non-invasive biomarkers for CRC screening and surveillance.

The results of one of her studies, aiming to investigate the potential fecal VOCs as measured by an eNose for CRC detection and follow-up, will be described in the next section.

Colonoscopy remains the cornerstone for screening and surveillance of CRC and its precursor lesions, advanced adenomas (AA). Not only does this procedure carry a burden on patients due to its invasive nature, it also has a small risk of complications and leads to high health care costs. Currently, population based screening is performed using fecal immunoglobulin test (FIT), which has lowered CRC mortality with 16-18%. However, 3-6% of participants have false positive results, leading to the performance of a large amount of unnecessary colonoscopies. In addition, 14-30% of the CRC patients (dependent on the cut-off value used) receive false negative results, which leads to a delay in CRC diagnosis. This underlines the need for improvement of our population based screening.

In addition, participants with high risk polyps or CRC detected during their initial screening colonoscopy are currently invited to take part in the surveillance program. In this program, a follow-up colonoscopy is performed after 3-, 5- or 10 years, dependent on the initial outcome. This program now accounts for 20% of our total endoscopy program, and thus far, no non-invasive biomarkers are available for this purpose.

Patients with a scheduled colonoscopy at the Amsterdam UMC, the Spaarne Gasthuis and OLVG West were asked to collect a fecal sample prior to bowel cleansing. In case CRC, AA or non-advanced polyps were observed during colonoscopy and confirmed in histology, patients were included as cases. Patients without any colonic abnormalities were included as healthy controls (HC). In addition, patients undergoing a polypectomy were randomly matched to HC and all were asked to collect a second fecal sample after 3 months.



Nanne de Boer and Sofie Bosch

Faecal samples were measured using an advanced eNose apparatus, the G.A.S. Flavourspec, which is based on gas chromatography-ion mobility spectrometry (GC-IMS). The data were split into three sets, 70% for training and validation and 30% as test set. Supervised machine learning classifiers were used to provide statistical results.

We included a total 16 CRC, 64 AA, 68 large non-advanced polyps (0.5-1.0cm), 126 small non-advanced polyps (0.1-0.5cm) and 227 HC. For the follow-up analyses, 32 patients with AA undergoing a polypectomy and 32 HC were included. CRC, AA and polyps were discriminated from HC with high diagnostic accuracies (AUC (95%), p-values: CRC vs HC 0.99(0.89-1), $p < 0.001$; AA vs HC 0.96(0.93-1), $p < 0.001$; large polyp vs HC 0.96(0.92-0.99), $p < 0.001$; small polyp vs HC 0.96(0.94-0.99), $p < 0.001$). No significant differences were found between any of the CRC and adenoma groups. Faecal VOCs could discriminate between subgroups of patients with AA and HC prior to polypectomy, but not after polypectomy (AUC(95%), p-values: AA vs HC T0 0.98(0.95-1), $p < 0.001$; AA vs HC T1 0.55(0.40-0.69), $p = 0.26$).

Future applications of eNose for CRC screening and surveillance

In conclusion, we found that fecal VOCs can discriminate CRC, AA and non-advanced polyps from HC but there was no difference in VOC profiles of CRC, AA and non-advanced polyps. In addition, fecal VOC patterns of patients with AA return to healthy state 3 months after polypectomy. From a screening perspective, these findings underline the potential of fecal VOCs as additional biomarker as they may reduce the number of false-positive results. For the surveillance program, these fecal VOC profiles may help to estimate the timing of surveillance endoscopy. This way, less unnecessary endoscopies may be performed, and the number of interval cancers (cancer developed during the surveillance interval) may be reduced.

The Dutch Pancreas Biobank Within the Parelnoer Institute: a Nationwide Biobank of Pancreatic and Periapillary Disease.

Pancreas 2018 Apr;47(4):495-50.

Marc Besselink and Marin Strijker on behalf of the Dutch Pancreatic Cancer Group

Nationwide collaborations on pancreatic diseases

Prof. Marc Besselink is a professor of surgery, especially pancreatic and hepatobiliary (HPB) surgery, in the Amsterdam UMC. His research group focuses on pancreatic cancer, pancreatitis, and minimally invasive surgery and interventions in HPB diseases. This work is done in close collaboration with numerous PIs and clinicians from AG&M, CCA, gastroenterology, medical oncology, radiology, anesthesiology and pathology, as well as several national and international research groups. In 2002, as a medical student, Marc Besselink was involved in founding the nationwide and multidisciplinary Dutch Pancreatitis Study Group (www.pancreatitis.nl) and subsequently became the first PhD of this group in 2008. In 2010, he was the co-founder of the Dutch Pancreatic Cancer Group (DPCG, www.dpcg.nl) which is the nationwide working group on pancreatic and periampullary cancer and pancreatic cystic neoplasms for which he chairs the scientific committee and prof. Olivier Busch, surgeon in the Amsterdam UMC, is the chair. Within the DPCG several nationwide randomized trials and prospective cohort studies are being performed. In 2014, Marc Besselink obtained an Alpe d'Huzes grant of €1,500,000 for the Dutch Pancreatic Cancer Project (PACAP). In 2015, he was the co-founder of the European Consortium on Minimally Invasive Pancreatic Surgery (E-MIPS; www.e-mips.org) which includes a European registry, pan-European retrospective studies and the ongoing international DIPLOMA trial.

Dutch Pancreatic Cancer Project

PACAP (<https://pacap.nl/>) is a project of the DPCG and aims to improve outcomes and quality of life for patients with both resectable and unresectable pancreatic cancer. PACAP is a large nationwide collaborative outcome registration and biobanking projects on pancreatic cancer and consists of the following components:

- a) Clinical data registry
 - Mandatory nationwide prospective surgical audit; Dutch Pancreatic Cancer Audit (DPCA)
 - Patient Reported Outcome Measurements (PACAP-PROMs)
 - The Netherlands Cancer Registry for pancreatic and periampullary cancer (NCR-pancreas) in collaboration with Netherlands Comprehensive Cancer Organization (IKNL)
- b) Dutch Pancreas Biobank
- c) Online expert panel
- d) The PACAP-1 trial; nationwide stepped-wedged cluster randomized controlled trial to implement best practices in pancreatic cancer care

Clinical data registry

The DPCA (<https://dica.nl/dpca>) started in 2013 and includes data on all pancreatic resections for both benign and malignant indications. The DPCA is a mandatory clinical audit and all 17 centers currently performing pancreatic surgery in the Netherlands participate. Each year approximately 1000 resections are added to this database. A system has been set up, in which Marin Strijker coordinates, together with her colleague Tara Mackay, the requests for data of the DPCA, NCR-pancreas and PACAP-PROMs which are then discussed in the scientific committee of the DPCG. DPCA data are also used for the Dutch Pancreas Biobank.

Dutch Pancreas Biobank (PancreasParel)

In her PhD-research Marin Strijker focusses on the development and evaluation of tools for a tailored approach to pancreatic cancer treatment, in close collaboration with prof. Hanneke van Laarhoven (medical oncology), dr. Maarten Bijlsma (CEMM; www.bijlsmalab.com) and prof. Casper van Eijck (ErasmusMC). Moreover, she coordinates the Dutch Pancreas Biobank (PancreasParel, www.pancreasparel.nl). The Dutch Pancreas Biobank is a nationwide biobank in which data and biomaterial of patients with pancreatic tumors, cysts, or chronic pancreatitis undergoing



Marc Besselink and Marin Strijker

pancreatic resection are collected. The biobank started in 2015 and is incorporated in the Parelsnoer Institute, which is a nationwide network established by the Dutch Federation of University Medical Centers (NFU). The Parelsnoer Institute aims to facilitate central data and IT infrastructure in the UMC's, striving for uniform data and biomaterial collection.

All patients undergoing pancreatic resection are included. After providing informed consent, data and biomaterials are collected. In the preoperative setting DNA, plasma (10 mL tube) and serum (10 mL tube) are collected. Directly after resection, biopsies (2x tumor tissue, 1x normal pancreatic tissue, 1x normal spleen/duodenum) from the resected specimen are obtained; samples are fresh-frozen and stored at -80°C . In the postoperative phase serum and plasma are collected at several moments during follow-up. This far, more than 1300 patients have been included in 12 centers; all 8 UMC's, but also several teaching hospitals participate. Research proposals for the use of samples are evaluated by the DPCG scientific committee.

ADAM12 as a stroma marker in pancreatic cancer

Recently, the first analyses of samples from the Dutch Pancreas Biobank have been performed. This study, supervised by dr. Maarten Bijlsma, evaluates the serum marker A Disintegrin And Metalloprotease 12 (ADAM12). Earlier research has shown that in patients with pancreatic cancer ADAM12 is upregulated specifically in the stroma of tumor tissue compared to normal pancreatic tissue. Moreover, in a cohort of 60 patients who underwent resection because of pancreatic cancer, high serum ADAM12 was associated with poor prognosis. In patients with metastatic disease treated with nab-paclitaxel and gemcitabine ($n=184$), low ADAM12 levels predicted response to treatment. The value of ADAM12 as a non-invasive biomarker in resected pancreatic cancer will be validated using samples from the Dutch Pancreas Biobank ($n=164$); the results are currently being analyzed.

Personalized Medicine in Rheumatoid Arthritis: Methotrexate Polyglutamylation Revisited

Expert Review Precision Medicine and Drug Development 2018;3(6):331-334

Robert de Jonge and Ittai Muller

Personalized medicine of the anti-folate methotrexate (MTX)

Prof. Robert de Jonge is an European Specialist in Laboratory Medicine, head of the department of Clinical Chemistry and vice chair of Division 9 (Laboratories). His research focusses on one-carbon metabolism (folate, vitamin B12). One of the research programs focuses on individualized treatment of the anti-folate Methotrexate (MTX) in auto-immune disease and leukemia in order to obtain maximal efficacy with minimal toxicity (medicijn op maat). In cross-sectional and in prospective cohort studies together with partners at Amsterdam UMC (Gastroenterology, Rheumatology, Hematology), Reade, UMCU (Gastroenterology, Rheumatology) and the Prinses Maxima Center Utrecht, prediction models for clinical response and toxicity are developed and pharmacokinetics/pharmacodynamics of MTX is studied.

Methotrexate

MTX is a folic acid analogue drug that was discovered in 1940's as one of the first chemotherapeutic drugs revealing potent activity in the treatment of acute lymphoblastic leukemia. Since then, following its success in cancer therapy, MTX has also been proven, though at low doses, to be very effective for the treatment for various chronic autoimmune disorders such as rheumatoid arthritis, sarcoidosis, Crohn's disease and vasculitis. The mechanism of action of MTX basically involves disruption of normal folate metabolism, which is a crucial pathway for cellular homeostasis as it provides essential nutrients (e.g. purines, pyrimidines, amino acids) for DNA synthesis and cellular proliferation and methylation reactions.

The important components in the cellular pharmacology of MTX are well documented. Following cellular uptake of MTX by specific transporters, one of the critical factors for the therapeutic effects of MTX involves the intracellular conversion into MTX-polyglutamates (MTX-PGn). This process is catalyzed by the enzyme folylpolyglutamate synthetase (FPGS),

which attaches multiple glutamate moieties (n=2-5, depending on the MTX dose and duration of infusion/treatment). MTX-polyglutamylation promotes the intracellular retention of the drug, a process hijacked from the intracellular retention of natural folates. The mechanism of action of low-dose MTX treatment used in autoimmune disorders relates to the inhibition of key enzymes in purine de novo biosynthesis pathway (i.e. 5-aminoimidazole-4-carboxamide ribonucleotide transformylase;ATIC) by MTX-PGn and the downstream release of the anti-inflammatory purine adenosine. Although MTX is relatively safe and effective, still about 30-40% of RA patients discontinue MTX treatment due to intolerance or inefficacy early in the treatment or do not respond any more after 3-6 months of therapy (MTX non-response or MTX resistance).

Therapeutic Drug Monitoring

The research in Robert de Jonge's group focuses on developing new analytical, molecular and computational methods helping to predict and monitor non-response and/or resistance to MTX in autoimmune diseases and cancer treatment. Specifically, the MTX-polyglutamylation process is revisited by employing current state-of-the-art technologies to identify novel predictive biomarkers and to sensitively and accurately measure MTX-PGn levels in disease-relevant cell types of patients.

Ittai Muller as PhD student and Marry Lin as technician are the ones who are actively involved in this project. Ittai obtained his Master's degree at the Vrije Universiteit Amsterdam (Oncology) during which he interned at Harvard Medical School (Boston, USA), where he investigated potential tumor microenvironment factors that predict breast cancer metastasis. After his graduation, he became coordinator of the Master Oncology and Master Cardiovascular Research before transitioning into academia to further his scientific career. He is currently investigating novel predictive biomarkers for MTX non-response in RA and leukemia under the supervision of



Robert de Jonge and Ittai Muller

Prof. dr. Robert de Jonge (Clinical Chemistry), dr. Gerrit Jansen (Rheumatology) and Prof. dr. Jacqueline Cloos (Hematology).

The main goal of this research is to set up and implement MTX therapeutic drug monitoring (MTX-TDM) combining analytical techniques (such as LC-MS/MS), molecular techniques (such as RNA-sequencing) and computational techniques (such as machine learning) to potentially aid clinicians in optimizing MTX dosing for personalized therapy. Recently, a novel and sensitive LC-MS/MS-based method was developed for measuring the enzymatic activity of FPGS in small numbers of patient cells. In addition, beyond traditional measurements of MTX-PGn in erythrocytes, improved sensitive LC-MS/MS techniques now allow MTX-PGn analysis in peripheral blood mononuclear cells, which as immune-related cells are more relevant from a disease pathophysiology perspective. Recently, Ittai's research revealed that alternative pre-mRNA splicing of metabolic enzymes in patients could have predictive value for drug response. Specifically, his research showed a significant association between whole blood expression of a partial intron 8 retention (FPGS 8PR) of FPGS pre-mRNA and disease activity score (DAS) in MTX-treated rheumatoid arthritis (RA) patients. These studies will now be extended to global pre-mRNA splicing patterns as predictive markers for drug response using next-generation sequencing techniques.

Altogether, the above-mentioned information can be implemented in novel drug response prediction models using machine learning algorithms. By combining novel data such as alternative pre-mRNA splicing events, MTX-PGn levels, and FPGS activity, together with clinical parameters, large databases can be analysed and used for predictive modeling of MTX-response through machine learning. In cooperation with the Computational Intelligence group of the VU University Amsterdam (Dr. M. Hoogendoorn), Helen Gosselt (PhD Candidate Erasmus MC) implements machine learning to improve models for RA MTX response prediction. These prediction models can then be used to aid rheumatologists in choosing the optimal treatment strategy but also help adjust individual patient MTX doses to compensate for inter-patient variability possibly preventing toxicity and improving efficacy.

While thus far most of the MTX-related TDM research has been performed on RA, in collaboration with Reade (Prof. Dr. M.T. Nurmohamed, Drs. R.C.F. Hebing), the research field is expanding to other disease areas in which MTX is the main therapeutic component. To this end, a multicenter, prospective study involving the UMCs and several top-clinical and peripheral hospitals has been initiated to study MTX-TDM in Crohn's Disease (Amsterdam UMC: Prof. Dr. G. Bouma, Dr. N. de Boer, Prof. Dr. R. Mathôt; UMCU: Dr. H. Fidder, Dr. B. Oldenburg, Dr. M. Bulatović-Ćalacan; PhD student: M. van de Meeberg) to build prediction models.

The pathogenesis and treatment of cholestatic liver diseases and itch. Unraveling Immunoglobulin G4 Associated Cholangitis and the 'biliary HCO₃⁻ umbrella'.

Ulrich Beuers and Jorrit van Niekirk

Prof dr. Ulrich Beuers has been appointed Professor of Gastroenterology and Hepatology since 2007 at the Amsterdam University Medical Center and Core Professor and Head of Hepatology in 2010. After being raised in Germany, he studied medicine in Gent, Berlin and Freiburg. He obtained his Dr.med. in 1983 in Freiburg. After a postdoc period in biochemistry in Göttingen, he was trained in Internal Medicine and Gastroenterology/Hepatology in Munich. During this time, he undertook a fellowship for two years at the Liver Center of the Yale University. He received his Dr.med.habil. ('Habilitation') in 1994 in Munich and became a Professor of Internal Medicine in 2001. In 2015, he spent a sabbatical again at the Liver Center of Yale University where meanwhile a considerable number of AMC students have performed their 'wetenschappelijke stage'.

For three decades, Beuers' research focusses on the pathogenesis and treatment of patients with cholestatic liver diseases. He has supervised over 20 PhDs and next to experimental laboratory work, he has initiated or participated in large clinical trials to evaluate treatment options for primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), intrahepatic cholestasis of pregnancy (ICP) and IgG4-related cholangitis (IRC) of which the pathogenesis remains incompletely understood. The prognosis of PBC and PSC without treatment is dismal, the diseases often lead to liver cirrhosis and eventually the need for liver transplantation. Common to all these diseases is the symptom of pruritus (itch) which may severely affect quality of life.

In search of a possible pathophysiological explanation, evidence from experimental, clinical and genetic studies led Beuers and his group to introduce the 'biliary bicarbonate umbrella hypothesis'. This hypothesis, that has been experimentally confirmed, states that cholangiocytes (and hepatocytes) create a protective apical alkaline barrier by secreting bicarbonate (HCO₃⁻) into the bile duct lumen. This (~30-50 nm) alkaline barrier, which is stabilized by the cholangiocyte glycocalyx, would retain bile salts in their

polar, deprotonated and membrane-impermeant state. When the apical HCO₃⁻ secretory apparatus is defective (as it is in PBC), the alkaline barrier would diminish, leading to partial protonation of bile salts, rendering the resulting bile acids apolar and capable of crossing the cholangiocyte membrane independent of bile salt transporter activity. These apolar bile acids have been shown to induce cellular damage and growth arrest.

Jorrit van Niekirk is currently working as a PhD fellow under supervision of Prof. dr. Ulrich Beuers and dr. Stan van de Graaf at the Tytgat Institute for Intestinal & Liver Research on the molecular regulation and stabilization of the 'biliary bicarbonate umbrella' in human cholangiocytes. By a close interplay between several ion channels and proteins targeting the apical membrane in cholangiocytes a pH nanoenvironment in close proximity of the apical membrane is maintained. Our group has recently shown that the integrity of this apical layer of bicarbonate is fine-tuned by intracellular signaling pathways mediated by bile salt sensitive receptors in cholangiocytes. This enables a potential therapeutic window for endogenous and therapeutic bile salts and bile salt analogues to regulate the apical membrane expression of key elements of the 'biliary bicarbonate umbrella', responsible for the protection of cholangiocytes from the detergent properties of biliary bile salts in human bile.

Another cholestatic liver disease entity of which the pathogenesis remains partly unknown is immunoglobulin G4-related cholangitis (IRC). Experimental work by Lowiek Hubers, PhD fellow under supervision of Prof. dr. Ulrich Beuers and dr. Stan van de Graaf, had disclosed Annexin A11 as the first IgG4/IgG1 autoantigen in IRC, and had shown that specific targeting of Annexin A11 by IgG1 in patients with IRC might be attenuated by IgG4. Work by his successor, Toni Herta, suggests that the IgG4/IgG1 autoantigen Annexin A11 might be a potential regulator of the intracellular trafficking of some of the key elements of the 'biliary bicarbonate umbrella' in human cholangiocytes. Thus, Annexin A11 dysfunction might play a role in the pathogenesis of IgG4-related cholangitis.



Ulrich Beuers and Jorrit van Niekerk

A common symptom of cholestatic liver diseases is pruritus which may reduce quality of life tremendously. The search for a particular pruritogen in cholestasis has been ongoing since decades. It has been inferred that potential pruritogens are made in the liver and excreted in bile; as a result of cholestasis, they might accumulate in the body and trigger the sensation of itch at itch neurons. Recent findings of the PhD fellows Andreas Kremer, Ruth Bolier and Jacqueline Langedijk supervised by Prof. Ronald Oude Elferink and Ulrich Beuers indicate that Lysophosphatidic acid (LPA), a potent neuronal activator, and autotaxin, the enzyme which forms LPA and the nonspecific cation channels TRPA1 and TRPV1,

which are also activated by LPA and responsible for pain and itch sensing are involved. All together they may form a key element of the long-sought pruritogenic signaling cascade in cholestatic patients. The identification and characterization of a biliary 'factor X' is at this moment the major focus of this research line. A multicenter international clinical trial, the FITCH trial ('fibrates for itch') resulting from the experimental work above, organized by the PhD fellows Elsemieke de Vries and Ruth Bolier and supervised by Ulrich Beuers, was just successfully finished; results will be reported later this year and might change international guideline recommendations.

The gut-brain axis in obesity

Richard IJzerman and Madelief Wijdeveld

The pathophysiological pathways that influence the CNS regulation of food intake are the focus of Richard IJzerman's research group.

Obesity is a major public health problem due to its pandemic occurrence and its association with adverse consequences. Comparable to the role of CNS reward and satiety responses in drug addiction, we and others have demonstrated that obese individuals are characterized by excessive eating due to altered central nervous system (CNS) reward and satiety responses to food.

To regulate food intake, signals arising from peripheral organs involved in food intake, digestion and storage, such as the gut, pancreas, and adipose tissue, convey information on hunger and/or satiety to the CNS. The ability of the gut to communicate with the CNS is known as the gut–brain axis.

Hormonal gut-brain axis

Glucagon like peptide (GLP)-1 receptor agonists showed positive results with regard to weight reduction in humans. Previous studies have demonstrated that gut-derived GLP-1 is important in the regulation of feeding by relaying meal-related information on nutritional status to the brain. In order to study its specific effects on neuronal activity in the brain, our group performed various functional MRI studies where people were exposed to both virtual and actual food stimuli. Various studies performed by our group have demonstrated that blocking the action of endogenous GLP-1 prevented meal induced reductions in CNS activation in obese T2DM patients. We also demonstrated by using fMRI that GLP-1 receptor activation (using a GLP-1 receptor agonist) acutely decreased food intake and also decreased brain responses to visual food cues, which may reduce food craving. In addition, GLP-1 receptor activation acutely increased responses to actual food intake, which may prevent overeating. After short term

treatment, patients using a GLP-1 receptor agonist also showed decreased responses to food pictures. Unfortunately, the CNS effects of the GLP-1 receptor agonist disappeared after 12 weeks, and weight loss with GLP-1 receptor agonists is on average only 3 kg. Thus, in order to develop more powerful preventive and therapeutic strategies, it is important to gain further insight into pathways that influence central reward and satiety circuits in the context of obesity.

Metabolic gut-brain axis

The last two decades have produced an avalanche of studies revealing that intestinal microbiota provide a substantial metabolic and physiological contribution to energy homeostasis in the host. Obesity has been associated with alterations in composition of intestinal microbiota, and transfer of “obese” microbiota can induce adiposity and hyperphagia in animals, suggesting that gut microbiota may influence host feeding behavior. The mechanisms underlying effects of intestinal bacteria on host appetite in animal studies are unknown, but may involve effects of short chain fatty acids (SCFAs), in particular acetate. Acetate may be an important player in the gut-brain axis. Acetate is produced when non-digestible carbohydrates undergo fermentation by the colonic microbiota. High amounts of acetate reach the peripheral circulation and can also directly affect host metabolism and function. Acetate crosses the blood–brain barrier in rodents, but the effects of acetate on food intake in animals are controversial. In humans, acetate has been shown to cross the blood–brain barrier and can be used as a substrate in the brain. In addition, there is some evidence that acetate increases short-term subjective ratings of satiety and reduces body weight in humans.

In collaboration with Max Nieuwdorp, PhD student Madelief Wijdeveld investigates the interaction between the SCFA acetate and brain circuits involved in the regulation of food intake in humans. Madelief



Richard IJzerman and Madelief Wijdeveld

applied and got selected for the Amsterdam UMC MD/PhD Scholarship in 2018, which provides a medical student with the possibility to perform combine their clinical internships with 3 years of PhD research.

We prospectively investigate the association of gut derived acetate on progression of obesity in relation to CNS responses to food stimuli after a follow-up of approximately 4 years in a population based cohort (the prospective Amsterdam HELIUS (Healthy Life in an Urban Setting) cohort). We selected the extremes, that is individuals with high and low intestinal acetate production based on the intestinal acetate converting activity. In these selected individuals we measure insulin responses upon a standardized mixed meal as well as CNS responses to food related stimuli (fMRI), BMI and weight gain in the following 4 years. Data collection is almost finished. In a new project, we will study the effects of direct acetate infusion into the peripheral circulation on CNS responses to food stimuli in obese and lean humans.

Conclusion

Insight into the pathophysiological pathways that lead to obesity may provide new therapeutic targets. Because acetate and other gut derived factors can easily be manipulated, the results from our studies may offer a tractable approach to improve activity in brain circuits involved in the development of obesity.

MD/PhD talent grant AMC 2018 Madelief Wijdeveld. Role of intestinal acetate in human food intake and insulin secretion.

Universiteit van Nederland. NWO. Waarom is dik worden zo makkelijk? https://youtu.be/dC4BAJV_7U4

AG&M Best Publication 2018

During the AG&M symposium “Complex Genetics of Metabolic Disease” on Friday March 15th 2019, the battle for best AG&M publication 2018 took place. Five nominees, Arwen Gao, Lowiek Hubers, Sophie Lodestijn, Sofia El Manouni El Hassani (for Daan Berkhout) and Ivo Hansen pitched their publication in 5 minutes each.



The audience voted, with a tie, for Sophie Lodestijn and Arwen Gao as winners of the battle with their publications entitled “Stem cell functionality is microenvironmentally defined during tumour expansion and therapy response in colon cancer” and “Natural genetic variation in *C. elegans* identified genomic loci controlling metabolite levels”, respectively.



Sophie Lodestijn

Sophie Lodestijn is a MD-PhD student in the group of Prof. Dr. Louis Vermeulen. She has a strong interest in the cell dynamics underlying tumor growth. At the Vermeulen lab they focus on elucidating the origin, evolution and heterogeneity of colorectal cancer. With a multidisciplinary group of scientist with various backgrounds (i.e. biomedical sciences, bioinformatics, physics, mathematics, medicine) they aim to approach scientific questions from different perspectives. One line of research in the lab aims to unravel the stem cell dynamics in different stages of colorectal cancer development. Stem cells are necessary to maintain homeostasis of most adult tissues. Previously, the lab identified stem-like cells that drive progression of colorectal cancer and described the impact of oncogenic mutations on the stem cell dynamics in the intestine, using different lineage tracing techniques in mice. Recently, using a similar lineage tracing method, they revealed the growth dynamics and the role of the microenvironment on stem cell behavior in established colorectal cancer.



Stem cell functionality is microenvironmentally defined during tumour expansion and therapy response in colon cancer

In the paper 'Stem cell functionality is microenvironmentally defined during tumour expansion and therapy response in colon cancer' published in Nature Cell Biology in 2018, unbiased quantitative lineage tracing data and mathematical modeling were combined to reveal the cancer stem cell (CSC) functionality in established colorectal cancer. The main finding of the paper is that stem cell behavior is fully regulated by the microenvironment, instead of being an intrinsic cancer stem cell property.

Colorectal cancer is a very heterogeneous disease, consisting of cells of different degrees of differentiation. It has been speculated that the ability to drive tumor growth and initiate metastasis, depends on the presence of cells with an immature phenotype, the so-called CSCs. Different CSC markers, such as LGR5 and CD133 have been discovered to identify these CSCs, mainly using transplantation assays in immunocompromised mice. Critically, using these assays, the original tumor organization is disrupted and therefore the stem cell properties are tested in an artificial way. Thus, these assays are inappropriate to study the stem cell functionality within an established tumor. Next to this, previously it was resolved that the number of cells expressing the CSC marker Lgr5 at the crypt bottom is much higher than the number of stem

cells that are functionally active. Hence, CSC marker expression and CSC functionality do not coincide in the normal gut.

To elucidate which cells are functionally active during tumor growth within an established colon tumor, a marker-free lineage tracing method was developed and combined with quantitative analysis. With this system the growth of sporadically labeled cells, during tumor growth and treatment, could be followed in their native environment. Clone size data of various time points after label induction was obtained, and a wide variety in clone sizes was observed next to an increasing average clone size over time. Next, this data was used in conjunction with a mathematical model to infer the underlying clonal dynamics. It was found that the cells that drive tumor expansion were predominantly located at the tumor borders. This model prediction was confirmed by an immunofluorescent staining of proliferating cells, residing at the tumor edges. Furthermore the macroscopically measured tumor sizes fitted best with an surface growth model. Although the functionally active cells were located at the tumor borders, a difference in CSC marker expression could not be observed between the tumor edge and center, by immunofluorescent stainings and RNA sequencing. Next to these phenotypical assays, also functional assays, like re-transplanting the tumor center and limiting dilution assays of cells derived from the tumor edge and center, did not show clonogenic differences when the microenvironment was similar.

These data all support the model prediction that the microenvironment defines the stem cell behavior rather than CSC markers expression. To identify microenvironmental factors that drive tumor growth, different factors using immunofluorescent stainings and in vitro clonogenic assays were investigated, and a clear correlation was observed between the clonogenic cells and the tumor stroma. Using the RNA sequencing data the research team identified Osteopontin, a protein secreted by the stroma, as a potential regulator of clonogenicity. To test the in vivo effect of Osteopontin, Osteopontin was overexpressed in the same colorectal cancer cell line as used in the original experiment and the lineage tracing experiment was performed again. The tumors grew faster and the outgrowth of the clonogenic cells was less dependent of the tumor

location, confirming Osteopontin to be a key regulator of in vivo clonogenicity. Finally the effect of treatment on the functional stem cell dynamics was studied by treating the mice with chemotherapy once a small tumor had formed. Although the tumor expansion was clearly inhibited and CSC marker expression was increased, the same underlying stem cell dynamics was found compared to the untreated tumors, in which the microenvironment, especially the stroma, regulates clonogenicity.

Based on these results of the experiments, the research team concluded that stem cell behavior is fully regulated by the microenvironment, instead of being an intrinsic cancer stem cell property.



Arwen Gao

Arwen Gao performed her PhD research in the group of prof. dr. Riekelt Houtkooper within the laboratory Genetic Metabolic Diseases. Work in this group is focused on understanding how (changes in) metabolism affects people's health, specifically inherited and acquired (e.g. through aging) metabolic diseases. But since basic science can't always be done in human subjects, the group also uses various model organisms. Arwen's PhD project was specifically focused on aging, using the worm *C. elegans* as a model. She developed innovative ways to measure metabolism in worms, using targeted and untargeted metabolomics. With this, Arwen made important contributions to the identification of novel aging biomarkers, new aging mechanisms, and new anti-aging treatments. Following her PhD graduation in October 2018 Arwen now holds a postdoc position in the world-renowned laboratory of prof. dr. Johan Auwerx at the EPFL in Lausanne, Switzerland.



Natural genetic variation in *C. elegans* identified genomic loci controlling metabolite levels

Just like your DNA is able to decide for you to have blue eyes while your cousin's are brown, your genes might be able to control your personal metabolism in a different way as well. In this manuscript, we studied this phenomenon with the use of two different worm (*C. elegans*) families. The worms were bred by crossing a family of British worms (from Bristol) with a family of Hawaiian worms. Just like British and Hawaiian humans, these worms have some DNA in common because they are the same species, and some DNA that is different because they are from different families. After about 20 generations of crossing between these families, the offspring consisted of varying degrees of Bristol and Hawaii DNA. This population of worms, termed "Recombinant inbred lines (RILs)" allowed us to collect metabolite profiles, in this case profiles of fatty acids and amino acids, in all of them and identify whether it was the Bristol or Hawaii DNA that influenced the abundance of these metabolites. As a result, we observed large variation in metabolite levels with

32-82% heritability between the RILs for both fatty acids and amino acids profiles. We performed metabolite-metabolite correlation analysis and detected strongly co-correlated metabolite clusters. To identify natural genetic variants responsible for the observed metabolite variations, we performed QTL mapping and detected 36 significant metabolite QTL (mQTL). We focused on the mQTL that displayed high significant linkage and heritability, including an mQTL for the FA C14:1 on chromosome I, and another mQTL for the FA C18:2 on chromosome IV. Using introgression lines (ILs) we were able to narrow down both mQTL to a 1.4 Mbp and a 3.6 Mbp region, respectively. Overall, this systems approach provides us with a powerful platform to study the genetic basis of *C. elegans* metabolism. It also allows us to investigate additional interventions, such as nutrients and stresses that maintain or disturb the regulatory network controlling metabolic homeostasis, and identify gene-by-environment interactions.

The manuscript "Natural genetic variation in *C. elegans* identified genomic loci controlling metabolite levels", was published in *Genome Research* (2018).





AG&M Grants 2018

In 2018, AG&M awarded 2 types of grants. The AG&M talent development grant (€75.000,00) for exceptionally talented researchers who are in the first 5 years after obtaining a PhD-degree and want to develop their own research line, and the AG&M innovation grant (€50.000,00) for innovative ideas beneficial to the AG&M research institute as a whole.



AG&M grant laureates 2018

The AG&M talent development grant



Charlene Diepenbroek

Ever since starting my PhD research, I have been interested in the role of the autonomic nervous system in the central regulation of glucose metabolism. During my PhD, at the department of Endocrinology & Metabolism of the AMC, I investigated the role of the brain as a mechanistic link between diet composition and glucose metabolism. I continued research as a postdoc at Yale University, where I investigated gastrointestinal-brain signalling, by the vagus nerve, and its role in ingestive behaviour. This project, and the techniques acquired, bridge the research from my PhD and the research I work on within the AG&M talent development grant.

The AG&M talent development grant allows me...

... differentiate myself with my own research niche, by generating fundamental knowledge in the innervation of the endocrine pancreas in diet-induced impaired β cell secretion in the development of type 2 diabetes (T2D).

Although it is known that autonomic innervation is altered in obesity, which is associated with T2D, little is known about the involvement of the autonomic nervous system in T2D development, e.g. vagal innervation of the β cell. Furthermore, there is a lack of knowledge in whether dietary components affect vagal-mediated insulin secretion, thereby contributing to T2D development.

I focus on the (dys)regulation of the brain and autonomous nervous system in the development of diet-induced impaired insulin secretion. In collaboration with Dr. Daniël van Raalte (Department of Internal Medicine and the Institute of Cardiovascular Research, VUmc), I will perform ex vivo experiments with isolated pancreatic islets. This technique enables us to investigate the innervation at the level of the β cell, and to delineate the endocrine from the exocrine pancreas. I combine this technique with neuroanatomical, chemogenetic, and physiological techniques in an animal model with a free choice high-fat, high-sugar diet paradigm to further investigate the brain-pancreas-axis in vivo. Altogether, this will provide novel insights in the development of-, and targeted treatment for T2D.



Charlene Diepenbroek



Maartje Singendonk

After having obtained my medical degree and a bachelor in mathematics, I started my job as a PhD candidate at the department of Pediatric Gastroenterology and Nutrition of the Emma Children's Hospital/ Amsterdam UMC. My PhD focused on three core domains. First, I performed pathophysiological motility studies of the upper gastrointestinal tract in relation to swallowing disorders such as gastroesophageal reflux disease and achalasia. As this research revealed important caveats in the diagnostic evaluation of motility disorders in children, I focused on improving diagnostic testing and validation of novel analysis techniques. Last, I implemented the results of the above to assess and predict treatment outcome in children with gastroesophageal motility disorders. I took advantage of the collaborative environment, learning from experts in the field and establishing contacts in different centers around the world committed to foster my independent development and to pursue my own ideas. I am curious and enthusiastic about my work and that of others, always trying to understand and explore potentials of multidisciplinary research and state-of-the-art technologies. I am an active member of several international working groups and co-authored the international guideline on pediatric gastroesophageal reflux disease. By initiating and conducting several pilot and validation studies, our group has built a strong body of evidence supporting our analytic approach of esophageal motility disorders in children.

The AG&M talent development grant allows me...

... to bring this analytic approach into practice in a randomized controlled clinical trial that evaluates two different treatment strategies for achalasia – a rare and severe esophageal motility disorder causing dysphagia and always requires treatment – in children. The grant also allowed a return visit to work with my former co-supervisor Prof. Omari and his team in Adelaide, Australia to work on the development and implementation of an online portal to share, store and analyze esophageal motility tracings in an online database (www.swallowgateway.com). The use of this portal will take our research on pediatric esophageal motility disorders to a next level by allowing multicenter research and knowledge sharing. In the next few years, I hope our work will lead to better understanding of the pathophysiology of pediatric esophageal motility disorders to provide better targeted treatment strategies.



The AG&M innovation grant



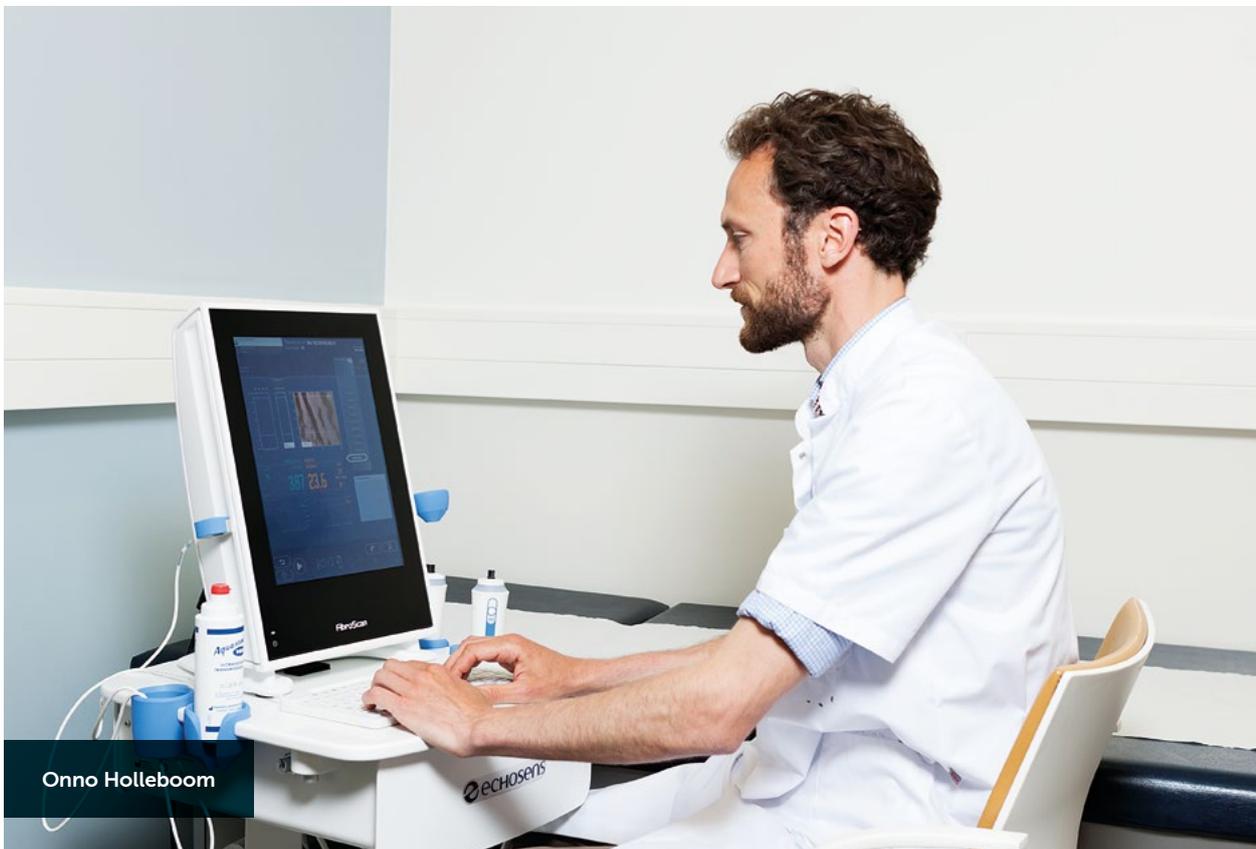
Onno Holleboom

*Internist-endocrinologist, Department of Vascular Medicine
Amsterdam UMC location AMC & Gastro-enterology and Hepatology,
location VUmc.*

Together with profs. Max Nieuwdorp and Ulrich Beuers and dr. Sandjai Ramsoekh, he has initiated outpatient clinics and a cohort study for patients with non-alcoholic fatty liver disease (NAFLD) at both locations of the Amsterdam UMC. In concurrence with obesity and diabetes mellitus type 2, the incidence of progressive forms of NAFLD with advanced liver fibrosis is increasing, requiring adequate care paths.

The AG&M innovation grant will allow us...

... to implement an innovative research tool in the Amsterdam UMC that we gained experience with during our collaboration with the University of Pennsylvania in recent years: redifferentiation of induced pluripotent stem cells into hepatocyte-like cells - iHeps. This liver cell model, alone or in co-culture with hepatic stellate cells, can be applied to test novel NAFLD candidate genes that come out of our cohort study, and to test potential new NAFLD drugs and probiotics. It can also be of general benefit to other liver-related research questions in the Amsterdam UMC, and it can serve as a model for inborn errors of metabolism, when induced pluripotent stem cells are derived from e.g. skin fibroblasts of the involved patients. Together, we aim to make iHeps a versatile new research tool for the Amsterdam UMC.





Sofieke de Jonge

From a young age the medical field and the gastrointestinal track intrigued me. This feeling was awakened during several gastrointestinal surgery internships as part of my study Technical Medicine. Being in such close contact with the tissue and its movement, the physiology of the organ grasped my interest. For this reason I started my PhD research focusing on capturing and measuring small bowel motility with dynamic MRI to explore this non-invasive technology as a biomarker for disease. I find it very exciting to develop and evaluate this imaging technology and explore the translation to applications in the clinical field of neurogastroenterology.

The AG&M innovation grant allows me...

... to continue my research as a postdoctoral fellow and evaluate the developed technique for MRI motility assessment in a patient population, chronic intestinal pseudo obstruction (CIPO), a very severe motility disorder. Together with PhD candidate Kyra van Rijn, I am working on projects in which we explore and improve the developed bowel motility MRI scans to gain insight in motility related bowel diseases for diagnostic and monitoring purposes. As a Technical Physician I am also involved in the clinical implementation of motility MRI at the Amsterdam UMC.

More recently we started a collaboration to expand our knowledge on small bowel motility to stomach and colon motility on dynamic MRI. In the next few years we hope our work will contribute to a better understanding of gastrointestinal motility and chronic intestinal pseudo obstruction.



Sofieke de Jonge and Kiera van Rijn



Michel van Weeghel

After a study in biomedical sciences, I started a PhD in biochemistry and metabolic diseases and performed a postdoc in analytical chemistry at the university of Leiden. Currently, I am the manager of the Core Facility Metabolomics (CFM) at the Amsterdam UMC, location AMC. The focus of the CFM is to develop and improve analytical methods to measure a wide range of metabolites in several matrices. My ambition is to maintain and expand the CFM in terms of state-of-art instrumentation and personnel. The analytical focus will be on developing new strategies in the metabolomics research field, including the development of tracer-based metabolomics. I believe that metabolomics will be able to help us understand metabolism in a broad sense and will be useful for several research disciplines within the AG&M, like metabolic diseases, oncology, immunology, endocrinology, and more.

The AG&M innovation grant allows me...

... to develop new analytical methods to understand dynamics in metabolism. The research technician Bauke Schomakers, who is funded by the AG&M innovation grant, is currently working on the development of tracer-based metabolomics (fluxomics) in which it should be possible to measure dynamics in metabolism using stable labeled isotope tracers. With unlabeled metabolomics methods we only measure static metabolism at a certain timepoint. With fluxomics we are able to trace metabolites through certain pathways in metabolism. This technique is already applied in several projects and will be better optimized in the future to be able to measure the severity of several metabolic diseases. This will help in predicting disease severity outcomes and will aid work on personalized treatments.

More recently, we were awarded grants from the Velux Stiftung and NWO that allowed us to acquire state-of-art high resolution mass spectrometers. These provided a significant boost to the development of metabolomics and fluxomics analysis by adding extra mass spectrometry capacity and improved mass spectrometry techniques.



AG&M Events 2018

AG&M annual retreat

APRIL



AG&M annual retreat

Bilderberg Hotel 't Speulderbos, Garderen

AG&M PhD-students retreat 2018: record numbers and setting a standard

This year's AG&M PhD retreat was a great success! With a record number of participants, we have not before had so many interesting and diverse talks during one retreat. Subjects included translational rodent and C. Elegans studies, cutting edge techniques such as gene editing using CRISPR-CAS and the use of organoids, and patient studies aimed at bettering and elongating patients' lives. No surprise this inspired many questions and suggestions from the audience!

Our four guest speakers mimicked this diversity. Prof. dr. Hugo Heymans (emeritus professor in pediatric at the University of Amsterdam) gave a worldwide perspective about the importance of the first 1000 days of life in shaping the growth and (cognitive) ability. Elaborating on this subject, the pediatric endocrinologist Martijn Finken (VU Medical Center) lead us through his research and findings on vertical transmission of glucocorticoids to mother's milk. Through simple diffusion blood cortisol of the mother influences the infant phenotype to prepare it for their postnatal environment.



Dr. Tristram Wyatt came especially from the University of Oxford and showed how difficult it can sometimes be to do good science in the face of popular beliefs by explaining and debunking the human pheromones myth. Last not but not least, prof. dr. Boudwijn Burgering (UMC Utrecht) showed us how metabolism of intestinal stem cells determines both stem cell functionality as well as intestinal differentiation. Together, these speakers complemented the students' presentation wonderfully.

Fitting with the AG&M's aim to discover, share and learn from each other, the program includes fun and networking activities aimed to facilitate our amalgamation into one institute. According to the positive feedback, I think the Organizing Committee pleasantly surprised all participants with a personal compliment and the seating arrangements during dinner. After a delicious dinner, Sahand Sahebdivani entranced us all with Arabian stories of brotherhood and communication. Where better to get to know each other than on the dance floor? This year was the first themed meeting; a fantastic boogie wonderland at the Disco Inferno. Tânia Garcia stole the show and won the best party outfit prize; don't stop till you get enough! On Friday, the traditional early morning boot camp revitalized the mind and helped gear up thoughts for the next sessions and our first interactive feedback meeting. Thank you all for your suggestions.

Last but not least; congratulations again to all winners! Suzan Knottnerus (Best Classical Presentation), Kyra van Rijn (Best Pitch), Joanne Donkers (Most Contributing Participant).



Suzan Knottnerus
Best Classical Presentation



Kyra van Rijn
Best Pitch

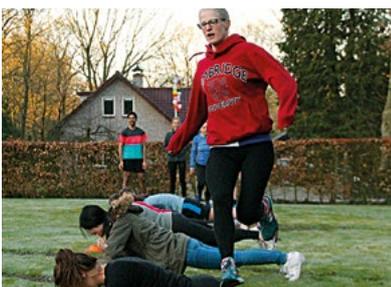


Joanne Donkers
Most Contributing Participant



Tânia Garcia
Best Party Outfit

The AG&M 2018 meeting has thus set a high standard for our future meetings. We thank you all for your participation and for sharing your ideas and science. We hope to see you all again next year!
On behalf of the Organizing Committee,
Myrtille Gumbs



AG&M symposia

MARCH

28th

AG&M symposium: "Nutrition"

Amstelzaal, VUmc, Amsterdam

Wednesday March 28th, AG&M organized the first symposium of 2018: "Nutrition" in the Amstelzaal of the VU medical center.

The symposium was opened by an inspiring movie featuring Dr. ir. Nicolette Wierdsma, Prof. dr. Daphne de Jong, Dr. Tim de Meij, Prof. dr. Andries Kalsbeek, Prof. dr. Ulrich Beuers and Dr. Michel van Weeghel, talking about nutrition and the relevance of nutrition to their own research. For movie see:

<https://www.amsterdamresearch.org/web/gastroenterology-and-metabolism/research-2.htm>

Hester Coppoolse and Anouk Hagemeyer from the Student and Nutrition Foundation talked about the mission and vision of their foundation.

Dr. Maarten Soeters discussed the physiology of insulin resistance and metabolic (in)flexibility and why that matters for AG&M. Prof. Ingeborg Brouwer reviewed the nutrition research at the VU on Nutritional factors and health, Undernutrition in old age, Nutrition and low social economic status and Obesity. Dr. Mireille Serlie closed the session before dinner was served with a lecture on the effect of nutrients on brain circuits involved in food intake.

After a nutritious dinner, the battle for Best publication of 2017 and the AG&M grant 2018 award ceremony proceeded the lecture of the keynote speaker Prof. Jaap Seidell, who discussed that unhealthy food patterns and obesity may contribute to systemic low grade inflammation and that this chronic inflammation may lead to a host of metabolic derangements and noncommunicable diseases.

Amsterdam Gastroenterology & Metabolism

AG&M symposium
"NUTRITION"

WEDNESDAY MARCH 28th 2018

16:00- 20:00h
Including dinner/buffet

Location:
Amstelzaal (ZH0A2), VUmc
De Boelelaan 1117
1081 HV Amsterdam

PROGRAM

16:00	Doors open	18:30	Best paper of 2017
16:15	Opening		- Sandra van Brunshot
			- Kasper ter Horst
16:25	Hester Coppoolse		- Davor Slijepcevic
	Anouk Hagemeyer		- Marijn Warners
			- Irina Milanova
16:30	Maarten Soeters		- Anneloes Opperhuizen
16:50	Ingeborg Brouwer		
17:10	Mireille Serlie	19:00	AG&M grant award ceremony
17:30	Dinner / Buffet	19:15	Jaap Seidell

am  Online registration deadline March 23rd VUmc 



SEPTEMBER 21st

AG&M/CCA symposium: "Colorectal Cancer"
Hotel Casa, Amsterdam

On Friday September 21st 2018, in hotel Casa in Amsterdam, almost 200 people came together for the Colorectal Cancer (CRC) symposium organized by Dr. Jurriaan Tuynman (gastrointestinal surgeon at location VUmc) and Prof. dr. Kees Punt (medical oncologist at location AMC) and sponsored by Cancer Center Amsterdam (CCA) and AG&M.



The goal of the symposium was to make plans for optimal collaboration between the region (Noord-West Nederland) and the new Amsterdam UMC. At the same time, preclinical and clinical research from AMC and VUmc to encourage cross-pollination between the two Amsterdam UMC locations.

Prof. dr. Hans Clevers (UMC Utrecht) concluded the very successful day, with representatives from all the hospitals in the region present, with a lecture on his world famous stem cell research.

**Colorectal Cancer Symposium
 Amsterdam**

Regional collaboration & Research



GENERAL INFORMATION

21.09.2018

VENUE

Hotel Casa Amsterdam
 Eerste Ringdijkstraat 4
 1097 BC Amsterdam

REGISTRATION

Registration on-line: www.epgs.nl
No registration fee

ACCREDITATION

Accreditation has been requested.

INFORMATION

<https://epgs.nl/colorectaal-symposium-amcvumc/crcsymposium@vumc.nl>

GRANTS BY

Amsterdam Gastroenterology & Metabolism (AG&M)

Cancer Center Amsterdam (CCA)



VUmc department of Colorectal surgery



DECEMBER  **13th**

AG&M symposium: "Obesity"
Pakhuis de Zwijger, Amsterdam

In the IJ zaal of Pakhuis de Zwijger, started the morning of Thursday December 13th, 2018 with a select group of people. Casper van Olden, Myrthe Reiche and Laura Draijer presented their work in the 'Meet the expert' session with the guest of honor, Prof. dr. William Dietz.

Later that morning the room was filled with more than 70 people that listened to Prof. dr. Hans Jonker, Drs. Eline van der Valk and Prof. dr. Roger Adan who talked about the critical regulator of adipose tissue homeostasis FGF1, a comprehensive clinical approach to obesity, and leptin resistance and neural circuits underlying obesity, respectively.

After lunch Dr. Ir. Rinke Stienstra continued the program with a talk on an immunometabolic perspective of obesity and diabetes, followed by Prof. dr. Karien Stronks with a lecture addressing the social determinants of obesity. The session was closed by Prof. dr. Patrick Schrauwen, who talked about circadian rhythmicity of skeletal muscle metabolism and its role in insulin resistance in humans.

Keynote speaker, Prof. dr. William Dietz, who came all the way from Washington, DC, concluded the day with a lecture discussing the changes in the paradigm for obesity prevention and care.





AG&M symposium OBESITY

THURSDAY, December 13, 2018
9:00h - 17:30h

Pakhuis de Zwijger: IJ zaal, 5th floor
Piet Heinkade 181 K, Amsterdam

PROGRAM

09:00 – 10:30	'Meet the expert' Prof. Dietz	 William Dietz
10:30 – 11:00	Coffee/Tea break	
	Start main symposium	
11:00 – 12:30	Session 1	
12:30 – 13:30	Lunch	
13:30 – 15:00	Session 2	
15:00 – 15:30	Coffee/Tea break	
15:30 – 16:30	Keynote lecture Prof. Dietz	
16:30 – 17:30	Drinks	


Hans
Jonker


Eline
v/d Valk


Roger
Adan


Rinke
Stienstra


Karien
Stronks


Patrick
Schrauwen

AG&M Tager Lectures

The AG&M research institute has a bimonthly 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 AG&M 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.

FEBRUARY

5th

Dr. Celine Riera

*Diabetes and Obesity Research
Institute, Department of Biomedical
Sciences, Cedars-Sinai Medical
Center, Los Angeles, USA*

Chemosensory neurons in the control of metabolic homeostasis

MARCH

8th

Dr. Clara van Karnebeek

*Departments of Pediatrics &
Clinical Genetics, Amsterdam UMC,
Amsterdam, The Netherlands*

Translating -omics data into diagnosis and treatment for neurometabolic diseases

MAY

24th

Dr. Thomas Langer

*Max-Planck-Institute for Biology of
Ageing, Cologne, Germany*

Proteolytic control of mitochondrial proteostasis

SEPTEMBER

13th

Dr. Ruben Nogueiras

*University of Santiago de
Compostela, Santiago de
Compostela, Spain*

Unraveling the metabolic role of p53

DECEMBER

6th

Dr. Sophie Steculorum

*Max Planck Institute for Metabolism
Research, Köln, Germany*

Central control of feeding and systemic insulin sensitivity

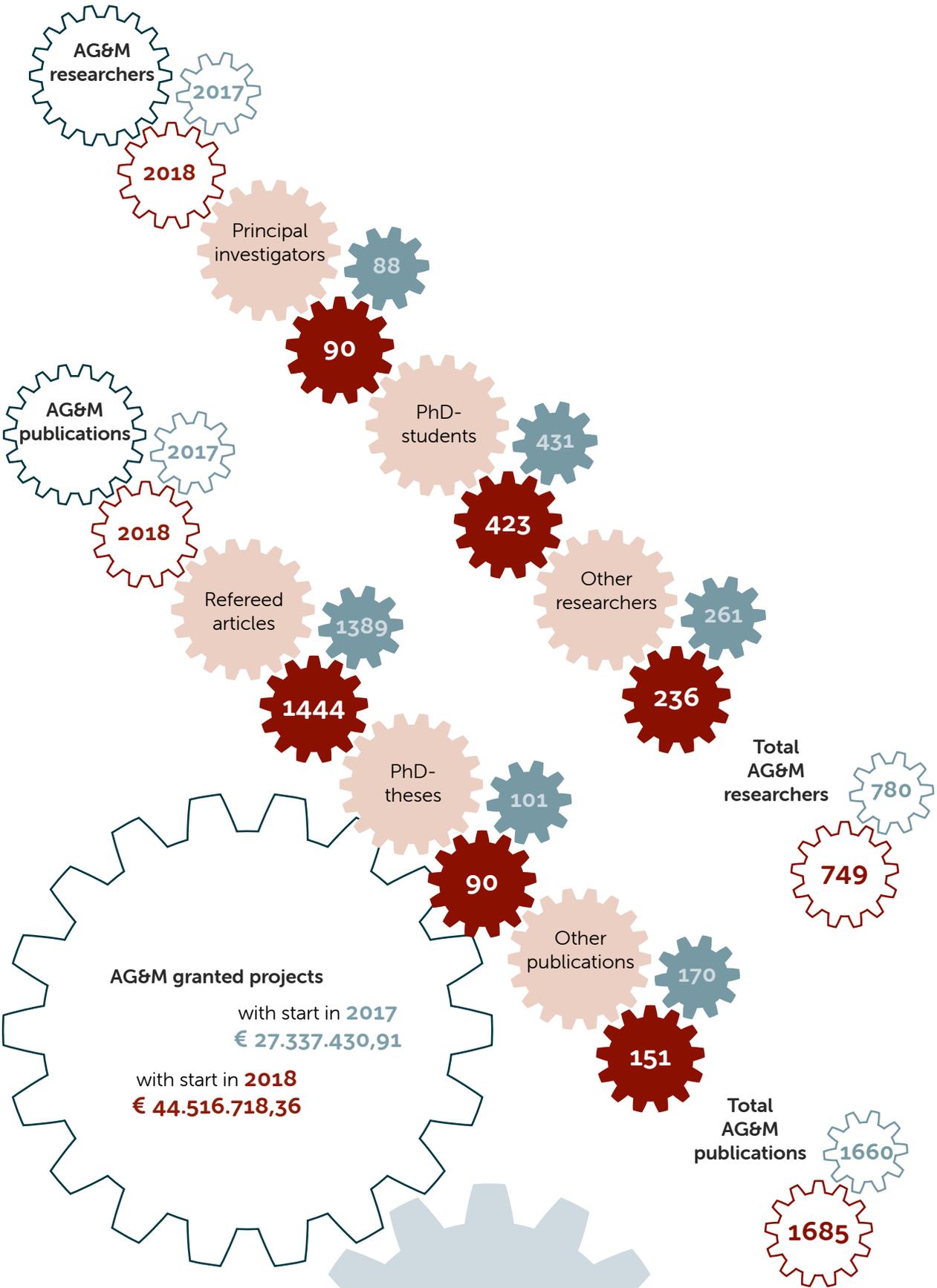
AG&M Numbers and Facts 2018

AG&M finances 2018

In 2018, the AG&M research institute had €500.000,00 (€250.000,00 from board of directors VUmc and €250.000,00 from board of directors AMC) plus €83.734,03 remaining from 2017 to spend. In the table below is shown how this money was budgeted and spend. Most of the 2018 budget was used for the AG&M grants (The AG&M talent development grant and The AG&M innovation grant).

	Budgeted 2017	Expenses 2017	Budgeted 2018	Expenses 2018
AG&M grants	€ 320.000,00	€ 300.000,00	€ 300.000,00	€ 300.000,00
Personnel	€ 75.000,00	€ 71.559,68	€ 50.000,00	€ 40.730,14
Meetings	€ 80.000,00	€ 37.580,32	€ 100.000,00	€ 53.512,93
Miscellaneous	€ 25.000,00	€ 7.125,97	€ 50.000,00	€ 3.054,64
Total	€ 500.000,00	€ 416.265,97	€ 500.000,00	€ 397.297,71

AG&M numbers 2018



AG&M researchers per research program

If a researcher is participating in two or more research programs this researcher is counted for both (or more) research programs, therefore the sum of the researchers in the different research programs is greater than the total amount of researchers participating in AG&M.

	Total AG&M researchers		PhD-students	
	2017	2018	2017	2018
Re-generation and cancer of the digestive system	395	400	211	212
Digestive immunity	387	394	211	214
Endocrinology, metabolism and nutrition	293	298	163	174
Inborn errors of metabolism	94	96	43	47

AG&M publications per research program

If the author of a publication is participating in two or more research programs this publication is counted for both (or more) research programs, therefore the sum of the publications in the different research programs is greater than the total amount of publications produced by AG&M.

	Refereed articles		PhD-theses	
	2017	2018	2017	2018
Re-generation and cancer of the digestive system	504	539	36	32
Digestive immunity	569	601	40	36
Endocrinology, metabolism and nutrition	597	685	42	47
Inborn errors of metabolism	172	183	9	11

Research input

Information about amount of researcher from the Amsterdam UMC is gathered at Amsterdam UMC, location VUmc, from departments by using data entry forms. The data entry forms include all researchers with active affiliations with research programs in the last year in the Research Information System Pure VUmc. When a department did not provide new data, then the most recent available data are used instead.

Grants

Information about funded research projects has been provided by the separate project administrations from location AMC and location VUmc.

Four categories of funding are distinguished by the Standard Evaluation Protocol from the VSNU: (1) direct funding, (2) research grants obtained in national scientific competition, (3) research contacts for specific research projects obtained from external organizations, and (4) other funds that do not fit into the other categories.

Research output

Research output from the Amsterdam UMC is mainly registered by researchers themselves at location VUmc and mainly by personnel from the Medical Library at location AMC. The reported data include all published research output as registered in the research information systems Pure VUmc and Pure AMC on 31 March 2019.

Theses

Theses are ascribed to organizational units based on the affiliations of the (co-)supervisors. A thesis can be ascribed to one or more organizational units depending on the affiliations of the (co-)supervisors.

Four categories of theses are distinguished by the Standard Evaluation Protocol from the VSNU: (a) internal research and internal graduation, (b) external research and internal graduation, (c) internal research and external graduation, (d) external research and external graduation. Research and / or graduation at the University of Amsterdam counts as internal for location AMC and research and / or graduation at the Vrije Universiteit Amsterdam counts as internal for location VUmc.

Publications

Publications are ascribed to organizational units based on the affiliations of the authors. A publication can be ascribed to one or more organizational units depending on the affiliations of the authors. The publications are categorized according to the Standard Evaluation Protocol from the VSNU. Academic publications are categorized by subtype: book, book chapter, conference paper, refereed article, non-refereed article, other research output. Professional publications and Popular publications are not divided into subtypes.

Collaboration

Research institutes have researchers at Amsterdam UMC, location AMC, location VUmc, University of Amsterdam, Vrije Universiteit Amsterdam and Amsterdam University of Applied Sciences. Refereed articles registered in the local Pure instances have been combined and deduplicated by using the Digital Object Identifier in order to calculate the overall output.



Appointed professors 2018



Prof. dr. C.Y. Ponsioen

Gastroenterology & Hepatology with special attention to Inflammatory Bowel Disease and Primary Sclerosing Cholangitis

In June 2018 Cyriel Ponsioen, gastroenterologist at the AMC location was appointed full professor of gastroenterology, with a special focus on inflammatory diseases of the bowel and bile ducts at the University of Amsterdam.

Twenty years ago Ponsioen started a research line on primary sclerosing cholangitis (PSC), a rare and devastating inflammation of the biliary tree, eventually leading to endstage liver failure. Since 2010 he also leads a research line on microbiota research in inflammatory bowel disease (IBD).

Because there is a close association between PSC and IBD the topic of one of his current research lines is on finding the missing link between the bowel and the biliary tree. On an international level, Ponsioen is currently co-chair of the International PSC Study Group, the leading global network of PSC researchers.

Did you know that...

... NFU and the minister of Health, Welfare and Sport have recognized the 'Centre for Immune-mediated and Genetic Cholestasis Syndromes' (PI: Prof. dr. Ulrich Beuers) as *Designated centre of expertise.*

... AG&M PI's Dr. Clara van Karnebeek and Prof. Hans Waterham established the foundation of United for Metabolic Diseases (UMD).

... Three out of five Top Abstract Prizes were awarded to the Dutch pancreas multicenter trials at the annual UEG conference in Vienna.

... AG&M PI Anje te Velde, together with an interdisciplinary research team, started a new project: MyOwnResearch, as it got funded by SGF (Samenwerkende GezondheidsFondsen) and Topsector Life Sciences & Health.

... AG&M interational student research fellow Jelmi uit de Bos published in Science (SFXN1 is a mitochondrial serine transporter required for one-carbon metabolism, Kory N et al. Science 16 Nov 2018: Vol. 362, Issue 6416).



Prof. dr. ir. P.J.M. Weijts

Nutrition & exercise with special attention to protein

In 2018 Peter Weijts was appointed full professor of Nutrition and Exercise, with special reference to Protein at VUmc. The new Department of Nutrition and Dietetics covers both VUmc and AMC location. His focus in research is a combination of nutritional and exercise science, which combines perfectly within protein metabolism. Although his research covers from young children upto old age, and from sports to intensive care, the theme remains a combined lifestyle approach both in prevention as well as in care setting.

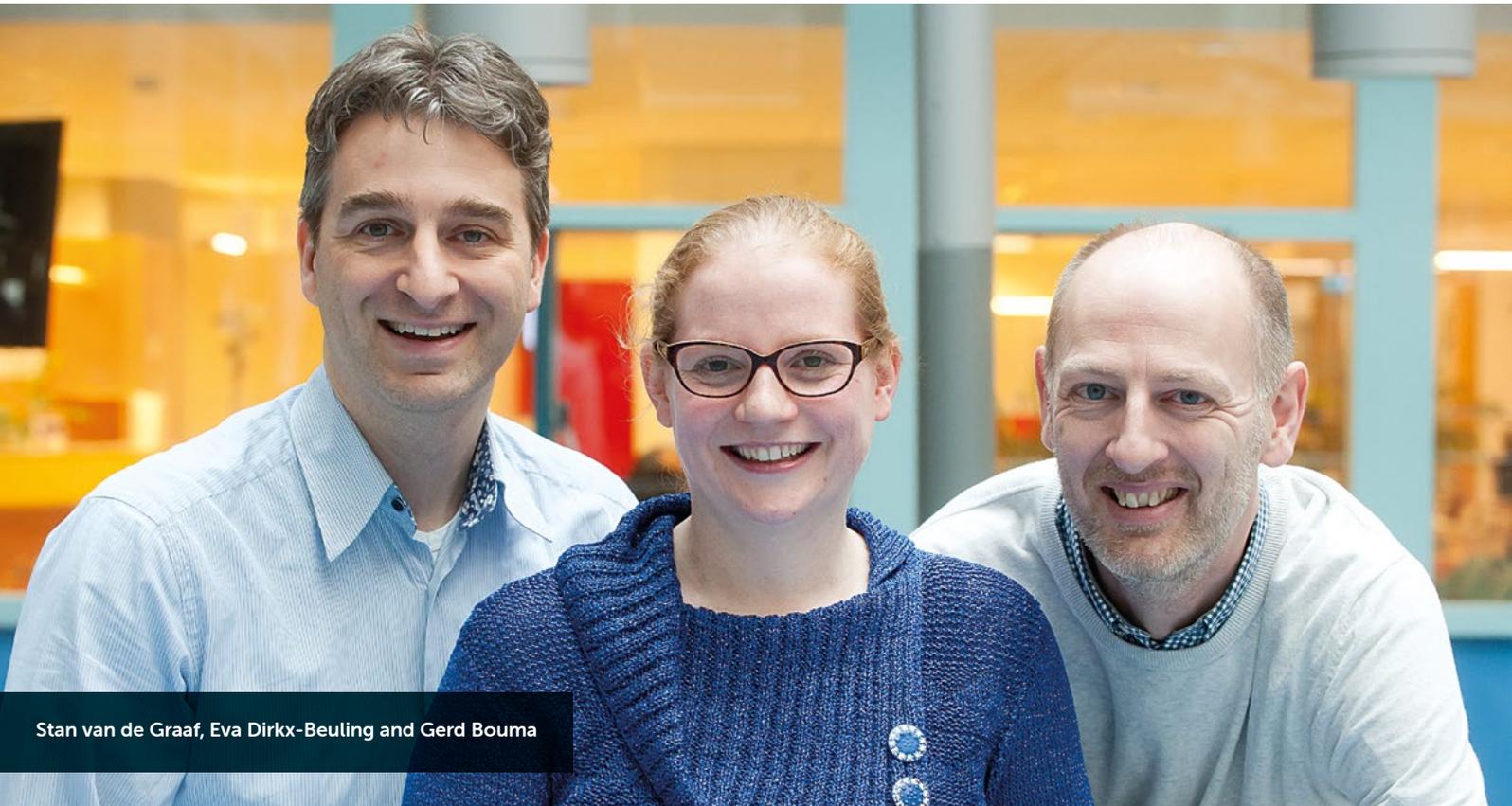
His more than 30 years of experience with protein has developed into a subject with societal impact, e.g. his studies concerning the importance of protein for the intensive care patient as well as nutrition and exercise intervention studies in (obese) older adults (with or without type 2 diabetes).

Since 2009 he is also professor of Nutrition and Exercise at the Amsterdam University of Applied Sciences. His research groups have now been combined into one. He is linked to the Zorg op het bord initiative within the AmsterdamUMC. Within VUmc and AMC, as well as OLVG, an intensive dietetic care path has been developed in combination with an exercise program for malnourished elderly (Pro-Intens), the stepped wedge design RCT will start by the end of 2019.





Future perspectives for the AG&M research institute



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

Having achieved a bridgehead, so to speak, as a research institute during its first two years, co-director Professor Gerd Bouma now wants to take the principles and policies laid down by the nascent AG&M to move forward to the next decade and beyond. He sees progress in science coming from two sources:

basic science which may take many years to find its way into the clinic; and, serendipity – making happy discoveries by accident – which may come from clinical observations and laboratory work. “We have to stimulate both and you can only do that by creating an environment where you are curious. Where you are

willing to discuss, to not take anything for granted, but to start to ask questions. This is crucial for teaching, it has to be in the DNA of a university hospital.”

He stressed the need to invest in basic science which may not pay off in the immediate future but may well, in the end, lead to really important breakthroughs. “That is difficult today. We are restricted in funding and need to be successful in a short period. However, if you want to bring science to a higher level you need people doing the basic research, building scientific discoveries over decades.”

Then there is serendipity which, like with luck, you may be able to help create yourself, simply by bringing together the AG&M’s main asset, its large number of brilliant clinicians and scientists. This can be achieved during the annual retreat but also in daily clinical practice. Bouma: “If you have scientists as part of ward rounds, they hear what is happening in daily practice, the struggles clinicians have. The clinicians can bring their observation to the scientists, who can, in turn, translate them into solid research questions and then can answer them. That is the key to serendipity in clinical science.”

Such connections will, argue both Bouma and his AG&M co-director Van de Graaf, become increasingly important in the future as both scientists and clinicians are, out of necessity, becoming “super specialists”. Van de Graaf: “you can’t study everything, so people are zooming in more and more, not just in basic science but among clinicians too, such as with the use of endoscopic retrograde cholangiopancreatography (ERCP) which requires a real level of specialization.”

At the same time the problems, such as the plethora of diseases associated with obesity, all happen to the same patient. Van de Graaf: “There remains a great need for overarching care. It makes little sense if one specialist ignores all the others. Super specialists should at least be aware that there is another super specialist next door.” Bouma agrees, scientists from different fields, “need to get to know each other”. “It is very easy to lose connections. It is a challenge to bring together scientists from other areas to learn from each other. That is something we try to achieve in meetings by having slightly different areas within a common theme,

such as genetics and metabolics. This then brings in people from different fields during a day or a meeting.”

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These meetings will, in the future, be increasingly geared towards bringing the people doing clinical research, together with the basic scientists, in translational research. Van de Graaf gives examples of very productive teams of clinicians and scientists already in existence such as Dr Mireille Serlie and Professor Susanne la Fleur working in endocrinology, and Professors Geert D’Haens, Manon Wildenberg and Wouter de Jonge in inflammatory bowel disease. Such teams create synergy where clinical presentation provides input for basic science and basic concepts are translated into clinical practice. For example with diabetes patients’ intestinal problems or problems with the developing gut of children born prematurely leading to necrotising enterocolitis. The clinicians can identify the problems and ask the basic scientists, “what is going on?”.

For the future Bouma believes that, as a research institute in a very large university hospital, it is important to, at least, attempt to define and incorporate the principal research questions, not just from a scientific, but also a societal point of view. Here, Bouma highlights the need to find solutions to the complications linked to obesity. “If we could find solutions, for example to fatty liver disease, we will have achieved something with enormous societal impact.” Van de Graaf adds that solutions for many (particularly lifestyle-related diseases) require collaboration between institutes. For example, cardiovascular aspects of the metabolic syndrome are intensively studied in the Amsterdam Cardiovascular



Science (ACS) institute, and prevention strategies are developed in the Amsterdam Institute for Public Health (APH). Another area highlighted is the urgent need to make swifter progress of pancreatitis and pancreatic cancer. Here, it is the experience within the AG&M in organizing multi-center studies which promises results in coming years. Promising too are diagnostic developments combining metabolics and genomics to tackle in-born errors of metabolism.

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Meanwhile both co-directors take hope in witnessing new people with new opportunities. Van de Graaf is excited by initiatives of AG&M investigators in including artificial intelligence in image-based diagnostics and in the use of gaming. Such “gamification” for example will allow clinicians to train in a virtual reality setting. For Bouma, the complicated but gradual merging of clinical groups brought together by the fusion of the two university hospitals points to the future. “What I like to see is how young scientists have paved the way for this hospital merge, young people at the beginning of their career who are not carrying 30 years of baggage. They see that in the other departments there is knowledge or technology which they don’t have and could use for their research. That is one of the core achievements in the early stage of this institute

And gazing ten years into the future, what would success look like for the AG&M? For Van de Graaf it is not about the greatest number of research publications, that is not such a relevant measure, but it is about someone creating something really original that makes a real difference to patient care or our understanding of a biological system. “Say we give money to two researchers today in 2019, who hardly

know each other, but met at one of our symposia, one works on a problem, another has an idea, and together they come up with a solution that didn’t exist before, to figure out how a disease really works. They find it, the team grows and with help from others in our Institute arrive at a new therapy, that’s the best, that would make me proud.”

Bouma agrees it is not about counting research papers but retaining a scientific curiosity which could change our society. “What I would like to achieve is that science in our Institute is highly competitive, but not a competition. I want people to be very dedicated to achievement, not so that in the end you win some sort of game, but so that you can contribute to the health and well-being of the society.”

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“We have to think how we value science, if as scientists we look back on our careers, do we need to do that in a numerical way or in a more narrative way, not counting the amount of funding or the number of papers, but rather what was our impact upon society, how have we created collaborations, brought science to the next level”.

Gerd Bouma, AG&M director

Stan van de Graaf, AG&M director

Eva Dirkx-Beuling, AG&M policy officer

Amsterdam Gastroenterology and Metabolism

