

EXPERTISE

CIRCLE OF LIFE

AMSTERDAM REPRODUCTION AND DEVELOPMENT

ANNUAL REPORT

2018

REPRODUCTION

DEVELOPMENT

RESEARCH

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A word from the directors

We proudly present our annual Amsterdam Reproduction & Development report 2018!

The year 2018 was from a reproductive and developmental view interesting; Jiankui He, a Chinese scientist, captured international attention. He claimed, using gene-editing tools, that the alterations in twin girls modified them and thereby protect them from HIV infection. In short, the world's first genetically modified babies. An international debate started with concerns about the data, which are still not published in an international journal, and ethical issues including if the risk weighted the benefits. Since then the ethical and legal responsibility on gene regulations are being discussed.

June 7th 2018 Amsterdam UMC was born; VUMC and AMC merged and created many opportunities including further stimulation of our research activities on both sides of the Amstel.

In December 2018, we had to say farewell to the founder of our Institute: Sjoerd Repping. We want to thank Sjoerd for his inspiring leadership and his ability to initiate to bring us all together!

Our research institute Amsterdam Reproduction & Development (AR&D) focuses on innovation and excellence in fundamental, translational, psychosocial and clinical evaluation research, as well as on research into nursing. Over 2018 AR&D has grown from child to adolescent. We harbour many excellent research groups that work on the different aspects of the circle of life, from preconception through pregnancy to child development and long-term health.

We stimulate young researchers to find their way in our expanding network. Much of the research by AR&D has a societal impact which becomes increasingly important in our changing society as illustrated by the gene-editing "human experiment". The current debates regarding reproduction and development are still ongoing.

The research at AR&D contributes to a better understanding of many aspects within the field of reproduction & development. The importance of our studies is underlined by the daily societal impact on clinical practice and society, illustrated by the STIDER study and the kick-off of the "Better start" ["Kansrijke Start"] initiative in 2018. In this annual report, we take you through an overview of our researchers, highlights and projects and introduce three AR&D PhD students and their mentors, and three new inaugurated AR&D professors. We are honoured to share our institute, their thoughts and future with you.

We wish you an interesting reading on the highlights from 2018!

Christianne de Groot & Lidewij Henneman
Directors Amsterdam Reproduction and Development



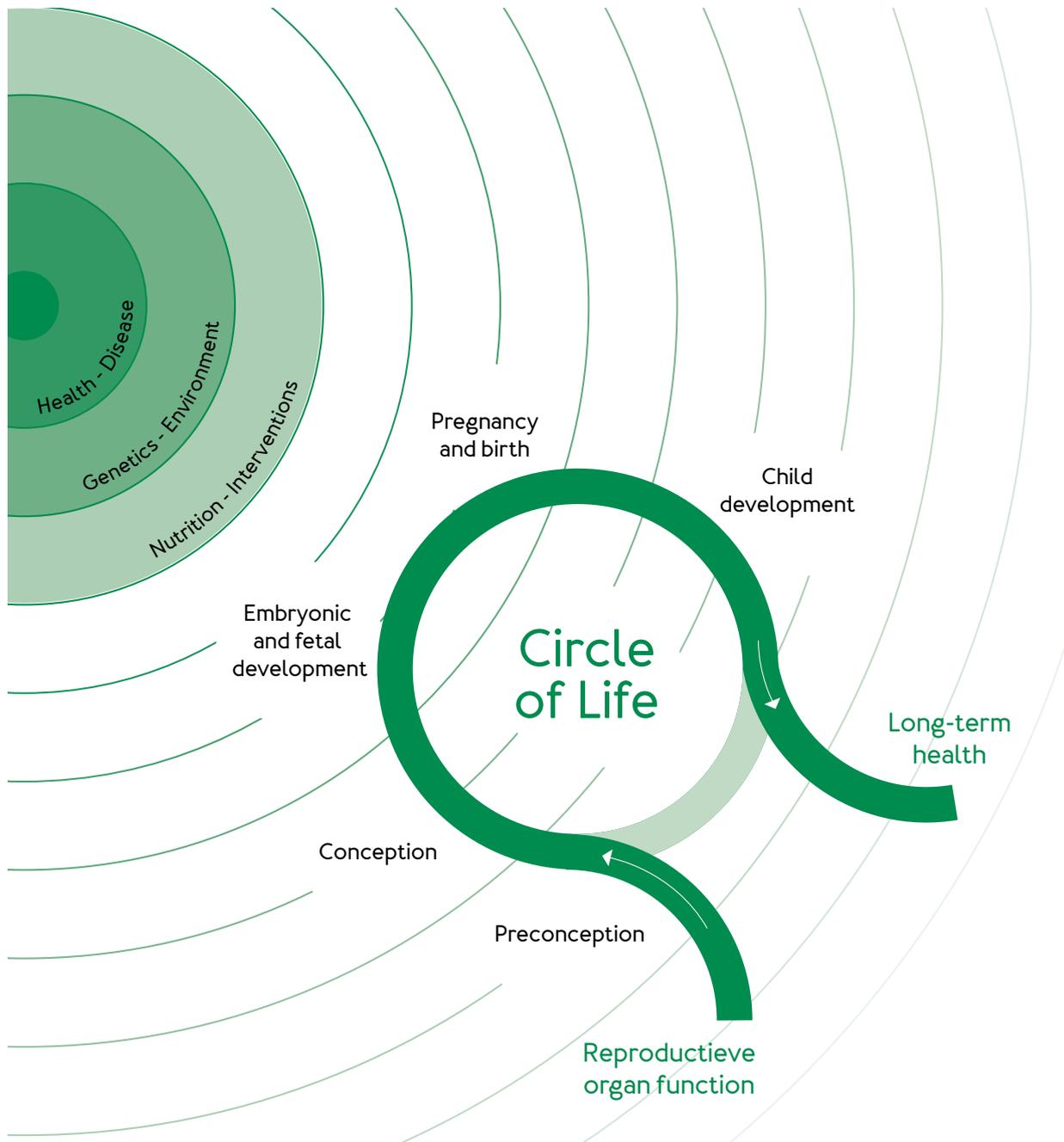
Starting the circle of life



The Amsterdam Reproduction and Development (AR&D) research institute is unique in its goals and ambition. The institute covers themes that comprise the Circle of Life: from preconception through pregnancy and child development to long-term health. It encompasses research that focuses on long-term health effects on both mother and child, of disease and interventions during preconception, conception, embryonic and foetal development, pregnancy and birth, as well as child development and effects on reproductive organ function (see Figure 1).

The ambition of AR&D is to enhance the field of reproduction and development nationwide and to sustainably improve health care for mother and child (future generations).

AR&D integrates various disciplinary approaches within the Amsterdam UMC and their affiliated centres and has connections with virtually all other Amsterdam UMC research institutes. AR&D researchers study the effects of genetics, environment, nutrition, disease and interventions on the developmental process from gamete to adult. In the institute, basic, translational, psychosocial and clinical research scientists work together to maximally improve health care. For more information and videos of AR&D, please visit www.amsterdamresearch.org.



Research Areas

○○○ FROM PRECONCEPTION TO CHILD DEVELOPMENT



PRECONCEPTION AND CONCEPTION

The desire to have children is a fundamental driving force for all species. We provide optimal care for people who have difficulty conceiving. Our prediction models provide accurate and reliable prognoses for medical help. Thus, we stand for optimal evidence-based shared decision-making. AR&D does not only offer novel medical treatments but we also evaluate whether they are truly of benefit for our patients. We investigate how to best counsel couples who are confronted with a high risk of serious genetic diseases in their future children, and to provide them with options for autonomous reproductive choice. We evaluate how medical professionals and other stakeholders view novel genetic and reproductive techniques and how innovative techniques should be ethically weighed and implemented. Within AR&D, we also study the process of spermatogenesis and oogenesis and the earliest stages of embryo development from fertilization to implantation and translate this knowledge to new therapies.



EMBRYONIC AND FETAL DEVELOPMENT

Humans all originate from a single cell, the fertilized oocyte, and developing through a fascinating highly orchestrated process to become the individuals that we currently are. AR&D studies how these processes are regulated, how perturbations can lead to congenital abnormalities or late onset diseases and how genetic and environmental factors affect development. We use experimental model systems to study and simulate human development and use our unique twin register to disentangle environmental and genetic contributions to health and disease. By focusing on embryonic development, we provide the basis for understanding a huge variety of human disease and disease susceptibility. We link these fundamental studies to clinical trials. We use highly sensitive ultrasound measurements and genetic tests to examine the developing foetus, and evaluate innovative implemented techniques. These are used for developing new tests to improve our clinical capacities.



PREGNANCY AND BIRTH

AR&D constantly strives to provide the best possible care for mother and child. Therefore, we routinely perform multi-centre clinical trials. With these trials, we aim to establish the benefit of specific interventions in reproductive medicine, gynaecology, obstetrics and neonatology. Results of these trials are integrated into clinical protocols so that we can provide the best possible treatment for our patients and to allow for truly informed decision-making. In addition, we are developing tailored made tools for the shared decision-making. Our trials are conducted in the context of national networks of collaborating hospitals, gynaecologists, midwives, neonatologists, and health care provides coordinated from Amsterdam. These professionals focus on optimally treating pregnancy complications and preventing premature delivery, as well as optimizing care for prematurely born infants. We study the requirements for responsible implementation of advancements in prenatal screening. We also investigate effects of environmental exposures during pregnancy on women's and offspring's health. This in order to learn more about how to give each child the best possible start in life.



CHILD DEVELOPMENT

Healthy child development is essential for later health and wellbeing. AR&D follows children through their development after they have spent part of their early life in the hospital. For instance because they were born prematurely. We monitor their behaviour, growth and development to better understand the long-term consequences of our treatments and to inform our patients more accurately. We develop online tools that help patients and their parents keep track of various aspects of child development. This covers the full range of psychosocial, mental as well as physical and behavioural aspects of life. We follow up children whose mothers participated in intervention trials. This provides insight into the underlying mechanisms of diseases before they become clinically overt. With the advancement of sequencing technologies, we strive to optimize the genetic diagnosis in children with developmental disorders. We monitor development and follow individuals as they become the parents of the next generation and the circle of life begins again.



**“Enhancing the field
of reproduction
and development
nationwide.”**



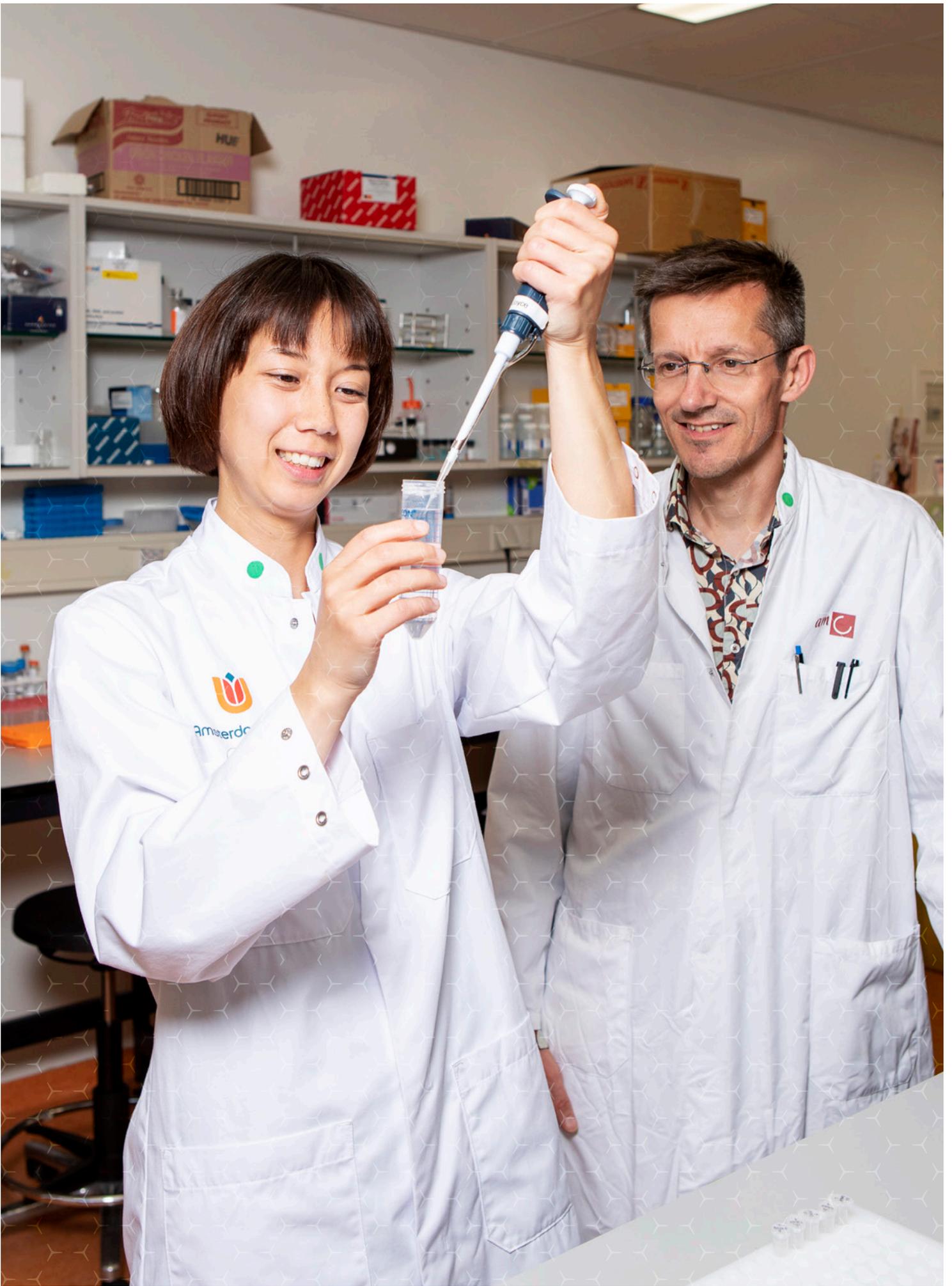
VINCENT CHRISTOFFELS
AND JOYCE MAN
*Researchers development
of heart and rhythm*

TESSA ROSEBOOM AND
VINCENT WEKKER
*Researchers early
development and health*

RESEARCH AT AR&D

BERNADETTE DE BAKKER
*Researcher clinical anatomy and
embryology*

LOTTE KLEINENDORST AND MIEKE VAN HAELEST
Researchers obesity genetics



Unravelling the mechanisms of congenital heart arrhythmias



Within the Amsterdam Reproduction and Development research institute, the research led by professor Vincent Christoffels focusses on the molecular genetic mechanisms of heart development and rhythm establishment.



Joyce
Man



Vincent
Christoffels

The development and homeostasis of organisms is orchestrated by the spatio-temporal patterns of gene expression. These, in turn, are controlled by gene regulatory elements in the genome, such as enhancers. Tissue-specific and developmental transcription factors interact with these regulatory elements and activate or suppress the activity of genes in a particular cell at a particular moment.

Misregulation of gene expression as a consequence of dysfunctional transcription factors or regulatory elements has a large impact on development or organ function. It can cause embryonic death, congenital defects or disease, the latter often arising later in life. The genome of every individual is slightly different, and therefore millions of base pairs may differ between individuals. From genome-wide association studies we know that some of these variants can have a large effect on the individual's development, phenotype or disease state. The majority of such effect-causing variants influence regulatory elements.

Vincent Christoffels' research aims to understand how particular genes important for heart development or heart function are regulated. His research team investigates how genetic variation influences gene regulation, causing an effect on heart development or rhythm, how mutated transcription factors cause cardiac defects or arrhythmias, how the pacemaker of the heart develops, and how diseased heart components can be regenerated.

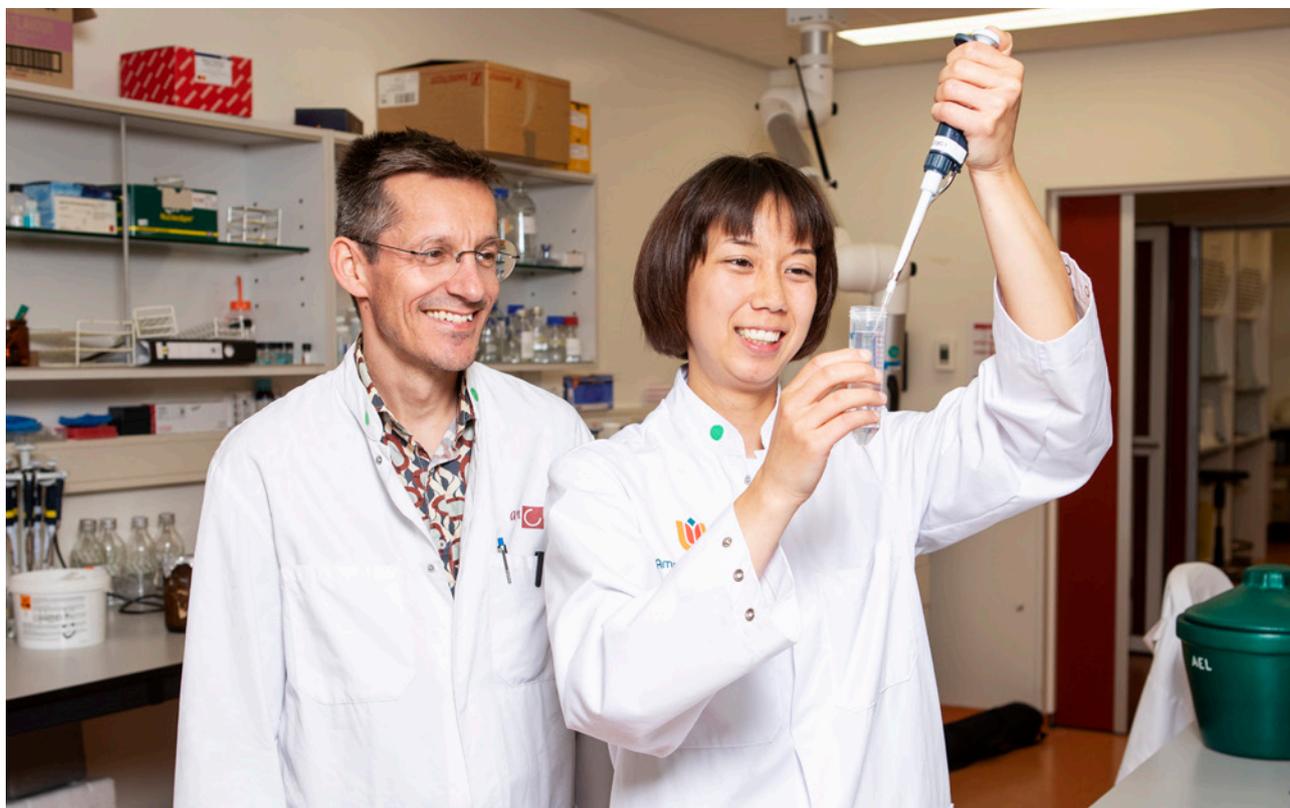
One of his research projects funded by Cardiovasculair Onderzoek Nederland (CVON) and the Leducq Foundation focuses on the transcriptional regulation of *SCN5A*, encoding the alpha subunit voltage-gated cardiac sodium channel Nav1.5, in heart development

“Understanding the molecular genetic mechanisms of heart development and rhythm”

and arrhythmogenesis. PhD candidate Joyce Man has the privilege to work on this challenging project under the supervision of Vincent. Cardiac sodium channels are essential for fast conduction of electrical impulses through myocardium and as such play an important role in excitation and contraction of the heart. Deletions and gain- or loss-of-function mutations in *SCN5A* are associated with a variety of arrhythmias including Brugada syndrome. Although Brugada syndrome is typically presents in young adults, it is also known to present in children and infants.

Only in about 25% of the Brugada syndrome patients, a mutation is found in the coding sequence of *SCN5A*, indicating a role of other genes or of other mechanisms affecting expression of *SCN5A*. Genome-wide association studies have identified genetic variants in non-coding sequences of the *SCN5A-SCN10A* locus associated with the velocity of impulse conduction. Vincent and Joyce identified a regulatory element cluster in the *SCN5A-SCN10A* locus, which drives localized cardiac expression in vivo and contains genetic variants

associated with conduction traits. They used genome editing tools (CRISPR-Cas9) to model and study the physiological roles of these regulatory elements in the *Scn5a-Scn10a* locus in mouse. In this way they could demonstrate that deletion of the cluster or its individual elements extinguished *Scn5a* expression from the modified allele in vivo. Conduction of electrical impulses through the heart were slowed down. Furthermore, homozygous deletion of the regulatory elements caused embryonic lethality. Deletion of the cluster caused a marked change in the 3D conformation of the locus, involving a reduction in contacts between other regulatory elements and promoters. These data indicate that the cluster enables other regulatory elements of *Scn5a* to activate expression by bringing them close together. This study reveals that a regulatory element cluster in the *Scn5a-Scn10a* locus is required for cardiac *Scn5a* expression, embryonic development and normal cardiac conduction, and suggest genetic variants affecting its activity may influence cardiac function. ●



“Driving for
more than
40.000 km
to visit the
participants.”



Window of opportunity to improve future health



Within Amsterdam Reproduction and Development, the research led by Professor Tessa Roseboom focusses on early development and later health. Her work investigate the impact of the early life environment on growth, development and health throughout life.



Vincent Wekker

Studies of the effects of environmental factors during the earliest stages of human development range from exposure to undernutrition during the Dutch famine of 1944-45 to the early embryo environment in assisted reproduction, obstetric interventions as well as public health interventions. Ultimately, these studies are aimed at providing each child with the best possible start in life.

The WOMB project is one of the international research projects that Tessa Roseboom coordinates. WOMB stands for “Women, their Offspring and iMproving lifestyle for Better health of both” and is funded by the Dutch Heart Foundation and the European Commission (H2020). Vincent Wekker was appointed as one of the PhD students to work on this international collaborative multidisciplinary project where 7 PhD students, 2 postdocs and several field workers work together with colleagues from various backgrounds including human reproduction, obstetrics, neonatology, paediatrics, nutrition, psychology, sexology, internal medicine, cardiology and epidemiology.

The overall aim of the project was to examine the effects of a lifestyle intervention before and during pregnancy on cardiovascular health in women and their children.

The intervention successfully improved lifestyle, and had consistent positive effects on women’s cardiometabolic health: the intervention significantly reduced body weight, waist and hip circumference, blood pressure, fasting glucose, insulin levels and insulin resistance. This resulted in a halving of the odds of metabolic syndrome. In addition, women felt physically better. Although the effect of the lifestyle intervention diminished after the end of the intervention, the effect on caloric intake was still detectable 5 years after the intervention, as women in the intervention group had significantly lower caloric intake than those from the control group. These effects were most pronounced among the women who made the largest changes in lifestyle during the intervention itself.

To include as many women and children as possible at the follow up, a research van was made to visit participants at their homes and minimise the burden of participating in research. The van was fully equipped with monitors to assess blood pressure, ECG and pulse wave velocity. It had a home-trainer for fitness testing and video cameras to perform observational studies of the children’s behaviour (in several delay of gratification tasks). The researchers drove more than 40,000 km to visit all the women and children who were



Tessa
Roseboom

willing to participate in the study. This is the equivalent of one trip around the world!

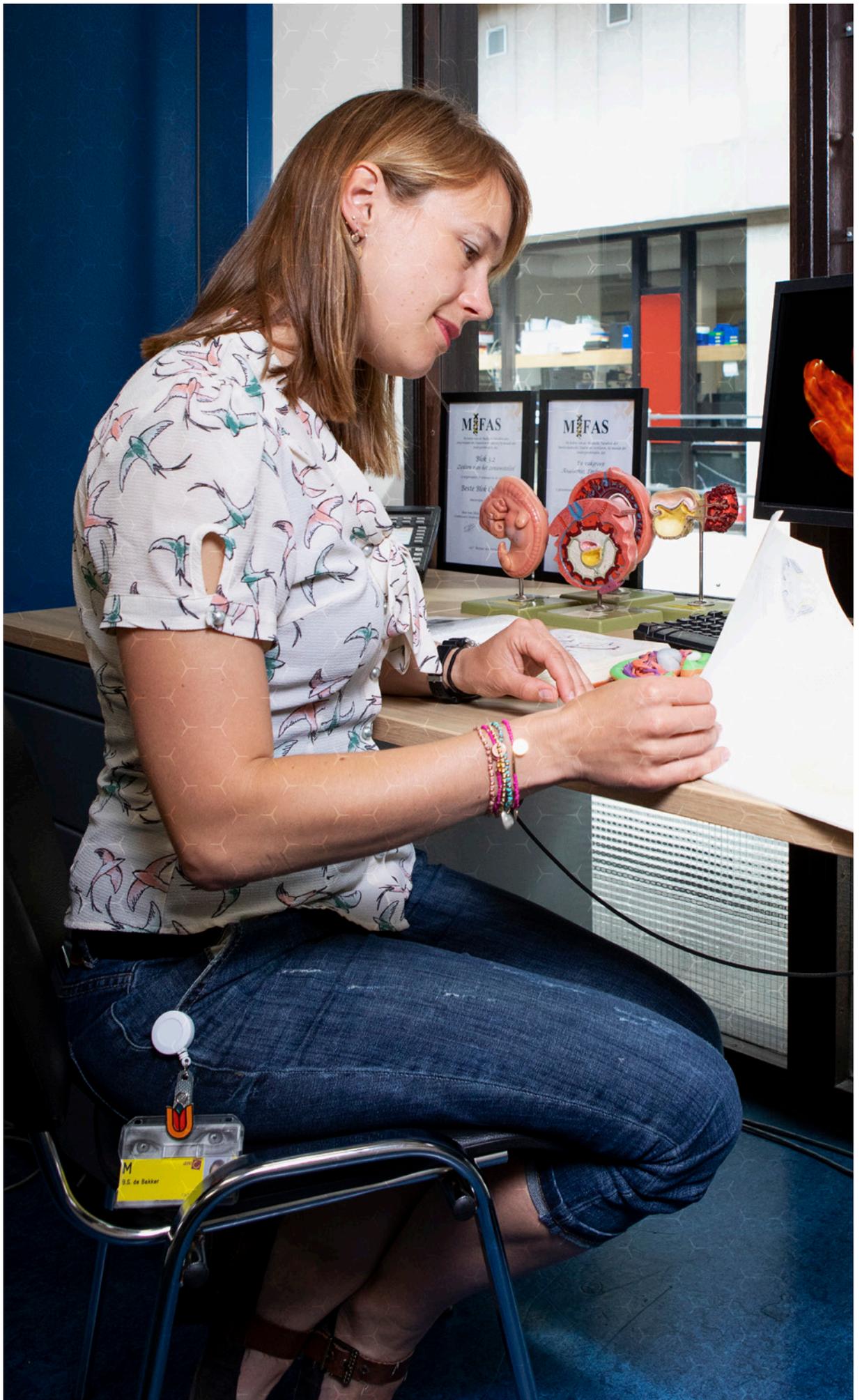
The follow-up study showed no evidence of sustained overall preconception lifestyle intervention effects on cardiometabolic health in the women. However, women who successfully lost weight during the intervention did have better long-term cardiometabolic health than those who did not change their lifestyle. Interestingly, the researchers of the WOMB project also found that women in the intervention group reported better outcomes for sexual health, even in the absence of any effects on weight. Others in the team investigated which factors contributed to successfully changing lifestyle, effects on mental health of women, while others investigated effects of the intervention on growth, development and health of the children.

As a part of the young talent development program of the WOMB project, Vincent benefitted from the opportunity to participate in an international exchange project and worked in Helsinki for several months. Another unique feature of the WOMB project was its dissemination program which included active dissemination through blogs

(with blogs being read by >10.000 individual readers online) and a public event that was freely available to all in the venue “De Nieuwe Liefde”, discussing implications for research, practice and policy.

Vincent successfully defended his thesis 7th of June 2019 and has started working clinically. He hopes to start his specialization in obstetrics soon. One of his fellow PhD students has recently started his training in pediatrics in the US, another one of his colleagues has started working as a post-doc in the US, while yet another recently joined the Netherlands Nutrition Centre [Voedingscentrum]. One of the postdocs obtained a Rubicon grant and will move to Oxford. Tessa is happy to see the WOMB PhDs and postdocs spread out to different disciplines in the clinic, in policy and in research in different parts of the world. ●

**“Improving
the health of
mothers and
their children.”**



BERNADETTE DE BAKKER

The 3D Atlas of Human Embryology: a unique project



As a PhD student, Dr. Bernadette de Bakker created the 3D Atlas of Human Embryology [Science, 2016], covering the first 10 weeks of pregnancy. By using state-of-the-art imaging techniques, she now expands the 3D atlas towards 24 weeks, building a reference resource for ultrasonographers.

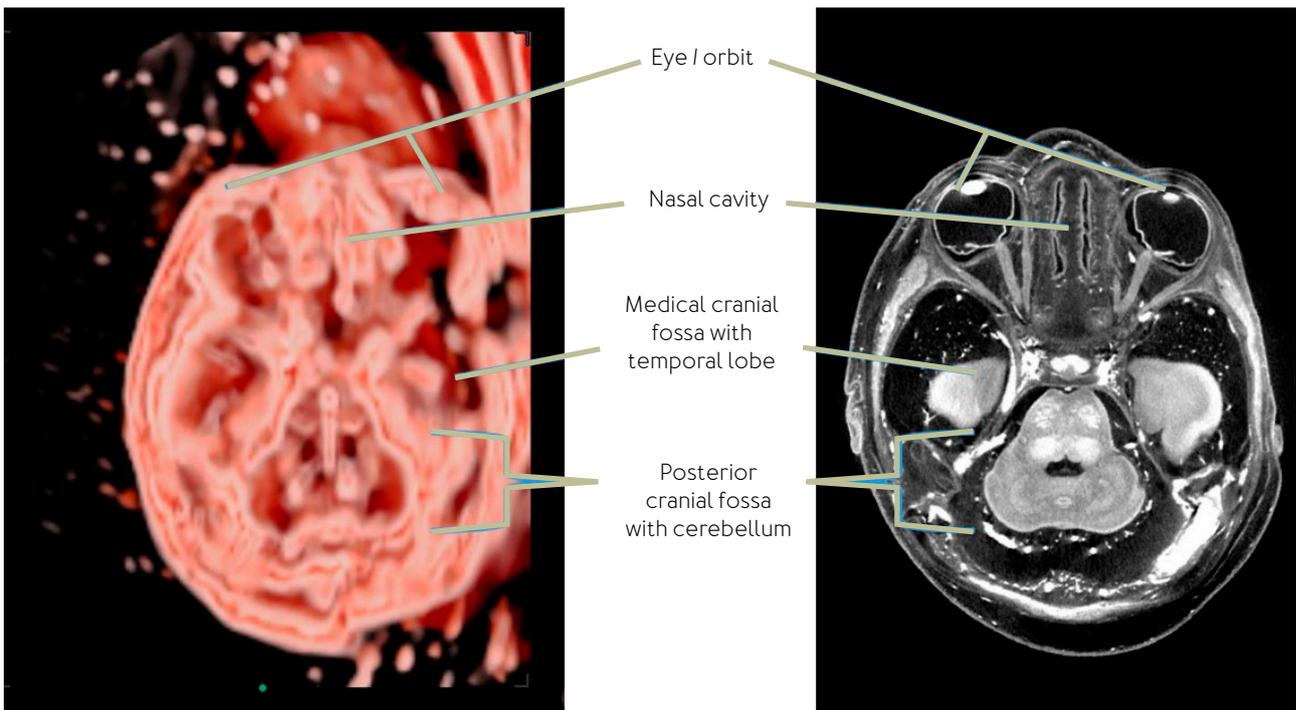


Imagine yourself, 20 weeks pregnant, lying on the examination bed in the ultrasonographer's office during the routine 20-week anatomy scan, waiting to hear whether your baby is healthy. The ultrasonographer looks carefully at the monitor; her gaze on the screen intensifies. After a couple of minutes of silence she calls in a colleague. Together they are now reviewing a specific part of your baby. They mumble: "What's that grey line over there?" "Should it be there, already at this age?" An embryologist is requested, but she cannot help. Unfortunately no foetal anatomy atlases exist to compare the ultrasound images with. 30 minutes later, you and your husband walk out the hospital with more questions than answers. The uninhibited happiness and enthusiasm for this pregnancy has given way to worry and uncertainty.

As the ultrasound techniques advance, more details can be seen even earlier in pregnancy. But proper reference materials to understand exactly what we are looking at is currently lac-

king. At the same time, 40 to 50% of the congenital malformations that can be detected are still missed. Therefore, the department of Medical Biology, makes an effort to create a *3D Atlas of Human Foetal Anatomy*.

Unlike the embryology atlas, which was based on historical specimens from the *Carnegie collection* (Washington DC, USA), Bernadette and colleagues collect the foetuses for the foetal atlas themselves. They are extremely grateful that the Medical Ethics Committee to give them the unique opportunity to set up a biobank for foetal material. Together with Prof. dr. Raoul Hennekam and Prof. dr. Eva Pajkrt and colleagues the biobank was opened in September 2017. Up until then parents had two choices after a termination of pregnancy before 24 weeks: to take the foetus home for a funeral/cremation, or to leave the foetus in the hospital for collective cremation. Since the foetal biobank was opened, parents in most hospitals in Noord-Holland and Flevoland are now given a third option:





Bernadette
de Bakker

to donate the foetus to science. Remarkably enough, this option also gives some meaning for many parents.

In the first 1.5 years since the opening of the biobank, 60 fetuses have been collected. When they receive a call about a new donation, the foetus is being picked up within two to six hours after birth, even at night. By doing so, the highest quality of the foetal tissue samples in the biobank can be guaranteed.

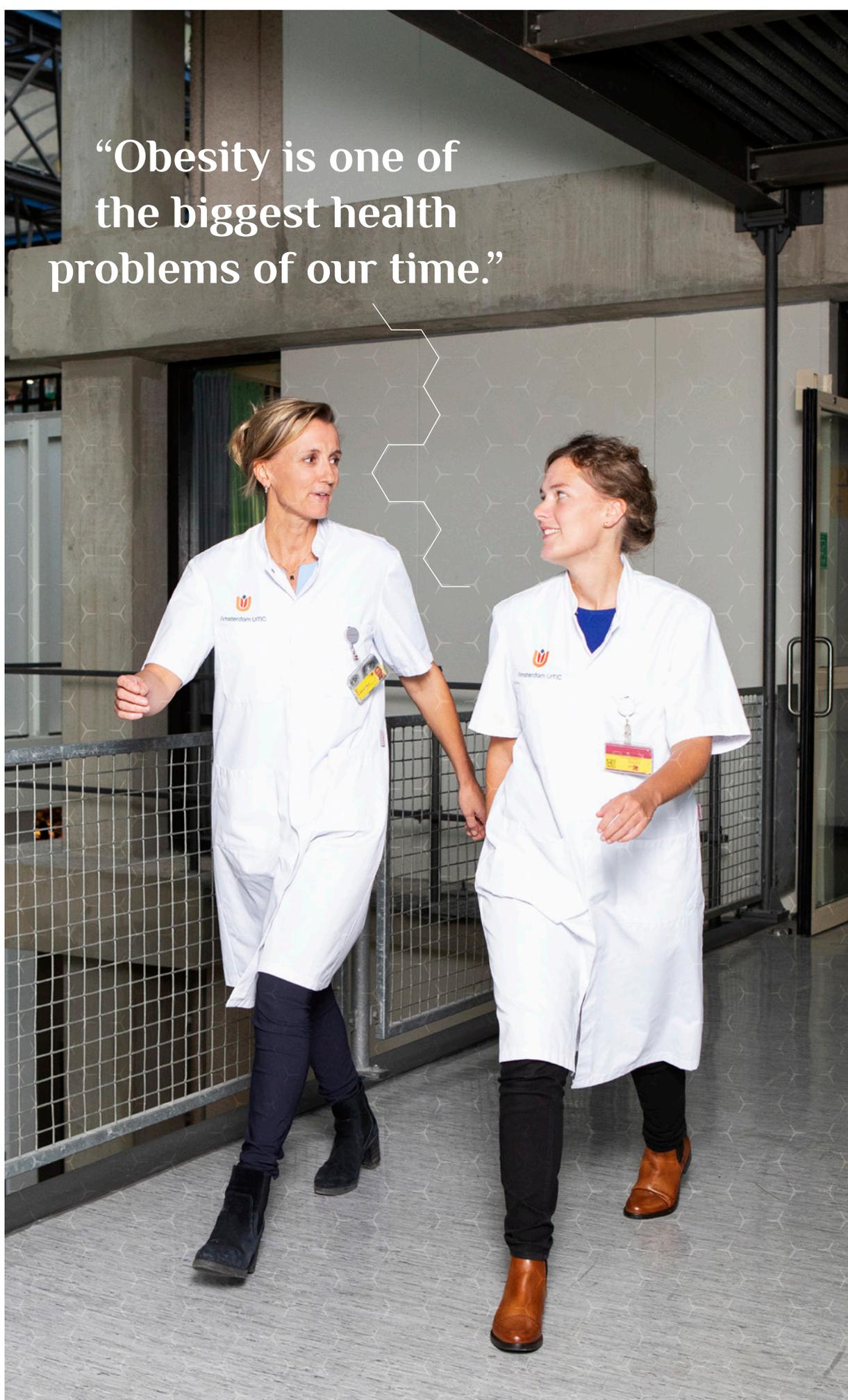
A grant from Amsterdam Research & Development enabled Bernadette to look for the best way to image human fetuses for the creation of the atlas. Would that be 3D ultrasound, or Dual Energy CT? Perhaps 7 Tesla MRI or even Micro-CT? One of the challenges she faced is that fetuses differ in size from 3 cm up to 30 cm. Another challenge is to image not only the foetal bony structures, but also soft tissues such as the organs, nerves, and vessels, which require the use of contrast. After a year of struggling and tweaking the protocol, PhD student Yousif Dawood now manages to get the most stunning images of fetuses with a

resolution up to 1 μm on a Micro-CT scanner at the University of Wageningen.

The Micro-CT images form a great reference resource for [3D] ultrasound. PhD student Marieke Buijtendijk currently verifies the latest 3D ultrasound software by Samsung, making use of the Micro-CT images as a reference. And just as they created the 3D embryology atlas with the help of 75 students, new students have already started reconstructing organs and structures in the microCT images of the fetuses, with promising results. With the 3D foetal atlas the ultrasound software can ultimately be trained to automatically detect malformations earlier in pregnancy and with higher accuracy. This feature will improve women's and foetal care worldwide. ●

“Creating the possibility to detect malformations earlier in pregnancy.”

“Obesity is one of the biggest health problems of our time.”



MIEKE VAN HAEIST & LOTTE KLEINENDORST

It's in our genes



Dr. Mieke van Haelst's research focusses on unravelling the pathogenicity of rare genetic disorders from gamete to adult.

The ultimate aim of her work is to enhance knowledge of normal and abnormal human reproduction and development caused by genetic alterations. Her research mainly involves paediatric genetics and genetics of obesity disorders.



Mieke
van Haelst



Lotte
Kleinendorst

At the moment she supervises six PhD students working on rare genetic disorders (Cantu Syndrome, Congenital Heart disorders in the Caribbean, Caribbean Genetics and Genetic Obesity Disorders). As a clinical geneticist and head of the section clinical genetics of the Department of Clinical Genetics, she directly translates the results of her research projects in daily clinical practice. The newly collected information about pathogenicity, prognosis and (future) treatment options for these disorders is invaluable for all health care providers and affected patients.

Within the Obesity Genetics Research group Mieke van Haelst supervises three PhD students: Mellody Cooman who evaluates the outcomes of bariatric surgery in patients with genetic obesity disorders; Anne-Mieke Oudshoorn, investigates obesity in the Dutch Caribbean; and Lotte Kleinendorst studies the phenotype and diagnostics of patients with genetic obesity disorders. Postdoctoral researcher Sanne Alsters is involved in the implementation of newly identified obesity genes in the diagnostic obesity gene panel that is being offered at Amsterdam UMC.

The overall aim of the Obesity Genetics Research group is to investigate rare genetic disorders of obesity and to find the best treatment options for patients suffering from these disorders. Obesity is one of the biggest health problems of our time, because of its high prevalence, morbidity, and mortality. In specific patient groups, genetic obesity disorders can be identified as the main cause of their obesity. Their extreme weight gain is often caused by a severe lack of satiety. Genetic testing in obesity is extremely important to understand the disease, for the development of personalized treatment, and to reduce obesity stigma. After all, obesity is not simply the result of 'eating too much and moving too little'.

In 2008, Mieke van Haelst designed and implemented a custom-made diagnostic obesity gene panel in daily medical care in the Netherlands. Ever since then, many diagnoses have been established and provide a first step towards personalized treatment for affected patients. To achieve this, international collaborations have been initiated, studying the complete field of obesity treatment; from pharmacological therapy and bariatric surge-

ry to psychological support in dealing with insatiable hunger. Clinical trials have already been initiated for rare genetic obesity disorders (setmelanotide for patients with homozygous or compound heterozygous LEPR mutations). The obesity genetics research group aims to further explore new (obesity) genes that could also interact the leptin melanocortin pathway genes so that affected patients could opt for such personalized medicine treatments as well.

The importance of obesity genetics research has become clear to other researchers as well. This year, Lotte Kleinendorst received the Publication Prize for “best obesity related publication” from the Netherlands Association for the Study of Obesity. The prize was awarded for the article “Genetic obesity: next-generation sequencing results of 1230 patients with obesity” in *the Journal of Medical Genetics*. This article shows that is important to prevent a diagnostic odyssey for obesity patients and to know which patients with obesity should receive genetic testing. We

“Obesity is not simply the result of ‘eating to much and moving too little’”

found that the highest diagnostic yield can be achieved in children with a very early-onset of obesity, whereas the diagnostic yield in bariatric surgery subgroups is relatively low.

Moreover, Lotte Kleinendorst received the AR&D Travel Grant and the KNAW Ter Meulen grant to study obesity and obesity genetics in Aruba in 2018. She is now in her last year of her PhD project and aims to start her specialization in clinical genetics. She hopes to continue her obesity genetics research after her thesis defence, since there is still a long way to go to personalized treatment for rare genetic obesity disorders. ●



Organization

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Prof. Dr. Sjoerd
Repping (until
December 2018)



MARTIJN FINKEN
(SINCE APRIL 2019)
Paediatrics



**CALLISTA
MULDER**



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OFFICE**

Research Highlights

○○○ AR&D IN NUMBERS

TOTAL
RESEARCHERS

2017:
505
2018:
467

PHD
STUDENTS

2017:
201
2018:
208

GRANTED
PROJECTS TO AR&D
RESEARCHERS:

START 2017:
€ 11.082.737,-

START 2018:
€ 7.641.874,-

DISCLAIMER RESEARCH INFORMATION

RESEARCH INPUT

Information about researchers is gathered at Amsterdam UMC, location VUMC, from relevant departments (both location AMC and VUMC) 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. 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 organisations, and (4) other funds that do not fit into the other categories. Information about funded research projects has been provided by the

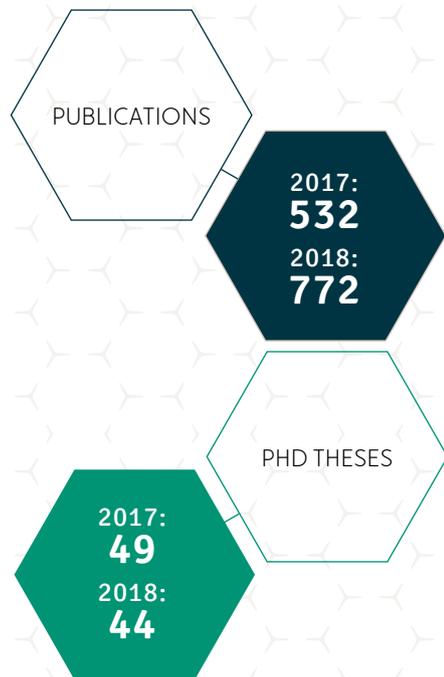
separate project administrations from location AMC and location VUMC.

RESEARCH OUTPUT

Research output at 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 organisational units based on the affiliations of the (co-)supervisors. A thesis can be ascribed to one or more organisational 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 organisational units based on the affiliations of the authors. A publication can be ascribed to one or more organisational 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 and journal impact factor quartile score of research institutes.

Grants and prizes

○○○ OBTAINED GRANTS

In 2018, AR&D researchers were very active in obtaining grants and prizes. Here are some highlights of the grants and prizes awarded to AR&D researchers.

PERSONALISED PROGNOSIS OF TRAUMATIC BRAIN INJURY IN CHILDREN (PEPR STUDY)

Project leader
Jaap Oosterlaan

Granted by
Janivo stichting and Cornelia Stichting
€65.000

DEVELOPMENT OF NATIONAL GUIDELINE 'PREVENTION OF PRETERM BIRTH'

Project leader
Martijn Oudijk

Granted by
Stichting Kwaliteitsgelden
Medisch Specialisten (SKMS)
€ 177.513

DEVELOPMENT AND VALIDATION OF AN EPIGENETIC BIOMARKER THAT PREDICTS TREATMENT SUCCESS AND ALLOWS PERSONALIZED MANAGEMENT IN CROHN'S DISEASE: EPIC-CD".

Project leader
Peter Henneman

Granted by
The Leona M. and Harry S. Helmsley
charitable trust
€800.000

COBRA SURGERY PRICE

Granted by
"Congres voor gynaecologische chirurgie"

Awarded to
Judith Huirne

GRANTS AWARDED BY AR&D

OUT-OF-THE-BOX GRANTS (€60.000 each)

Awarded to
Marie van Dijk for the project:
"Exploration of a novel minimal-invasive prenatal diagnostic technique".

Bernadette de Bakker for the project:
"High Resolution 3D Imaging of Foetal Anatomy".

Thijs van Mens for the project:
"Obstetric antiphospholipid syndrome: the etiological role and therapeutic potential of the gut microbiome".

TRAVEL GRANTS (€1000 each)

Awarded to
Laura Bleker
to go to the International Marcé Society Biennial Scientific Meeting 2018 in Bangalore, India.

Lotte Kleinendorst
for her work visit to the Dr. Horacio E. Oduber Hospitaal (HOH), Pediatrics, Oranjestad, Aruba.

Anna van der Miesen
to visit the World Professional Association for Transgender Health (WAPTH) conference, Buenos Aires, Argentina.

Antoinette van Ouwerkerk
for her visit to the EMBL Transcription and Chromatin congress, Heidelberg, Germany

Joyce Man
to go to the Cardiovascular Development Meeting 2018, Marseille, France.

AR&D Symposium

5 JULY 2018

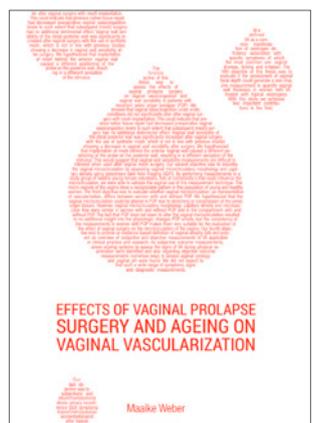
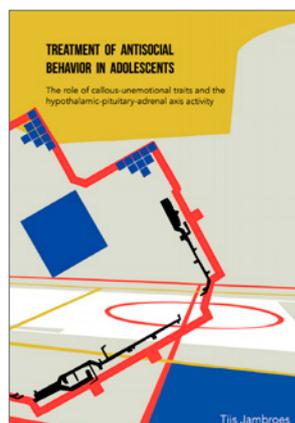
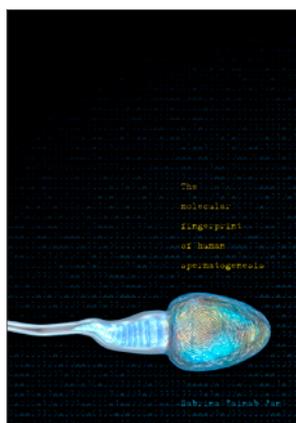
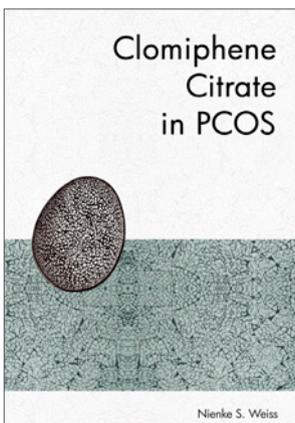
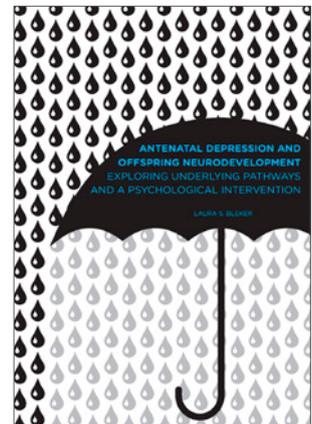
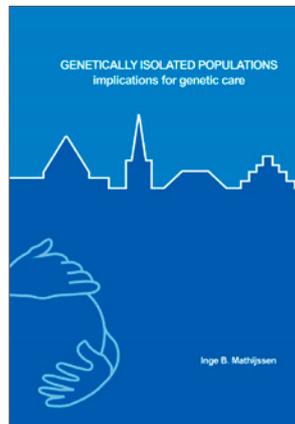
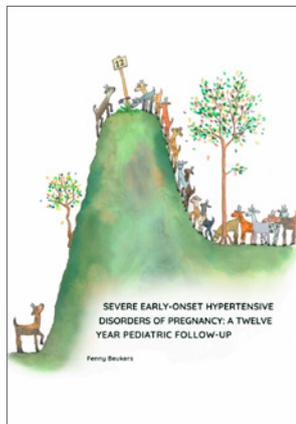
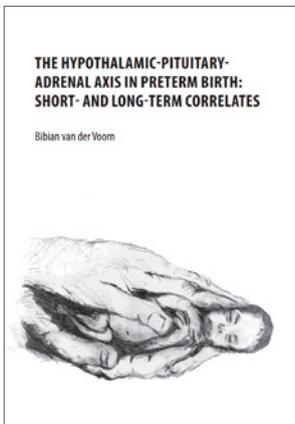
The AR&D symposium took place on the 5th of July in the hip and happening Volkshotel Amsterdam.

After passing the indoor caravan, 80 participants enjoyed a lovely lunch, good company and of course inspiring talks of among others Prof. Dr Marianne Rots (UMCG) on epigenetic editing and Prof. Dr. Arnoud Verhoeff (UvA) on the new Sarp-hati research institute. AR&D researchers Ivy van Dijke, Hel- een Schuster, Marie van Dijk and Tamara den Harink revealed their impressive work, and the travel grants winners were announced. Last but not least, we said goodbye to AR&D colleague Sanneke van Vliet, but not before thanking her for all the work she has done for AR&D and letting her step into the limelight to tell about her next step in her career.



○○○ PHD THESES

In 2018, 44 researchers obtained their PhD in the area of
Reproduction & Development. Here below a cross section of the PhD theses.



○○○ KEY PUBLICATIONS

2018 was a very productive year. Here is an overview of peer-reviewed publications that were highlights for our researchers.



- **WEN ET AL.**
Effect of high dose folic acid supplementation in pregnancy on pre-eclampsia (FACT): double blind, phase III, randomised controlled, international, multicentre trial.
BMJ
- **VAN DER VOORN ET AL.**
Maternal stress during pregnancy is associated with decreased cortisol and cortisone levels in neonatal hair.
Horm Res Paediatr.
- **BEUKERS ET AL.**
Maternal psychological distress after severe pregnancy hypertension was associated with increased child behavioural problems at the age of 12.
Acta Paediatr.
- **VAN DIJKE ET AL.**
The ethics of clinical applications of germline genome modification: a systematic review of reasons.
Hum Reproduction
- **VAN BRUGGEN ET AL.**
Women's decision making regarding prenatal screening for foetal aneuploidy: A qualitative comparison between 2003 and 2016.
Midwifery
- **BERKHOUT ET AL.**
High-quality human preimplantation embryos actively influence endometrial stromal cell migration.
J Assist Reprod Genet.
- **KREUKELS ET AL.**
Gender dysphoria and gender change in disorders of sex development/ intersex conditions: results from the dsd-LIFE Study.
Journal of Sexual Medicine
- **PELS ET AL.**
Detailed statistical analysis plan for the Dutch STRIDER (Sildenafil TheRapy In Dismal prognosis Early-onset fetal growth Restriction) randomised clinical trial on sildenafil versus placebo for pregnant women with severe early onset foetal growth restriction.
Trials
- **BARTELS ET AL.**
Childhood aggression and the co-occurrence of behavioural and emotional problems: results across ages 3-16 years from multiple raters in six cohorts in the EU-ACTION project.
Eur Child Adolesc Psychiatry.
- **ELIVELD ET AL.**
The risk of TESE-induced hypogonadism: A systematic review and meta-analysis. Human Reproduction Update

BOOK PUBLICATION “DE EERSTE 1000 DAGEN”



Also, in 2018 AR&D professor Tessa Roseboom published her book “De eerste 1000 dagen”. The message of this popular scientific book is how important a good start in life is. The book describes the influence of the environment on us during the first 1000 days of human life (from conception to our second birthday) and how these influences can affect us throughout the rest of our lives.



Meet the professor



In 2018 3 professors were appointed at AR&D.

ANS VAN PELT

Prof. Dr. Ans Van Pelt is a stem cell biologist and head of the AMC's Laboratory for Reproductive Laboratory, at the Centre for Reproductive Medicine, location AMC. Ans van Pelt's research focuses on male fertility. She conducts preclinical research in innovative therapies and technologies with the aim to

treat infertility in men. Her research focuses mainly on men with no sperm or a reduced sperm count. In the latter case, the production of sperm cells appears to have stopped in the testes, but the testes still contain the precursors stem cells. Using these human testicular stem cell, van Pelt aims to develop these cells into mature sperm or propagate

them in vitro for transplantation therapy purposes.

One of the main research lines is on fertility preservation for young boys with childhood cancer, in which a testicular biopsy is cryop-

“Ik heb gezegd.”

reserved for potential use in future clinical transplantation therapy to treat infertility in adulthood. With respect to education, Van Pelt teaches medical and medical biology students on laboratory skills and the biological background of potential future clinical reproductive therapies, and also addresses their academic development in general and more specifically on translational research within reproductive medicine.

LEONTIEN KREMER

Prof. Dr. Leontien Kremer is a paediatrician and principle investigator at the Department of Paediatrics at the Amsterdam UMC (location AMC) and at the Prinses Maxima Centre for paediatric oncology. Her work is focussed on epidemiological studies in paediatrics and survivorship of childhood cancer and on evidence based medicine tools to improve care for children such as guidelines. In her inaugural lecture she had a clear message on how to safeguard optimal paediatric clinical practice: by working in networks. The care for these children is complex and therefore intense crosstalk is required between the parents, children, nurses, paediatricians in different hospitals to provide the best care possible. The aim of her future projects is to ultimately facilitate and improve decision-making between care providers and [parents of] sick children.

KATIA BILARDO

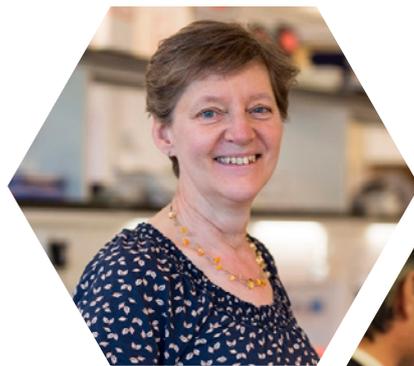
Prof. Dr. Katia Bilardo is a fetal medicine expert internationally-renowned. She worked in the eighties at King's College Hospital in London, with as mentors prof. Stuart Campbell and Prof. Kypros Nicolaides,

who are considered the fathers of obstetrical ultrasound and fetal medicine respectively.

After her relocation to the Netherlands her name has been associated with the development and implementation of early screening for chromosomal and structural anomalies. After working for 18 years at the AMC, she was appointed as professor in fetal medicine in 2011 in Groningen. Since October 2017 she is back at the Amsterdam UMC, location VUMC, where she is head of the department of prenatal diagnosis and fetal medicine. Her research interests include all aspects of screening for congenital anomalies and [early] diagnosis of all congenital defects and diagnostic invasive procedures. In her 30 years' experience she has supervised many PhD students. As chair of the education committee of

the International Society of Ultrasound in Obstetrics (ISUOG), her mission is to disseminate high level education worldwide. By increasing the number of skilled doctors and sonographers in this field, ISUOG aims to improve the health outcomes of women, mothers and their children.

In her recent inaugural lecture at the Amsterdam UMC, Katia Bilardo advocated the inclusion of a 13-week ultrasound examination in the screening offered to all pregnant women. This will enhance early diagnosis of severe structural and genetic disorders offering women the chance of an informed and timely decision on the future of the pregnancy, as opposed to the currently standard 20-week ultrasound. ●



Ans van Pelt



Leontien Kremer



Katia Bilardo



**“The ambition
of AR&D is to
enhance the field
of reproduction
and development
nationwide, and
to sustainably
improve health
care for mother
and child
and future
generations.”**

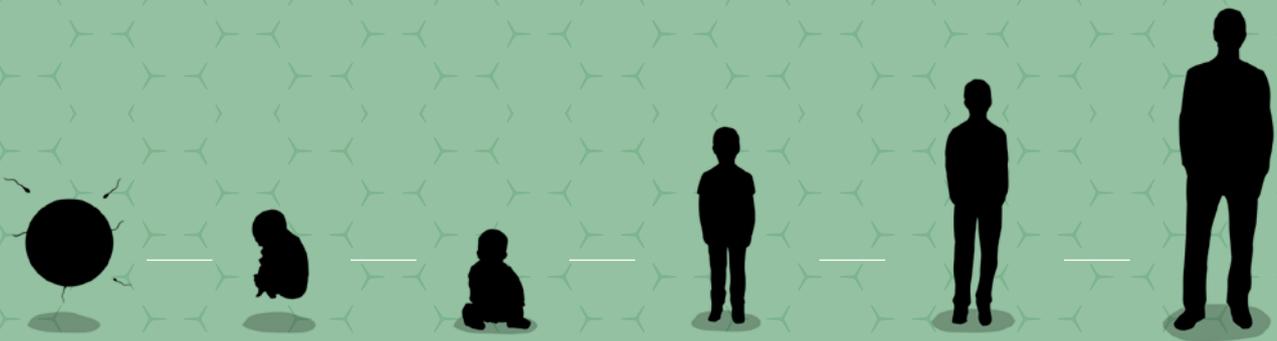
EXPERTISE

DISCIPLINES

INNOVATIVE RESEARCH

INCREASE IN
SCIENTIFIC
OUTPUT AND THE
ACQUISITION OF
NATIONAL AND
INTERNATIONAL
FUNDS FOR
RESEARCH

AR&D WANTS TO BE
AN INTERNATIONAL
KNOWLEDGE HUB



“Unique about the research institute Amsterdam Reproduction & Development is that we pay attention to reproduction and development in its totality: the stage before pregnancy, conception, pregnancy, childbirth, the child as it’s growing up, and the resulting health of the adult stages of life”