Regenerative Medicine Utrecht

Crossing frontiers at Utrecht Life Sciences

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Foreword

Regenerative Medicine in Utrecht represents the journey from the lab bench to patient therapy. It holds much promise for customized therapies, which are based on an individual's unique genetic blueprint. In order to harness this potential of finding the right treatment for individual human and animal patients, we've initiated a program, called Regenerative Medicine Utrecht (RMU), to converge our strengths in this field: (1) fundamental science, especially stem cell and developmental biology; (2) new technologies, such as bioprinting and innovative imaging techniques; and (3) clinical application, in the form of new treatment modalities, novel drugs and alternative approaches.

The unique mixture of scientists and clinicians (human and veterinary) in Utrecht will bring about new ways of thinking and produce unique approaches to the field of regenerative medicine.

There are several initiatives and institutes with an RM focus in the Utrecht area, and all are developing synergistically with the aim of rapidly advancing this field: the strategic program of the UMC Utrecht, Regenerative Medicine & Stem Cells (RMSC); the RM research program of the Faculty of Veterinary Medicine, Utrecht University; the Hubrecht Institute for Developmental and Stem Cell Biology; and Utrecht Life Sciences, an open innovation network with RM & Stem Cells as one of its focal points. Their interactions are well-illustrated through scientific collaboration, education, and medical advances. Together, these form a strong platform to address unmet patient needs and to bring healthcare solutions to patients as quickly as possible.

We hope this book provides you with an inspiring overview of Regenerative Medicine in Utrecht.

Wouter Dhert and Paul Coffer
Co-Chairs, Regenerative Medicine Utrecht

Welcome

Regenerative medicine: from science to society
Regenerative medicine is a dynamic and rapidly advancing life sciences field in which a variety of biomedical research areas and clinical care converge. It aims to develop novel therapies to restore or regenerate living tissues in response to tissue degeneration, ageing, trauma and cancer.

"Regenerative medicine addresses the ability to regenerate organs and tissues instead of treating symptoms or replacing tissues or organs," says Wouter Dhert, Chair of the Regenerative Medicine & Stem Cells (RMSC) program at the UMC Utrecht. "Doctors replace a patient's hip, in the case of osteoarthritis; carry out a kidney transplantation; or implant an artificial heart valve - but that's all repair or replacement – and doesn't restore the original patient's own tissue. Regenerative medicine is about bringing back tissue in its original, healthy state. Stem cells, new materials and growth factors, present potential means of restoring instead of replacing organs and tissues."

Stem cells: body's own healing power
Regenerative medicine has the potential to quickly bring fundamental research directly to patient treatment. "Bench-to-bedside has been a buzzword for some time, but regenerative medicine truly applies this principle," says Paul Coffer, Co-Chair of the RMSC program. It focuses on using the body's own building blocks, such as stem cells, which are capable of regenerating damaged tissues. It is hoped that a wide variety of (degenerative) diseases can be treated either by directly applying stem cells to a patient, as has been used for decades in bone marrow transplantation, or by stimulating the body's own stem cells into action. "Regenerative medicine," explains Coffer, "is important in trying to utilize the body's own healing power as a therapy for previously difficult or impossible-to-treat diseases."

Mission

To inspire innovation and integration of biomedical research, technology and clinical care.

Regenerative Medicine Utrecht (RMU) is an internationally leading center for regenerative medicine and stem cell research. Our goals are (1) to develop novel regenerative/stem cell treatments for patients; (2) to conduct high-quality biomedical research that attracts talent; and (3) to provide state-of-the-art education & training for future biomedical professionals.

Vision

To build a world-class center for innovation in regenerative medicine with a focus on patients and society.

Regenerative Medicine in Utrecht facilitates the convergence of biomedical research, novel technologies and clinical care. We aim to develop novel therapies to restore or regenerate living tissues that are damaged or lost because of degeneration, ageing, trauma or cancer. Our approach is multi-disciplinary, and we create momentum and coherence among our stakeholders – *innovation happens together.*

Establishing Regenerative Medicine in Utrecht

In 2006, a coherent program in regenerative medicine was initiated in Utrecht, with an aim to harness the potential of this large, multidisciplinary field. The program is headed by Wouter Dhert (Chair), Professor of Regenerative Medicine and Director of Orthopedic Research, UMC Utrecht, and Paul Coffer (Co-Chair), Professor of Stem Cell Biology at the UMC Utrecht. "We're becoming a recognized and internationally leading center for regenerative medicine and stem cell research with a strong focus on patients and society," says Dhert. "Our mission is three-fold: we're developing novel regenerative or stem cell treatments for patients; we perform high-quality biomedical research that attracts talented scientists; and we provide state-of-the art education for future biomedical professionals."

We recognize that successful translation of scientific research into clinical application requires interdisciplinary approaches, and in Utrecht, we're integrating the talents of cell biologists, biomaterials experts, scientists who have experience utilizing complex animal models and clinicians. "It's impossible to bring a new therapy to the patient alone," adds Coffer. "A focus in the area of regenerative medicine and stem cells helps bring diverse talents together, enabling rapid knowledge transfer and the development of novel therapeutic strategies".

Growth and expansion of the program

The nature of this field requires the formation of new entities from individual disciplines - medicine, (molecular) biology, genomics, chemistry, ethics, engineering, technology, imaging. "All clinical divisions at the UMC Utrecht participate in this program, covering many medical professions and biomedical science disciplines," describes Dhert. "The Hubrecht Institute for Developmental Biology and Stem Cell Research and the Faculty of Veterinary Medicine are also strongly involved. Before 2006, we were less well connected, but now we collaborate with many national and international partners."

In a relatively short time span, we've built a program with high earning capacity, excellent scientific output, national and international visibility, and a campus-

Utrecht Science Park

wide educational platform on regenerative medicine with different courses/ programs at various levels. In addition, the UMC Utrecht houses the only GMP-accredited cell therapy facility within an academic center in the Netherlands; and the only Faculty of Veterinary Medicine in the Netherlands is in Utrecht. In addition, we're also a global leader in the development of novel technologies such as 3D bioprinting and unique imaging and animal models. "We've introduced several new regenerative therapies into the clinic and for the European health-care market such as cell-based therapies for cartilage defects in the knee and stem cell-based therapies in pediatrics," explains Dhert.

Our potential

By aiming to restore tissues and organs, regenerative medicine in a sense, tries to mimic Mother Nature. A rather ambitious endeavour, Dhert admits. "People are made of a few cells that proliferated into a whole human being. We aim to understand this extremely complicated developmental process. We make bone or cartilage out of stem cells, for instance, and try to regenerate the original tissue, but regenerating organs and tissues is extremely complex."

Coffer also emphasizes that many questions still remain unanswered. "Since regenerative medicine is a relatively young field of Life Sciences and has so many diverse aspects, education is critical," explains Coffer. "It's important that scientists and clinicians understand each other and can communicate well. A good education program helps facilitate this and is vital in training the next generation of regenerative medicine researchers."

The campus infrastructure is excellent and will be further strengthened with the new investments of Utrecht University and by the building of the Utrecht Regenerative Medicine Center with funding from the UMC Utrecht. This will also include the new Utrecht Biofabrication Facility with dedicated funding from Utrecht University. The rapid growth and success of the program builds upon the energy and enthusiasm of a relatively young group of Principle Investigators, prepared to contribute to scientific and educational innovation. "The topic of regenerative medicine is now integrated into all three life sciences faculties – UMC Utrecht, Veterinary Medicine, and Science," Dhert proudly concludes. "We also have strategic alliances with the technological universities in Eindhoven and Twente. This all gives the program a strong position to for future growth."

Wouter Dhert and Paul Coffer, Co-Chairs, Regenerative Medicine Utrecht

Who We Are

Regenerative Medicine in Utrecht comprises a variety of investigators, working in different disciplines and on different topics. One unique aspect is the interaction between basic scientists and clinicians (both human and veterinary) on a daily basis, which forms effective channels of communication and collaboration. RMU consists of more than 60 principal investigators and their labs. Our range of disciplines and knowledge illustrates the diversity of our expertise, not only in the basic sciences, but also in technology development and clinical care.

Leadership
RMU is headed by a board consisting of members who represent the three central themes, as well as the primary institutes involved. The board meets every 4-6 weeks and liaises with the rest of the program members and with other scientific and educational programs in the area.

Prof. Wouter Dhert, MD, PhD Chair	UMC Utrecht Utrecht University	Musculoskeletal RM Theme
Prof. Paul Coffer, PhD Co-Chair	UMC Utrecht	Stem Cell-Based Therapies Theme
Prof. Pieter Doevendans, MD, PhD	UMC Utrecht	Cardiovascular RM Theme
Prof. Niels Geijsen, PhD	Hubrecht Institute Utrecht University	Stem Cell-Based Therapies Theme
Prof. Marianne Verhaar, MD, PhD	UMC Utrecht	Cardiovascular RM Theme
Sarah Opitz Program Manager	UMC Utrecht	

Where are we located?
We're embedded within the Utrecht Science Park in the center of the Netherlands, which connects us closely with the overall profile of this location, 'Public Health, Cancer, Regenerative Medicine & Stem cells and Healthcare Innovation' (see www.utrechtlifesciences.nl). Here, we have access to high-tech shared facilities, for example advanced microscopy; RNA/DNA analysis; proteomics & metabolomics; bioinformatics & computing; high-throughput screening; and the Utrecht Biofabrication Facility.

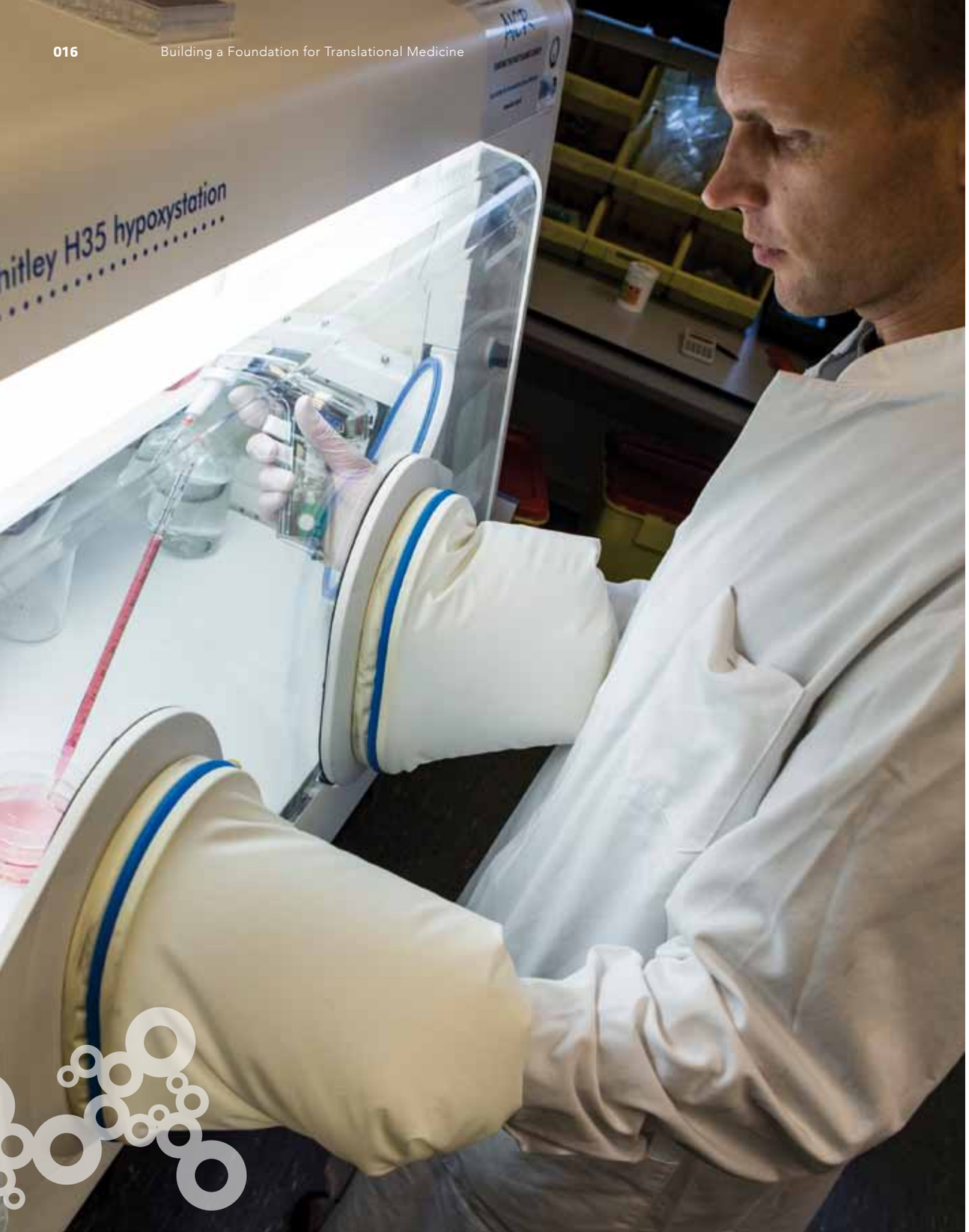
RMU consists of three primary institutes

1. University Medical Center Utrecht (UMC Utrecht, an academic hospital). All divisions are active in this field: Biomedical Genetics; Brain; Heart and Lung; Julius Center (medical and research ethics); Imaging; Internal Medicine and Dermatology; Laboratory and Pharmacy; Pediatrics; Surgical Specialties; Women & Baby.
2. Hubrecht Institute for Developmental Biology and Stem Cell Research (a research institute of the Royal Netherlands Academy of Arts and Sciences, KNAW).
3. Utrecht University: Faculty of Veterinary Medicine and Faculty of Science

One unique aspect is the integration of the Faculty of Veterinary Medicine, Utrecht University. This is the only veterinary faculty in the Netherlands and is ranked in the top 5 of veterinary institutes in the world. Close interaction, through joint projects and shared professorships, broadens our resources and affords RMU a wide variety of large animal patients, such as dog, horse and pig.

Both the UMC Utrecht and the animal clinic at the Faculty of Veterinary Medicine, provide researchers direct access to patient populations. More importantly, it ensures that our researchers continuously consider patient needs and how best to contribute positively to society.

We're expanding our boundaries and have established new exciting partnerships, for example, with Eindhoven University of Technology (TU/e) and University of Twente. We've created joint positions for scientists and are combining our strengths in biomedical and technological sciences. More recently, a joint effort between RMU, universities in Australia and Germany has resulted in the first formal biofabrication educational programs (PhD and summer school) worldwide, and investment in the Utrecht Additive Biofabrication Facility.



Building a Foundation for Translational Medicine

At the core of all patient treatment is fundamental science. Scientists contribute to our understanding of stem cell biology, normal developmental processes, and molecular pathways that govern disease progression. Their findings serve as a guide for how best to approach translating science into medicine.

Alain de Bruin, PhD - *Professor of Pathobiology*
Faculty of Veterinary Medicine
Utrecht University

Unraveling control mechanisms of cell proliferation
"We try to understand the molecular mechanisms controlling cell division cycles. For tissue regeneration, new cells are required after tissue injury or loss. New cells are reproduced by a sequence of events in which the DNA is first duplicated and then divided. This cycle of duplication and division, known as the cell cycle, is regulated by countless regulatory mechanisms that can speed up or slow down cell proliferation. These control mechanism are often misregulated in geriatric patients.

When people get older, organs take much longer to regenerate. Cell cycles become less efficient, there are fewer cell divisions and cells regenerate slower. Ageing also reduces the number of stem cells and thereby impairs regeneration. Moreover, mutations of cell cycle genes can also lead to increased cell proliferation and thereby promote cancer formation. Our research efforts are focused to identify regulatory proteins of the cell cycle that can improve tissue regeneration or suppress tumor formation.

We use transgenic mouse and zebrafish models to determine the role of cell cycle proteins during tissue regeneration and cancer. We generate animal models where the expression of cell cycle proteins is altered in particular organs.

BM bone marrow **CLEM** correlative light electron microscopy **CLI** critical limb ischemia **EPCs** endothelial progenitor cells **ESCs** embryonic stem cells **HSCs** hematopoietic stem cells **HSCT** hematopoietic stem cell transplant **iPSCs** induced pluripotent stem cells **MSCs** mesenchymal stem cells **RM** regenerative medicine

We then evaluate whether this influences the morphology and function of different tissues by microscopic and molecular analysis. These analyses are performed in our newly established Dutch Molecular Pathology Center (DMPC) at the Faculty of Veterinary Medicine in Utrecht. This unique worldwide collaboration research center specializes in the analysis of genetically modified animals.

By studying animal pathology, we hope to unravel the molecular mechanisms behind (dis)regulation of cell growth and division. This fundamental knowledge can help to develop new therapies. In the upcoming years, we expect to extend life expectancy and quality of life by suppressing cancer formation, and improving tissue regeneration in elderly patients."

Jacqueline Deschamps, PhD - *Group Leader*
Hubrecht Institute

Understanding embryonic development
My lab is working on unraveling the regulation of embryonic axial stem cells and their niche during mouse development. In particular, we focus on Hox and ParaHox genes encoding transcription factors, and the signaling pathways that they regulate, Wnt, Fgf and retinoic acid. Our studies have relied on characterization of loss and gain of function mutants, on genetic rescue experiments and on embryo grafting techniques. Currently, we have initiated two new approaches in our investigations: a genome-wide screening of DNA binding sites of the key transcription factors steering axial growth, and cell lineage analysis by live imaging to track the behavior of stem cells and their descendants in the posterior growth zone of early wild type and mutant mouse embryos. We also work on the role of specific developmental transcription factors in the specification of the identity of adult stem cells of the mouse intestine.

Arjan Brenkman, PhD - *Associate Professor*
Metabolic Disease & Netherlands Metabolomics Centre
UMC Utrecht

Physiology of cells
Metabolic processes are sequences of biochemical reactions that take place in our bodies to maintain life. Metabolomics focuses on understanding the many small molecules that result from these processes. There are are several thousand human metabolites, and together, they create a fingerprint of the chemical processes within our cells. This not only gives us an instantaneous picture of cell function at a given moment, but can also take into account the influence of post-transcriptional and translational protein regulation and environmental conditions. Metabolomics can help us understand relationships between genotype (genetics) and phenotype (what we look like). We can also use metabolomics to study the physiological effects of drugs and other therapies. By validating our findings, for example, in well-characterized cancer models, we can directly integrate and translate our chemistry into biology.

Fulvio Reggiori, PhD - *Assistant Professor*
Cell Biology
UMC Utrecht

Maintaining equilibrium
Autophagy is a mechanism by which cells break down molecules. In particular, it contributes to both maintaining the cell energy balance and preventing cellular damage - these two functions are also key for stem cell physiology. Autophagy also plays a major role in development and tissue reorganization, principles also intricate to the field of regenerative medicine. In addition, we're developing new investigative technologies, especially in the field of electron microscopy. In this context, we use various viruses as a biological tool to investigate autophagy. The goal of my laboratory is to understand the molecular mechanism and regulation of autophagy in order to be able to modulate this pathway for the benefit of human health.

Madelon Maurice, PhD - *Associate Professor*
Cell Biology
UMC Utrecht

Zooming in on Wnt proteins
"We aim to understand how cells communicate in the human body. Cells commonly send and deliver their messages via secreted proteins. The underlying mechanisms by which cells interpret these messages fascinate us. We study one particular group of proteins, called Wnt proteins. These signaling proteins dictate the shape and growth of the different tissues during embryonic development. Wnt proteins also control the maintenance of adult tissues, particularly in self-renewing tissues such as skin, breast and intestine.

A critical role of Wnt proteins is to maintain the population of tissue stem cells in optimal condition, which places them center stage for the area of tissue regeneration. Many human diseases – most notably cancer – are linked to defects in Wnt signaling. Cancer cells typically misuse the instructive Wnt signals, leading to unrestrained growth and tumor formation. Due to acquired mutations, cancer cells simply fail to communicate properly and become indifferent to instructions from the surrounding tissue.

In my research group at the Department of Cell Biology, we focus on two central questions: how do cells receive orders at the cell surface and process the message to bring about a cellular response? And how do mutations derail these signaling systems in cancer? We study how the biochemical signal is transferred into the cell nucleus, which is a highly regulated process. We aim to understand how the Wnt protein receptors become activated at the cell surface and how they relay signals into the interior of the cell. Understanding the molecular mechanisms will allow us to design strategies to modulate these proteins' activities. This could be helpful in the development of regenerative therapies or cancer treatments. A lot of questions remain to be answered! It is exciting to discover a novel molecular role or activity. This is why I love this research."

Peter Luijten, PhD - *Professor of Functional Medical Imaging*
Image Sciences Institute
UMC Utrecht

New MRI imaging techniques
My research focuses on the development of new (MRI based) imaging methods based on endogenous contrast mechanisms for the non-invasive assessment of in vivo tissue and cell proliferation. In the near future, we're interested in generating fast imaging methodology to monitor changes in tissue morphology and composition over time to assess the effects of regenerative medicine in human subjects.

Judith Klumperman, PhD - *Professor of Cell Biology*
Cell Biology
UMC Utrecht

Novel electron microscopy methods
My research aims to understand how genetic mutations lead to cellular disorganization and disease, with special emphasis on cancer and diseases related to the cellular digestive system, the endo-lysosomes. In addition, we're developing (electron) microscopy methods, including immune-electron microscopy, tomography, and correlative microscopy. Specifically, we are interested in correlative light electron microscopy (CLEM), which combines light and electron microscopy: we can image in vivo dynamics at ultrastructure resolution within a cell at a given moment. We are developing CLEM techniques in order to further understand cellular changes during stem cell development and to follow the routes of (cancer) stem cell in healthy and pathogenic conditions.

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Anton Martens, PhD
Cell Biology
UMC Utrecht

Humanized mouse model help study cancer

"When I was 20 years old, my cousin developed a specific kind of leukemia. She died within 9 months. Sadly enough, her leukemia is now one of the most curable types. Ever since, I've been interested in blood stem cells and leukemia. When I started working in the 1970s at the Radiobiological Institute TNO in Rijswijk, studying normal and leukemic stem cells for my PhD, I had the luck to enter the right environment. Later, during my research on bone forming stem cells in regenerative medicine research, I had this clever idea of using a mouse model to study bone-dependent tumors such as Kahler's disease (multiple myeloma), an incurable cancer of plasma cells that affects around 750 new patients in The Netherlands each year.

Together with my colleague, Richard Groen, we developed a novel humanized mouse model to study clinical tumors in a human environment in mice. We take cells from myeloma or leukemia patients, isolate and inject these cells in scaffolds that are placed under the skin of mice. In these scaffolds we first created a human bone marrow-like structure and surprisingly, tumor cells only grow in this human environment and not in mouse tissues. The tumors cells are marked with the firefly luciferase gene to detect the location and size of tumors, using imaging techniques. This enables us to follow the growth of tumors and measure the effect of different therapies and predict patient tumor responses.

Our mouse model attracts a lot of interest from other research groups and pharmaceutical companies. We collaborate with several Dutch, European and American Institutes and together we hope to find new drugs for specific tumors, so cancer will eventually become a chronic disease."

Stem Cell-Based Therapies

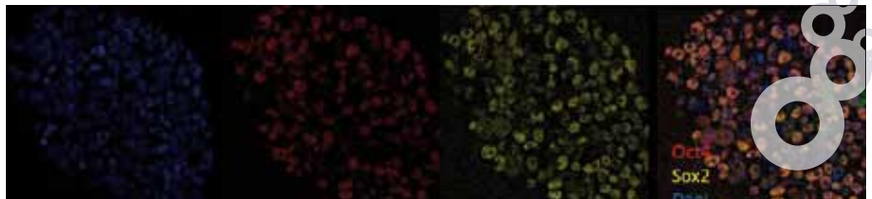
Stem cells play an important role in maintaining and renewing tissues. They have the potential to restore function after tissue has been damaged, thereby treating or even curing the cause of degenerative disease. “For degenerative diseases it is necessary to replace damaged tissues either by transplantation or by stimulating a patient’s stem cells to do the job themselves,” says Paul Coffer, Co-Chair of the Regenerative Medicine & Stem Cells program in Utrecht. “Until recently, our understanding of stem cell biology was insufficient to realize this goal, but this has changed over the past decade. Now, it’s truly becoming reality.”

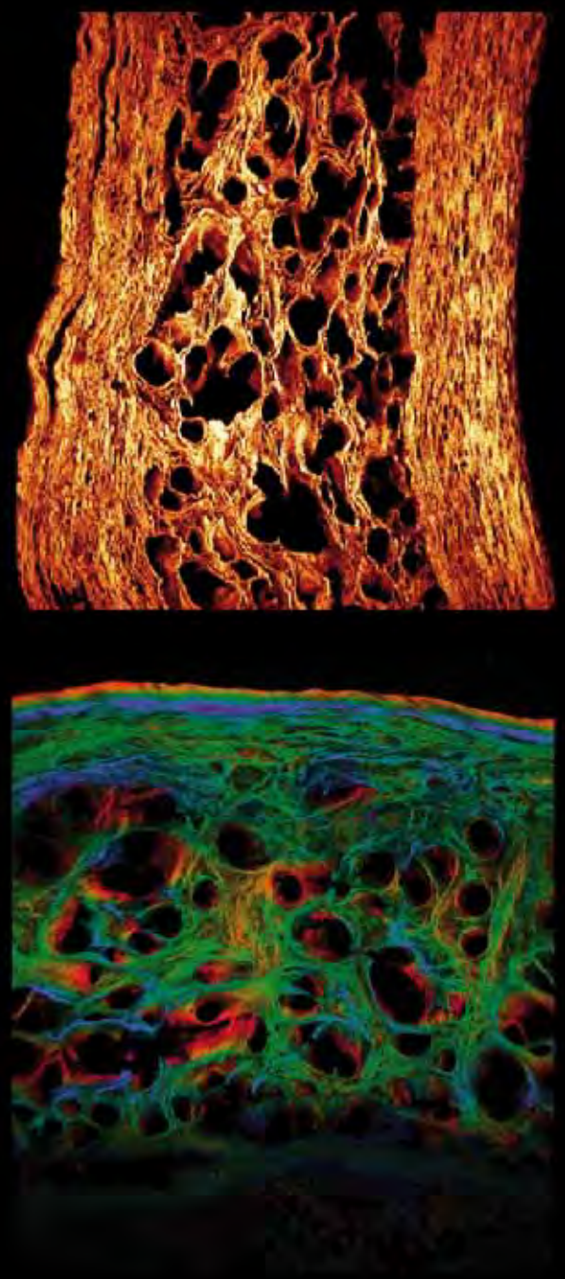
Paul Coffer, PhD - *Professor of Stem Cell Biology*
Cell Biology
UMC Utrecht

Stem cell therapy: possible cures for various diseases

The paradigm of successful stem cell therapy is bone marrow transplantation. For the last half century, patients with leukemia, immune deficiencies or metabolic diseases have been treated by transplantation with ‘matching’ donor bone marrow containing stem cells. “This approach has become a relatively routine therapy in many cases,” explains Coffer, “and has demonstrated how successful stem cell therapy can be. Reproducing these successes for other tissues, either by stem cell transplantation or by kicking a patient’s own stem cells into action, will have dramatic consequences for a wide variety of diseases.”

Pluripotent mouse ESCs. Image courtesy of Geijsen lab





Collagen staining/confocal image of a tissue engineered small caliber vessel. Image courtesy Kluin lab

Considerable promise

Regenerative Medicine has considerable promise. Although it sometimes suffers from the negative effects of hype, it has recently demonstrated its potential in a variety of therapeutic areas. "Our understanding of stem cell biology has increased dramatically over the past decade and this has significant implications for the development of regenerative medicine therapeutic approaches," Coffer continues, "One clear example is the ability to "reprogram" somatic cells to what are called induced pluripotent stem (iPS) cells. This Nobel Prize winning achievement has demonstrated that it's possible to routinely generate pluripotent stem cells from almost any adult tissue, and from any individual. Something that was unimaginable only 10 years ago."

These iPS cells have a wide variety of therapeutic applications – from developing personalized therapies and drug testing, to potential tissue regeneration and transplantation. "This is just one example of many, highlighting how recent advances in the field of stem cell biology will impact on patients in the future," adds Coffer, "With currently increasing international efforts in the various aspects of regenerative medicine, I'm sure that novel therapies, certainly for degenerative diseases, will become available in the next decade."

Novel treatment strategies

Research is a constant learning experience; trying to solve the next piece of the puzzle. "For me personally, the fascination has always been with molecular and cell biology; trying to understand how a specific type of cell does its job, and how the components of each cell work together to this end. More specifically, my interest is focused on how the extracellular environment can modify a cell's function, primarily through regulation of its molecular machinery. In the case of stem cells, this information will hopefully lead to insights that can be applied to the use of such cells in novel treatment strategies. Without a good, fundamental understanding of stem cell biology it will not be possible to fully harness their potential in clinical applications."

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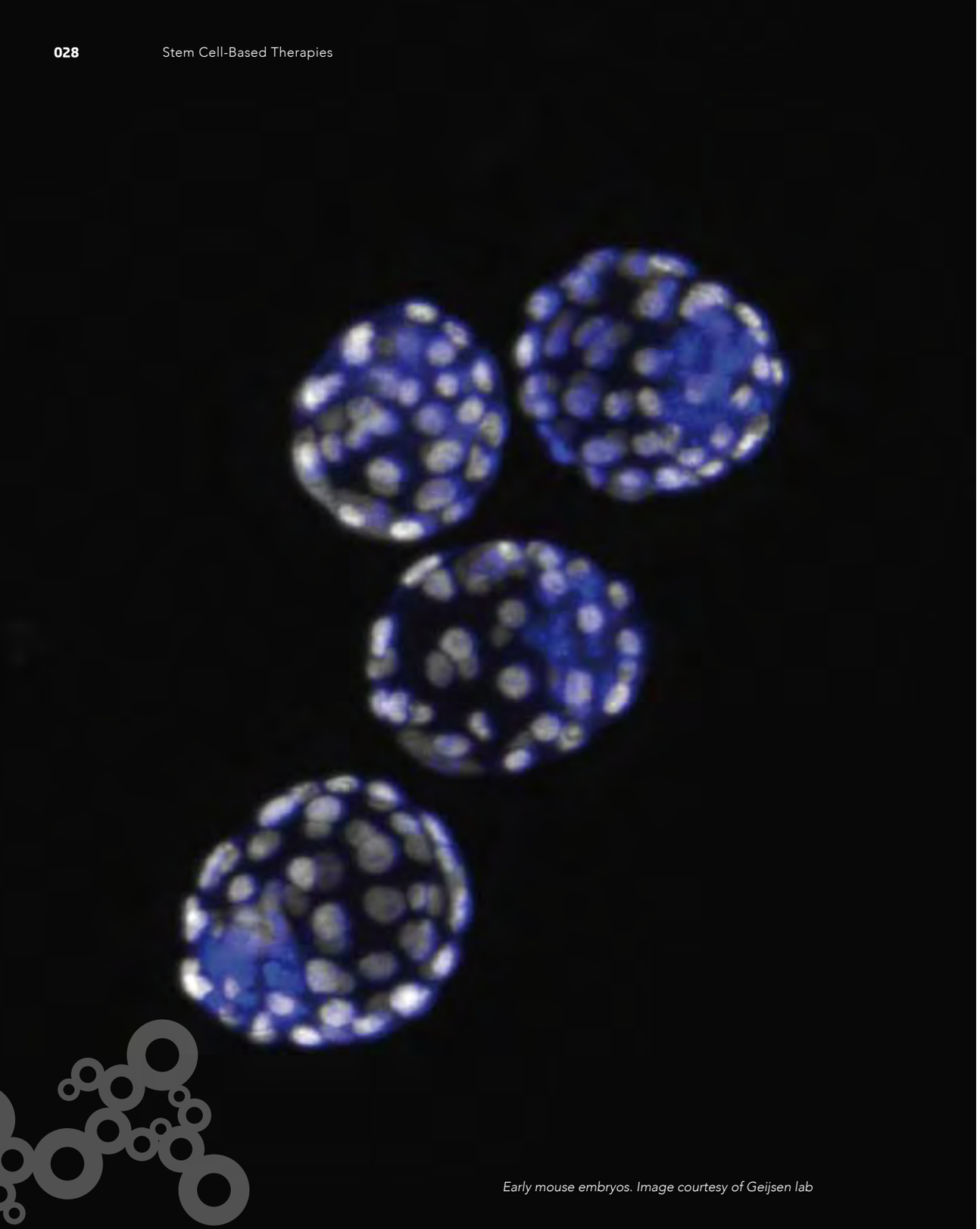


Early mouse embryos. Image courtesy of Geijsen lab

Niels Geijsen, PhD - *Professor of Regenerative Medicine*
Hubrecht Institute
Faculty of Veterinary Medicine, Utrecht University

Using stem cell technology to study genetic disease

"Studying the cause of human disease is not always easy, as some human cells are difficult to obtain or available in very limited quantity. My lab studies a special type of stem cells, called pluripotent stem cells. These stem cells have the unique ability to give rise to every cell type in our body, for example, skin, nerve cells, or liver. This makes them extremely useful for medical research. These cells do not exist naturally in the adult human body, but are made in the lab from simple skin cells. We can make these cells "forget" their skin identity and turn them into stem cells that can then generate virtually every cell in our body. This cell "reprogramming" is an ingenious biochemical process that enables us to make stem cells from patients and study their diseases in a petridish.

My group is using stem cells to study genetic disorders that currently have no cure. It's a real challenge to 'fix' genetic errors in human cells. We're developing a technological toolbox, creating new methods for the repair of disease-causing gene mutations. Applicability, efficiency and safety are important focus point of the research process. Our hope and goal is to develop our gene-editing technologies into practical applications for gene repair in the clinic.

Manda Arbab - *PhD candidate*
Hubrecht Institue
Faculty of Veterinary Medicine, Utrecht Unviersity

Unraveling spinal muscular atrophy

Manda Arbab is a PhD student in the Geijsen lab and works on a neural disease called Spinal Muscular Atrophy (SMA). "In SMA, the nerve cells that spur muscles to contract, called motor neurons, degenerate and die off. Infants with this disease become paralyzed, and most die before the age of two. In the past, it was difficult to study neural tissue of SMA patients but now, with induced pluripotent stem cell technology, we can. We use skin cells of patients with SMA and in the lab, turn these cells back into very early stem cells, a process called reprogramming. Basically, the cells 'forget' their skin cell identity and become a stem cell that has the ability to form any cell type in our body.

Next, we turn these stem cells into motor neurons to study what goes on in these cells. We've found a set of genes that are expressed differently in patients compared to healthy individuals, which indicates that they may contribute to the disease. Hopefully, we'll be able to find a target for drug development. Ever since my Master's internship, I find stem cells a fascinating subject to study. I like working at the Hubrecht Institute because it's filled with smart, collaborative people that do great innovative research."

Jeroen Pasterkamp, PhD - *Professor of Translational Neuroscience*
Brain Center Rudulf Magnus
UMC Utrecht

Understanding neuronal connections (in ALS and epilepsy)

The focus of my lab is directed towards understanding the signaling events and molecular mechanisms involved in the formation of neuronal connections during development; and also the molecular mechanisms underlying changes in or loss of neuronal connectivity during neurological disease. In particular, we study amyotrophic lateral sclerosis (ALS) and epilepsy. These conditions represent major health care issues, and the underlying molecular mechanisms for both are still poorly understood. We use an integrated approach involving molecular biology, cell biology, neuroanatomy, (in vivo) functional proteomics, imaging, high-content screening, and genetics. We're investigating molecular neuronal network changes, especially during disease progression, with the aim of uncovering new therapeutic interventions, for example, regenerative approaches to alter neuronal connectivity, and the design of novel stem cell-based cellular models for disease.

Frank van Bel, MD, PhD - *Professor, Neonatologist*
Neonatology
Wilhelmina Children's Hospital, UMC Utrecht

MSCs as a tool for therapy in preterm infants

We're performing research related to the "repair" of perinatal brain damage due to hypoxia-ischemia (lack of oxygen), perinatal arterial ischemic stroke (PAIS) and white matter disease (which affects the nervous system) in extremely preterm neonates. We focus on using mesenchymal stem cells (MSCs) and our ultimate aim is to develop MSCs as a clinical tool. Recently, we discovered that MSCs can be used to ameliorate perinatal brain damage after ischemia/hypoxia in a mouse model. Interestingly, non-invasive nasal application of allogeneic MSCs worked as well as intracranial therapy, which is very important for future use in the newborn. In a united approach, we're collaborating with MD Anderson Cancer Center and the Southwest National Primate Research Center in Texas, USA, in an attempt to decrease brain damage in the (preterm) neonate. In addition, future possibilities include using allogeneic MSC therapy to treat and reduce bronchopulmonary dysplasia (chronic lung disease) due to severe idiopathic respiratory disease (thickening and scarring of the lung tissue) in the preterm neonate.

Onno Kranenburg, PhD - *Associate Professor*
Medical Oncology
UMC Utrecht

Cancer stem cells in colon cancer metastasis

The research in my group is focused on metastatic colorectal cancer. The major goal is to identify processes that contribute to metastasis formation and tumor recurrence. We have generated a living biobank of 'colonosphere' cultures derived from primary colorectal tumors and liver metastases that have been resected at the UMC Utrecht. This culture collection forms a novel platform for translational research and for testing hypotheses derived both from clinical data and from basic research.

We use gene expression profiling, proteomics and gene interference technologies to study the biology of colon cancer stem cells in vitro and in mouse models. In particular, we're studying the relationship between tumor cell invasion, stemness and epithelial-to-mesenchymal transition during metastasis formation. Another important line of research is to understand how 'death receptors' (which normally induce apoptosis) promote invasion and metastasis in colon cancer. In addition, we're using patient-derived tumor material to generate gene expression profiles in order to link patterns of gene expression to clinical parameters. The hypotheses that are generated by these studies can subsequently be tested in the lab. Where possible, we use the results from these studies to design clinical trials and test the clinical relevance of the findings.

Patient with rare intestinal disorder (atypical microvillus inclusion disease) and organoids derived from patient recapitulate phenotype. Image courtesy of Sabine Middendorp

Sabine Middendorp, PhD - *Assistant Professor*
Pediatric Gastroenterology
Wilhelmina Children's Hospital, UMC Utrecht

Using patient-specific organoids to study disease
Our research uses intestinal and liver organoids as patient-specific models of disease. We collect biopsies from patients with diseases of the liver and intestine, such as rare congenital diseases, inflammatory bowel disease and celiac disease. We generate organoids (structures that resemble organs) from these patients in the lab. We study what goes wrong within the intestinal epithelial cells and can develop personalized medicine to treat the disease. In the future, we aim to perform a first-in-man study by transplanting intestinal organoids into patients with a congenital intestinal disorder, microvillus inclusion disease. In addition, we aim to set up the European Patient-Specific Intestine and Liver Organoid Network (EPSILON) center, in which we will generate organoids from patients with (rare) diseases and use them as individual model systems of disease.

Caroline Wiegerinck, MD - *PhD candidate*
Pediatric Gastroenterology
Wilhelmina Children's Hospital, UMC Utrecht

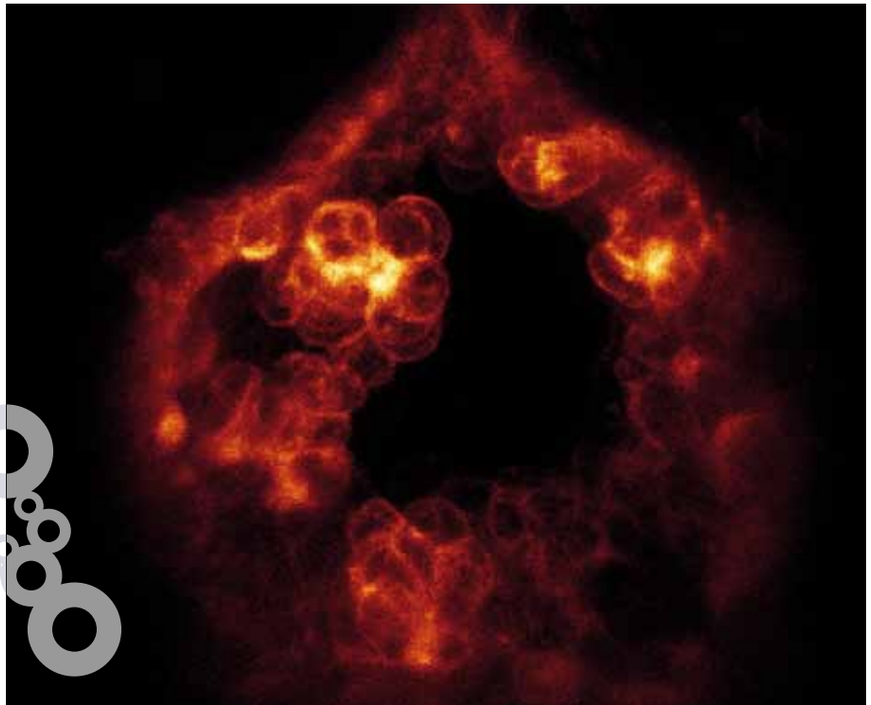
Can we treat congenital diarrhea with organoids?
"I work on a rare but severe disease that affects little children: congenital diarrhea. Their gut is incapable of absorbing nutrients from food. We're growing mini-guts, so-called intestinal organoids, from stem cells. Eventually, we hope to be able to transplant these into patients. But first we want to know more about this disease. I studied medicine in Amsterdam and chose to work at the Wilhelmina Children's Hospital because of their aim to take research from bench to bedside, and because there is a strong collaboration with the Hubrecht Institute. I want to play a role in the translation of science into the clinic when I become a pediatrician. Now that I have more knowledge of the field, the tools and techniques and I'll be better able to work together with scientists."

Catherine Robin, PhD - *Associate Professor*
Hubrecht Institute

Understanding how blood cells are made

We study blood development. We're interested in deciphering which signals dictate the production of blood cells. If we can understand how blood stem cells originate and develop, we may be able to create more effective therapies for blood-related diseases. Through a truly collaborative effort, we devised a new approach to precisely image the anatomical and cellular origin of blood stem cells (hematopoietic stem cells, HSCs). We use time-lapse confocal imaging, together with variations on dissection procedures of non-fixed mouse embryos. This has meant that for the first time we are able to visualize the dynamic emergence of the HSCs from the ventral endothelial floor of the aorta. With this novel technique, we will better understand the mechanisms that govern the generation and expansion of blood stem cells and mature blood.

The first blood stem cells are part of cell clusters attached to the endothelium of the mouse embryo aorta. Image courtesy of Robin lab



Tuna Mutis, MD, PhD
Clinical Chemisty & Hematology
UMC Utrecht

Developing more effective therapies for blood diseases

My group works on allogeneic stem cell transplantation and related research. We're aiming to improve graft-versus-tumor effects and minimize the risk of graft-versus-host disease. The use of therapeutic antigens as vaccines is becoming more viable (antigens induce immune responsesd in our bodies). To this end, we're conducting three clinical trials in which host or donor dendritic cells are loaded with specific peptides (minor H antigens), and used as vaccines to improve the therapeutic effect of allogeneic stem cell transplantations.
We hope to identify 5-10 new minor H antigens for therapy. Another focus of our research is the use of iPSC technologies to generate undifferentiated antigen-specific T cells, which are now considered effective tools for the treatment for hematological and non-hematological tumors. Finally, we're investigating how tumor cells can escape the tumor microenvironment in the bone marrow, in order to develop more effective vaccines or adoptive immune therapies for blood cancers.

Jaap Jan Boelens, MD, PhD - *Pediatrician*
Pediatric Stem Cell Transplantation
Wilhelmina Children's Hospital, UMC Utrecht

Improving hematopoietic stem cell transplantation (HSCT)
Our research focuses on safer and more effective HSCT, and we're also interested in HSCT in rare non-hematopoietic diseases, for example, lysosomal storage diseases and Epidermolysis Bullosae (EB).

In close collaboration with Stefan Nierkens, PhD of the Immunology Department, we've initiated a project, U-DANCE (Utrecht – Dendritic Cells against Cancer), that focuses on the development of Dendritic Cell Tumor vaccines from unrelated cord blood stem cells. We expect to run two dendritic cell vaccines in clinical trials in the near future, one for acute myeloid leukemia (granted start 2015) and the other in neuroblastoma. There is extensive experience with running CCMO-approved clinical trials using ATMPs over the last years (CCMO is the Dutch Competent Authority). These ATMPs are manufactured under GMP-conditions within the Cell Therapy Facility of the UMC Utrecht, which is headed by Ineke Slaper-Cortenbach, PhD.

U-DANCE also focuses on the immune-reconstitution after allogeneic HSCT: pharmaco-kinetics and dynamics of ATG (anti-thymocyte globuline), which is given prior to HSCT and has impact on the immune-reconstitution. A good, predictive reconstitution is of importance to predict the effect of the DC-vaccine.

The UMC Utrecht is the national referral center for HSCT in lysosomal storage diseases and EB. Recently, the CCMO approved a study protocol for a cord blood stem cell therapy in EB (the first in Europe). This clinical study will start early 2014. Furthermore, we collaborate closely with the San Raffaele-Telethon Institute for gene therapy in lysosomal storage diseases and immune-deficiencies. We plan to bring this therapy to Utrecht.

Bart Spee, PhD - *Assistant Professor*
Faculty of Veterinary Medicine
Utrecht University

Regenerating liver
The shortage of donors for liver transplants is a growing problem. In Europe alone, 22% of patients on the waiting list for a liver transplant die. Alternatives are needed to treat the increasing number of patients with liver diseases. We're investigating the use of stem cells, ranging from adult stem cells (organoids) to mesenchymal stem cells, for functional recovery of liver diseases. To prove the efficacy and safety of these stem cell therapies, my group uses a unique large animal model, the dog, to bridge fundamental science to human clinics. In addition, the differentiation of induced pluripotent stem (iPS) cells into hepatocytes or the generation of directly reprogrammed induced hepatocytes (iHEP cells) from patient material have great potential in toxicology and/or personalized medicine.

Hedwig Kruitwagen, DVM - *PhD candidate*
Faculty of Veterinary Medicine
Utrecht University

Using stem cells to repair diseased liver
"If you remove part of the liver, it'll restore itself. In patients with liver disease, this doesn't happen and they need a liver transplantation. Dogs have naturally occurring liver disease due, for example, to a genetic flaw, just like humans.

We see a lot of metabolic liver disease in our veterinary clinic; in the human hospital across the street, they see this mainly in children. For them, the current method of treatment is a whole liver transplant; however, this is very invasive and these children remain on lifelong immunosuppressants. In dogs, this option is unavailable. We're searching for alternatives and hope to figure out how to active adult stem cells that naturally exist in the liver. I try to discover how stem cells could aid in repairing a diseased liver, in both dogs and human patients. In collaboration with the Hubrecht Institute we grow mini-livers, organoids, from these stem cells. We've translated this technique from mice to dog patients and are transplanting organoids into our dogs with metabolic liver disease. We believe the dog can bridge the gap between a lab-mouse and human clinical application. Ideally, we'd like to be able to make organoids (which contain liver stem cells from the specific patient), correct their genetic defect, and re-transplant them back into the patient. This would remove the need for immunosuppressants and hopefully provide the patient with life-long proper liver function.

In the future, we'll be able to translate this technique into the human clinic, together with the Wilhelmina Children's Hospital. This project is unique and can only take place in Utrecht – the Veterinary Faculty, the Hubrecht Institute and the Children's Hospital are all within walking distance of each other – and I'm able to interact with a very diverse number of people."

Cardiovascular Tissue Regeneration

In the Netherlands, about 300,000 people suffer from heart failure and almost one million from heart disease. Cardiovascular disease is the number one "killer disease" for women and heart failure is a clinical problem with high societal relevance. The UMC Utrecht tries to use stem cells to optimize the treatment of people who have had a heart attack. In collaboration with international parties in China and the US, large-scale studies are conducted to find the best treatment for heart problems.

Pieter Doevendans, MD, PhD - *Professor, Cardiologist*
Division of Heart and Lungs
UMC Utrecht

Searching for the best treatment for heart problems
"At the UMC Utrecht's Department of Cardiology, we treat patients with heart problems," says Pieter Doevendans. "People with severe forms of heart failure come to us for a cardiac transplantion or sometimes we opt to give them a ventricular assist device. We also do a lot of work treating people with acute myocardial infarction. We're on call to treat them night and day, trying to keep the myocardial damage to a minimum."

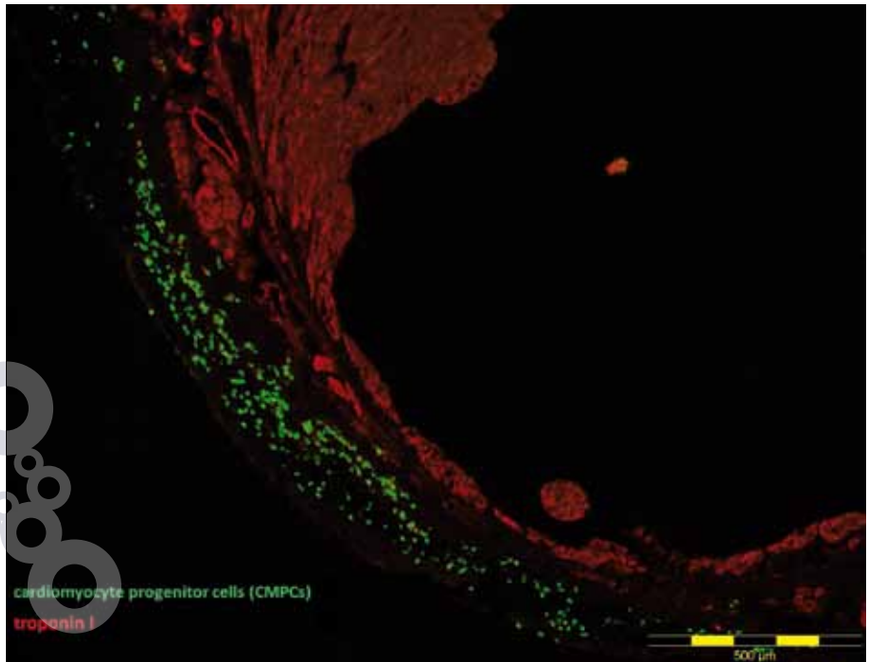
Long way to go
Doevendans and his colleagues are also exploring regenerative medicine to treat limb ischemia, cardiac failure and valve disease. "We're studying stem cell therapy for cardiovascular tissue regeneration. The heart has only limited regenerative capacity. A scar is the most prominent effect of a heart attack, but scars hinder myocardial tissue repair. Early treatment reduces scar formation, therefore patients with a heart attack should be treated as quickly as possible," describes Doevendans. "We're now making myocardial tissues for mice and rats, but we don't have the right tissue for human patients yet," he continues. "The body's immune response is very strong and that also complicates cell and tissue transplantation. Therefore, general tissue might not be suitable for everyone."

Working with stem cells and tissue regeneration stays close to biology. “There’s something really fascinating about bringing back an organ in its original state with biological materials. However, we still have a long way to go. We’ll never, ever be able to completely fix a damaged heart but will always need external technology to support the pump function of the heart in some patients. The heart is contracting 70 times a minute life-long! This poses a big challenge. Technology provides a highly reliable tool compared to biology, which is variable and less predictive. Everybody thought repairing tissues would be easy, but it’s far more complex than we thought. Mother Nature is difficult to imitate, not to mention, improve.”

Fascination for cardiology

When Doevendans was a 12-year-old boy, his father died from a heart attack in his sleep at the age of 41. He still clearly remembers the day, September 11th. This tragic event triggered his fascination for the heart and made him decide to become a cardiologist. He never regretted his choice. “What I like most is treating patients with myocardial infarction. It takes only ten minutes to open the blocked coronary artery, which gives patients immediate relief. Acute myocardial infarction causes a lot of pain, people feel sick, are nauseated, sweating and stressed. They come in crying, but leave the room smiling. Helping those patients is really rewarding.”

Image courtesy of the Sluijer lab



Joost Sluijter, PhD - *Associate Professor*
Cardiology
UMC Utrecht

Cardiac-derived progenitor cells

In my research group, we are studying the role of cardiac-derived progenitor cells, called cardiomyocyte progenitor cells (CMPCs), for their use in repair after damage to the heart. We are exploring the use of biomaterials, cells, and the secreted vesicles, called exosomes, to further understand cardiac repair mechanisms and thereby improve clinical cell therapy approaches. Additionally, we explore the use of implementing miRNA therapeutics into regenerative medicine and their role for diagnosis of myocardial damage.

Eva van Rooij, PhD - *Associate Professor*
Hubrecht Institute
Cardiology, UMC Utrecht

MicroRNAs and heart disease

A major challenge in the field of cardiovascular biology is to decipher the relevance of different signaling mechanisms during disease. Our lab is interested in molecular mechanisms underlying cardiovascular disease conditions by studying the complex interplay between gene expression and microRNAs. Groundbreaking discoveries in the field of microRNA biology by our group and others have shown that these small, non-coding RNAs have a very potent and relevant influence during disease. Using molecular in vitro and in vivo gain and loss-of-function studies, applying both genetics and oligonucleotide-based approaches, we aim to further delineate the morphological and functional relevance of different signaling molecules. Our long-term goal is to increase our understanding in how changes in gene expression and microRNA function contribute to disease to allow for the development of novel cardiovascular therapeutics.

Eric Duckers, MD, PhD - *Interventional Cardiologist*
Cardiology
UMC Utrecht

Treating damaged hearts

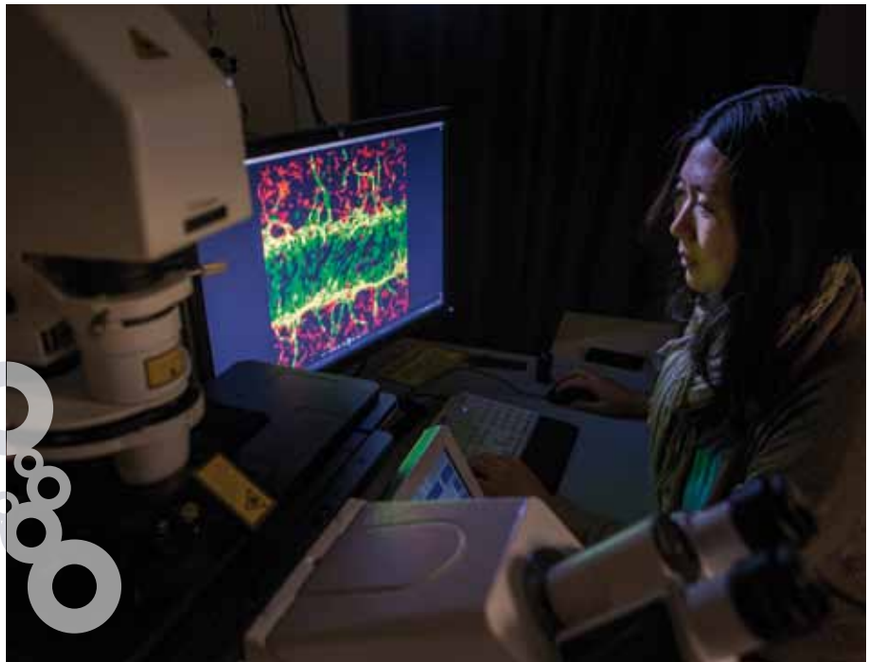
Our work focuses on transferring our basic research knowledge into clinical benefit for patients suffering from cardiac damage or disease. We're involved in several clinical studies, most recently, the ADVANCE trial, which evaluates the use of adipose (fat)-derived stem and regenerative cells (ADRCs) in patients soon after a heart attack; and most recently, the AMICI (Allogeneic Mesenchymal precursor cell Infusion in myoCardial Infarction), which is the first trial to evaluate this type of therapy in patients. We're drawing upon the knowledge we gain from the results to improve heart function and repair damaged heart muscle in our patients with minimally invasive methods.

BM bone marrow **CLEM** correlative light electron microscopy **CLI** critical limb ischemia **EPCs** endothelial progenitor cells **ESCs** embryonic stem cells **HSCs** hematopoietic stem cells **HSCT** hematopoietic stem cell transplant **iPSCs** induced pluripotent stem cells **MSCs** mesenchymal stem cells **RM** regenerative medicine

Caroline Cheng, PhD - *Associate Professor*
Nephrology & Hypertension
UMC Utrecht

New blood vessels

My group is interested in understanding the mechanisms that regulate new blood vessel formation (angiogenesis) and vascular growth in normal development and disease. In particular, we're studying the regulatory function of established vessels and how they promote new growth. To do this, we're dissecting molecular pathways during embryonic development of zebrafish and identifying new key genes. In the retina, for example, there's a two-week window of development during which new vasculature is laid down. We've identified a few candidate genes and are working with a biotech company to develop new methods of promoting blood vessel formation. We're also studying this in the context of chronic kidney disease and myocardial infarction. Another aspect my lab focuses on is the interaction between different cell types in a vessel and how they're influenced by mechanical stimuli, for example, shear stress. It's interesting that the environment can stimulate certain cell types to adapt to a different purpose, thus creating a completely different vasculature.



Jolanda Kluin, MD, PhD - *Cardio-thoracic surgeon*
Cardio-Thoracic Surgery
UMC Utrecht

Tissue engineered heart valves

The objective of our research is to develop tissue engineered heart valves and small diameter arteries. We focus on the development of instructive, synthetic scaffolds of heart valves and small diameter arteries for the in vivo repopulation by circulating cells. In other words, we're implanting bare scaffolds and are trying to stimulate the body to act as a bioreactor for generating its own heart valve or artery that can grow with the patient. In the next years, we focus on large animal experiments as a final step towards translation to the clinic. We'll conduct very intensive preclinical animal studies to test new scaffolds and new designs and to fulfill all the required legislation to bring this technique from bench to bedside. Hopefully, we can reach this translation within the next 10 years.

Vera Verhage - *PhD candidate*
Cardiology
UMC Utrecht

Cardiac exosomes promote vessel growth

"The physiology of the heart is intriguingly perfect and cool. But after a heart attack, the heart cannot heal itself. In the lab we induce a myocardial infarction in mice, by blocking a coronary artery. Some years ago our lab identified human cardiac stem cells. Injection of these stem cells in the heart can improve healing of the damaged tissue and keep the heart functioning well. However, the etention and survival of the injected stem cells is limited due to the lack of oxygen and inflammation in the heart. Within this field, I explore the role of small secreted vesicles, called exosomes, that are released by human cardiac stem cells. These vesicles serve as communication tool between cells and contain proteins and genetic material. Applied under the skin of a mouse, exosomes promoted the growth of blood vessels. My research investigates if we can we use exosomes from cardiac stem cells as therapy after a heart attack, which would be great. In the end, there are fewer ethical issues and practical problems with injecting vesicles than with transplanting living stem cells from a donor."

Marianne Verhaar, MD, PhD - *Professor, Nephrologist*
Nephrology & Hypertension
UMC Utrecht

Tackling chronic kidney disease

"In the department of Nephrology and Hypertension, we see many patients with chronic kidney disease. This disease is a serious health care problem that will become even more prevalent over the next few years, with people getting older and growing numbers of patients suffering from diabetes, obesity, and arteriosclerosis. Kidney damage is an important problem because it tends to get worse and can eventually lead to kidney failure and the need of dialysis or kidney transplantation. Furthermore, chronic kidney disease – even in a milder form – is associated with a high risk of cardiovascular disease.

Our research aims to tackle these problems using regenerative medicine, for instance by encouraging the body's natural recovery within the kidney and the blood vessels. We investigate whether administration of stem cells, either bone marrow-derived or kidney specific, can prevent progression of kidney disease. In collaboration with the Hubrecht Institute, we also investigate whether we can use a patient's own stem cells (induced pluripotent stem cells) for clinical organ or renal tissue replacement. Together with the Dutch Kidney Foundation and others, we are developing a wearable bioartificial kidney. In addition, we run several projects on developing new regenerative strategies for treatment of vascular disease.

Chronic kidney disease is a major burden for patients – and expensive for society as well. Dialysis has been a great improvement: it keeps people alive, but it isn't a very pleasant life, associated with many health problems. We should improve further, either by preventing people from reaching the stage of end-stage renal failure, or by improving renal replacement techniques. The kidney is an extremely complex organ, however, I expect that regenerative medicine will provide new treatment options to reduce the burden of chronic kidney disease for our patients."

Rachel Giles, PhD - *Associate Professor*
Nephrology & Hypertension
UMC Utrecht

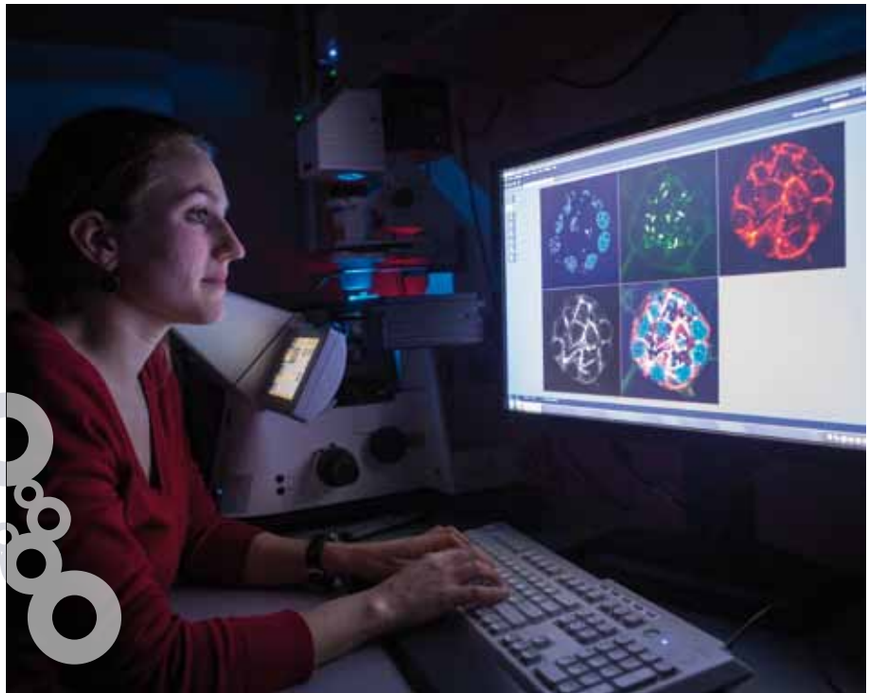
The role of cilium in kidney disease

My lab focuses on understanding how the cilium regulates renal epithelial regulation. Our questions focus on studying ciliary regulation of the cell cycle and cell signaling using in vitro renal cell culture and proteomics, ex vivo whole kidney culture, and in vivo zebrafish models of renal cell carcinoma and renal ciliopathies. We apply our understanding of kidney cell regulation to renal regeneration. We have invested in an integrated systems biology approach to understand the cilium in proliferative states such as tissue regeneration and nephronophthisis/polycystic kidney diseases. Finally, the generation of iPSC cells from our pediatric patients aids renal disease modeling and drug screens.

Gisela Slaats - *PhD student*
Nephrology & Hypertension
UMC Utrecht

Studying damaged cilium in kidney disease

During my PhD thesis, I'm studying cilia, hair-like organelles present on almost every cell type of the body. For instance, they help to work out mucus in the airways or sense fluid flow in the kidney. The ciliopathy I work on is called nephronophthisis. The kidneys of patients with this disorder are small and form scar tissue (fibrosis) and cysts. Affected children need a transplant when they are teens. I'm trying to understand whether molecules that regulate DNA damage signaling in kidney cells play a role in this disease. I'll visit a lab at Stanford University in the USA to learn techniques to study DNA damage signaling. When we know what is disturbed at a molecular level during the development of nephronophthisis, we may be able to design a therapy that slows the progression of this disease. Or we may find a way to regenerate cilia.



Joost Fledderus, PhD - *Research Fellow*
Nephrology & Hypertension
UMC Utrecht

Stimulating the body to repair itself

I work on molecular pathways that protect the cell during times of exogenous stress, for example, oxidative stress and toxins, which also impair the regenerative capacity of the body. The pathway I study is regulated by the transcription factor Nrf2, which induces the cell's enzymatic machinery in response to cytotoxic substances that directly activate Nrf2. I'm investigating this in the context of cardiovascular and kidney diseases and my hypothesis is that this pathway is epigenetically inhibited during disease and also in an aging vascular system. We're looking for novel ways to (re-) activate this pathway, and interestingly, many of the compounds that activate this pathway are not toxic and can be found in cruciferous vegetables, such as broccoli. Can we stimulate this pathway and thus, improve vascular health through diet? This would be a non-invasive way of stimulating the endogenous regenerative capacity. This alternative way of thinking is what has guided me in my career. I've always followed my (broad) interests, which has led me through very interesting internships, collaborations and scientific experiences – I feel that I'm in the right place.

Clinical Trial: JUVENTAS

Rejuvinating endothelial progenitor cells via transcutaneous intra-arterial supplementation.
Critical limb ischemia (CLI) is a chronic condition caused by severe blockage of the arteries, most commonly due to atherosclerosis, thereby reducing blood flow to the lower extremities. Affecting 1000 in a million, it is not a particular disease, but a syndrome that may develop from a number of different pathologies. Patients experience severe pain, even at rest, non-healing sores and wounds, tissue necrosis and gangrene. Risk factors associated with CLI are similar to those for atherosclerosis, including diabetes, obesity, high blood pressure/cholesterol, smoking, and family history of atherosclerosis and poor circulation. It is often associated with high short-term cardiovascular ischemic event rates and increased mortality.

Treatment

Current treatment options are limited and approximately 40% of patients are ineligible for surgical intervention or endovascular revascularization. Often, amputation is a last resort. With the discovery of bone marrow-derived circulating progenitor cells, researchers can coax stem and progenitor cells into supporting neovascularization in ischemic tissues. This new concept of postnatal vascularization has brought about the use of progenitor cell-based therapies in patients with advanced ischemic conditions. However, several groups have demonstrated a reduction of circulating endothelial progenitor cells (EPCs) in patients with CLI. To date, published data on cell therapy clinical trials for CLI provide unclear results, as they have been small and non-double-blinded.

Clinical Trial

The JUVENTAS trial was the first large (n=160) double-blinded, randomized, placebo-controlled trial for CLI patients. Led by Marianne Verhaar, investigators hypothesized that CLI patients house dysfunctional and reduced numbers of EPCs, resulting bone marrow depletion, and that infusion of bone marrow (BM)-derived mononuclear cells could provide an angiogenic environment to stimulate growth of collateral vessels. A total of 160 patients underwent repeated intra-arterial infusion of autologous BM-derived mononuclear cells or placebo.
The trial aims to assess safety and clinical efficacy of autologous BM mononuclear cell therapy and to characterize stem cell dysfunction and relate stem cell function with clinical outcome.

Supporting research

Verhaar and her group also conducted fundamental research, in vitro and in animal models, on the role of adult stem and progenitor cells in vascular and renal regeneration and the functional characteristics of BM-derived progenitor cells in healthy and cardiovascular and renal disease conditions.

Outcome of the clinical trial

The JUVENTAS trial concluded in 2013. Preliminary analysis seems to indicate that in this study, cellular therapy does not have significant benefit over placebo in patients with CLI. The results do not allow conclusions on potential benefit of other cell sources or subpopulations, different administration routes or in patients with milder disease. Further study is needed to investigate these options. The JUVENTAS study group is currently optimizing BM-derived cell therapy for the treatment of CLI. They are investigating whether selecting, expanding and differentiating BM cells towards EPCs in the lab, followed by pretreatment of EPC, improves their function. This may result in a new cellular therapy product that improves treatment of CLI patients. A clinical trial will be performed to study the clinical effects of such optimized BM-cell therapy.

Musculoskeletal Tissue Regeneration

Musculoskeletal Tissue Regeneration, one of the three overall themes within the Regenerative Medicine & Stem Cells program, focuses on fundamental, translational and clinical research for bone and cartilage regeneration.
"At the UMC Utrecht's Orthopedics department, we treat patients with problems in their bones and joints," says Wouter Dhert, Chair of the RMSC program. "These problems could be the result of an injury, disease, an accident, or simply the effect of wear and tear. We call this osteoarthritis. Osteoarthritis can arise in any joint, such as the hip, knee, or spinal column. Patients could, for instance, have pain in their lower back and the orthopedic surgeon might want to fuse some of the vertebrae together by adding some bone along the vertebrae that grafts onto them. People could also get a hernia or a prolapsed disc in their back. In such a case, the surgeon may decide to remove the disc or to insert a prothesis."

Wouter Dhert, MD, PhD - *Professor of Regenerative Medicine*
Orthopedics
UMC Utrecht
Faculty of Veterinary Medicine, Utrecht University

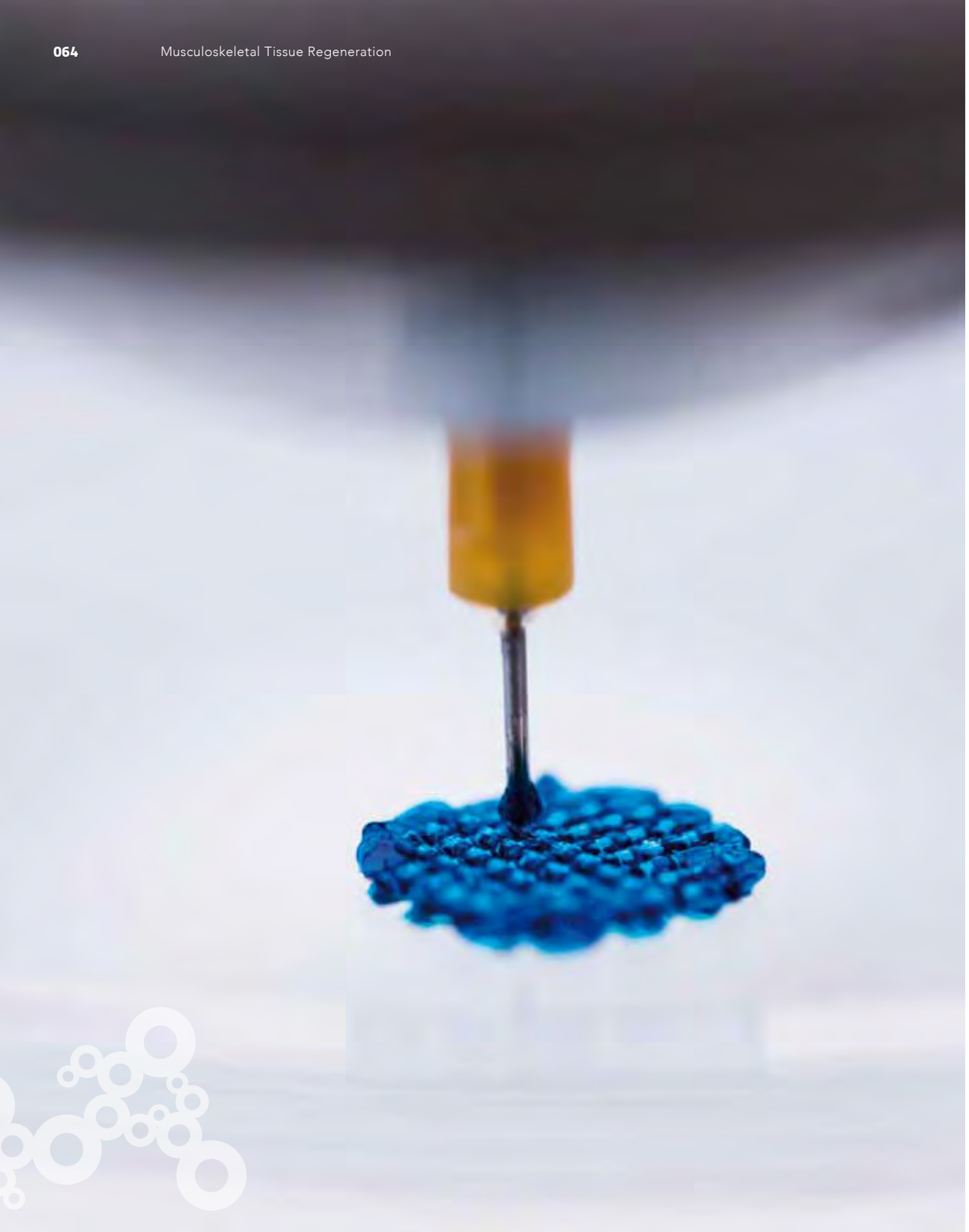
Regenerating tissues for bone and joint problems
The UMC Utrecht tries to find solutions that enable researchers and clinicians to regenerate these tissues, rather than fixing, replacing or removing them, or inserting a prosthesis. "Using laboratory techniques, we want to create these kinds of tissues and make sure the body has healthy tissues again. We call our approach 'dual translational'. This means that we translate the problems that patients come in with into research questions for our lab. Eventually, we hope to come back with new solutions for patients."

Searching for the holy grail
Over the past 10 years, knowledge has increased enormously but many issues remain. "Regenerating tissues is a big challenge! Tissues are complexly organized structures with cells, vessels and blood. So far, we've only been able to develop simple tissues in the lab," explains Dhert. "Our holy grail is understanding the regeneration process well enough to be able to encourage the body to regenerate tissue itself, maybe with intelligent scaffolds… rather than cultivating tissue in the lab." Successful musculoskeletal tissue regeneration in patients also requires studying the role of the local environment of the joint and tissue (homeostasis) in the individual patient. Clinicians and researchers in the field are working closely together to unravel the environmental effects on regeneration.

Helping patients
Dhert obtained a Medical Degree and a PhD in Orthopaedic Biomaterials 20 years ago, but he has been working as a fulltime scientist ever since. "I love to operate in a translational environment where our research is aimed at helping patients. We have to take our responsibility to society and spend the funding we receive as optimally as possible. The RMSC program is absolutely fantastic, but our aims have to remain realistic. Regenerative medicine will not be able to solve every disease, however, it has the potential to help many patients and will bring new solutions to problems in health care such as osteoarthritis, organ transplants, and tissue regeneration."

Daniël Saris, MD, PhD - *Professor, Orthopedic Surgeon*
Orthopedics
UMC Utrecht
University of Twente

Integrating technology with clinical application for cartilage repair
Our goal is patient-centered progress and thus, translating unmet medical need into relevant basic science questions, as well as finding clinical application for technological innovations. We're building effective group dynamics in this multi-disciplinary field and are striving to put the Netherlands center stage in the international regenerative medicine arena. Currently, we are focusing on arthoscopic delivery of cartilage repair, in the first-in-man clinical trial, IMPACT; advanced imaging and diagnostics, on the rapid diagnosis of joint homeostasis, important for (re)development processes; and on the modulation of joint and disc environment for repair and to slow degeneration.



Laura Creemers, PhD - *Associate Professor*
Orthopedics
UMC Utrecht

Cartilage regeneration

My research focuses on improving regeneration of cartilaginous tissues, such as the intervertebral discs and articular cartilage (which covers bone ends in a joint). We study inflammatory pathways and epigenetic changes involved in the regeneration and degeneration of these tissues. Our strategies involve the development of biomaterial-based local controlled release systems, and non-viral genetic modulation (in particular by RNAi) to enhance a regenerative phenotype in native and retransplanted cells. For my research, the embedding in a group containing clinicians keen on bringing new treatments to the patient has been very stimulating. In addition, the BioBank facility is important in providing human material indispensable for our research. The research environment in the UMC Utrecht is pleasant and most groups are open to collaboration or sharing of equipment.

René van Weeren, DVM, PhD - *Professor*
Faculty of Veterinary Medicine
Utrecht University

Understanding joint (cartilage) problems in horses

My group specializes in the biology of the musculoskeletal tissues, especially articular cartilage and tendons and regeneration thereof. Damaged cartilage is difficult to repair, which makes it a very interesting research challenge. We have a special interest in how biomechanical loading and exercise influence developmental aspects of joints, as we feel herein lies a main clue for the prevention of degenerative joint disease that occurs later in life. As a veterinarian, I've chosen to work with horses, as they are, like humans, prone to joint disorders. This makes the horse a perfect animal for translational research, because outcome is of direct benefit to the species and will enhance equine welfare, one of our main focus points. At the Faculty of Veterinary Medicine, we're fortunate to have a patient clinic where we can diagnose and treat horses with joint problems. We take information from the clinic and use it as a basis for our investigations in cartilage regeneration.

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Nicole Willems, DVM - *PhD candidate*
Faculty of Veterinary Medicine
Utrecht University

New treatments for chronic back pain

"My research in the field of regenerative medicine specifically focuses on new treatments for back pain, which is related to degeneration of the discs. We study the Beagle dog. The discs of these dogs degenerate spontaneously, similar to human discs. Currently, people and dogs with such degenerated discs receive pain medication, physical therapy and, as a last resort, surgery. We try to regenerate the discs by injecting hydrogels or microspheres loaded with specific substances, for example pain medication and/or growth factors. These substances are slowly released from these delivery systems. When we have developed a working therapy, we can use it to treat veterinary and human patients with debilitating chronic back pain. This project brings me more than I had expected. As a veterinarian, I learn about new therapies, and exchange ideas with people in the hospital. I am happy to see that medical doctors are increasingly aware of the similarities in human and veterinary medicine and the advantages of our collaboration on both our patient care."

Cumhur Oner, MD, PhD - *Professor of Spine Surgery*
Orthopedics
UMC Utrecht

Translational regenerative research of the spine

As a spinal surgeon, I'm interested in developing less invasive surgical treatments of traumatic and pathological fractures of the spinal column. My group focuses on translational regenerative research in the bone and intervertebral discs of the spine. In particular, we're developing bone graft substitutes that involve MSCs, growth factors (BMPs), bioactive materials and use of inflammatory pathways. In addition to our goals of improving the treatment of spinal injuries, we're also developing global classification and outcome measurement systems for traumatic and metastatic fractures of the spine. Our scientific and clinical aims depend on close cooperation between surgeons and basic researchers, which we experience on a daily basis.

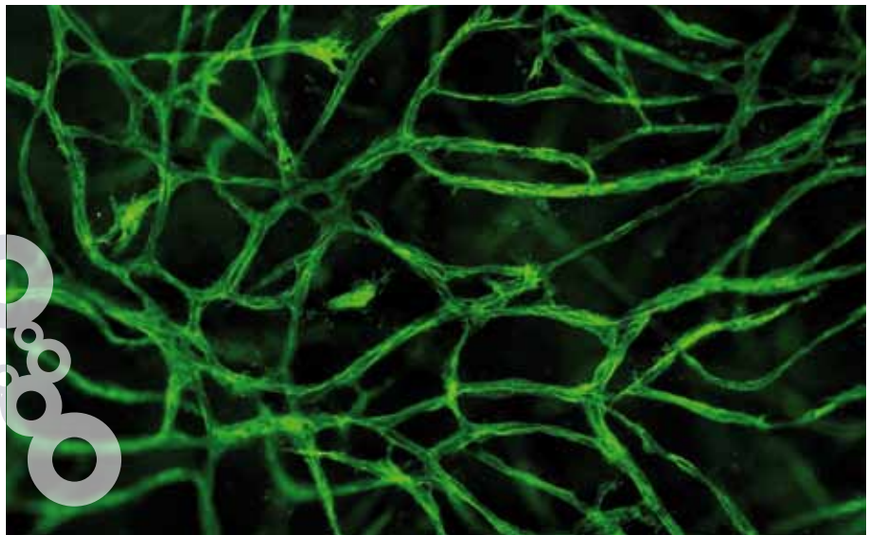
Ronald Koole, MD, PhD - *Professor, Surgeon*
Oral-Maxillo-Facial Surgery
UMC Utrecht

Building better bone grafts

My group is dedicated to bone surgery in the mandibular-maxilla and skull region. In the clinic, we focus on reconstructing the aveolar cleft, which is necessary for patients (both very young and old) with both a cleft lip and cleft palate. We mainly reconstruct defects with autologous bone grafts, taken from the patient's iliac crest or chin. We're currently developing a bone construct and substitute for this to avoid the additional surgery. In the future, we aim to develop commercially available bone substitutes for the skull, midface region and lower jaw; the latter is still very challenging and innovative. What's unique in our research is the collaboration between Oral-Maxillo-Facial Surgery, Orthopedics, the Regenerative Medicine & Stem Cells Strategic Program of the UMC Utrecht and Xpand Technologies, a company that builds instructive bone grafts. Together, we're integrating multiple disciplines, such as biofabrication, biological mechanisms (osteoinductive, osteoconductive, cell-cell interaction), biomaterials (resorbable), and biomechanics (stress-bearing).

In the near future, we'll explore the applicability of stem cell-based regeneration of bone for OMF surgeries. Besides employing the endochondral route of bone regeneration (i.e. bone regeneration from a cartilaginous template), we'll take on the challenge to create a patient-specific vascularized bone graft for mandibular reconstruction.

A prevascular network formed in vitro by stem cells. CD31 (green) in 3D, indicating endothelial cells that line the interior of blood vessels. Image courtesy of the Gawlitta lab

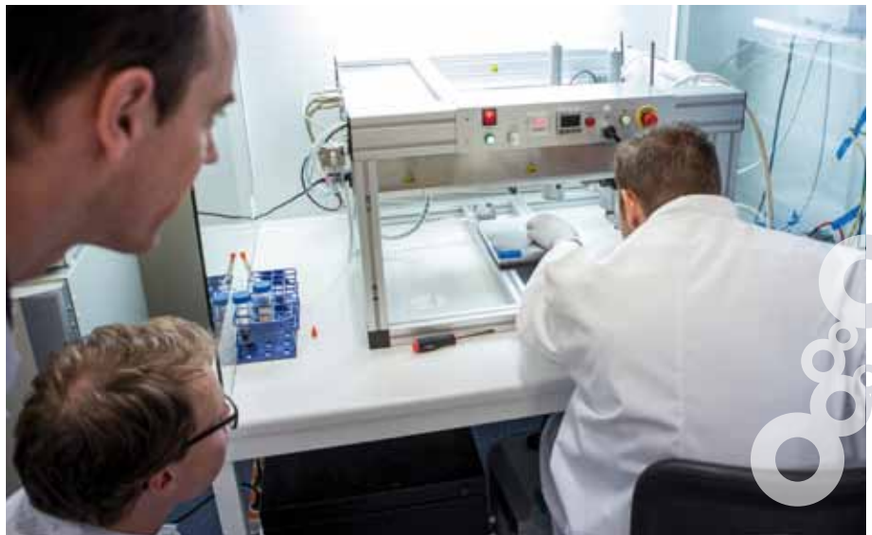


Jacqueline Alblas, PhD - *Assistant Professor*
Orthopedics
UMC Utrecht

Bone tissue engineering

My research activities are mainly focused on regeneration of bone. Our aim is to develop hybrid constructs in which scaffold material and cell stimuli are optimally combined with the regenerative potential of adult stem cells. Our main focus points are tissue architecture, vascularization, gene delivery and immunological aspects of bone substitutes.

Printing of living cells, which we developed in our lab, has received a lot of attention in the last years, and has expanded considerably. Using this technology, we've developed and optimized dedicated biomaterials suitable for bioprinting, and we're now ready for further functionalization. We're using these to investigate the role of self-organization of cells and matrix components in tissue repair. We aim to generate 3D models of various disease-specific tissues and cells, as well as to print blood vessels and large tissue replacement constructs. Our research requires intense integration of immunology and orthopedics, which is an enjoyable environment to work in.



Loek Loozen, MD - *PhD candidate*
Orthopedics
UMC Utrecht

Stimulating bone formation
"By the end of med school, I took a course in biomedical engineering at the Technical University in Delft. That really interested me. Regenerative medicine is a bit of everything: engineering, biology, and medical science. There are undiscovered areas everywhere you look, and I like to pioneer. In spinal surgery, the growth factors that are used to induce bone formation have side effects and I try to turn stem cells in a fracture zone or bone defect area into bone producing cells by inserting DNA. We remove a piece of bone from the spine of a rat and fill the gap with hydrogel, DNA, and ceramic particles on which bone formation can start. We hope it will work without adding extra stem cells. The therapy would be faster and cheaper then."

Floris Lafeber, PhD - *Professor of Experimental Rheumatology*
Rheumatology & Clinical Immunology
UMC Utrecht

New treatment postpones the need for joint replacement
"Rheumatic diseases, such as rheumatoid arthritis and osteoarthritis, are very common. To give an idea: one in 10 people suffer from osteoarthritis, conditions of the joints that can lead to considerable disability. At present, there is no cure for osteoarthritis, so eventually it's necessary to perform joint replacement surgery. Although a successful surgical procedure, the prosthesis replaces the

original joint by a metal implant. Moreover, the prosthesis has a limited life span, specifically in young and active patients, with subsequent costly revision surgery needed. As such, there is a clear unmet need to postpone joint replacement surgery in young active patients with severe osteoarthritis.

The departments of Rheumatology & Clinical Immunology and Orthopedics at the UMC Utrecht have developed a new technique to treat severe osteoarthritis of the knee using joint distraction. This treatment can postpone the need for a joint prosthesis for a long time. In this approach, the ends of the bones that form the joints are slightly separated ('distracted') for six weeks using an external frame. This technique is, at present, the only one in the world that enables cartilage, damaged by osteoarthritis, to recover. We were able to demonstrate that it results in substantial cartilage repair and has very good clinical effects, lasting for at least five years now – something thought to be impossible. Researchers and clinicians within the musculoskeletal tissue regeneration theme of the RMSC program in collaboration with the Maartens Kliniek Woerden and several orthopedics departments in the Netherlands are now investigating which patients could be helped most effectively by this treatment.

In the lab, we're collaborating with international partners to determine whether stem cells can play a role in tissue recovery, and how mechanical stress and the inside milieu of joints are involved. We're continually linking laboratory and clinical research, trying to improve the treatment of patients with rheumatic conditions. These issues are of great social and economic importance, judging

from the support by the Dutch Arthritis Association, ZonMw, and interest from the community. Our goal is to further improve this treatment and to implement it worldwide."

Simon Mastbergen, PhD - *Assistant Professor*
Rheumatology and Clinical Immunology
UMC Utrecht

Regeneration in osteoarthritis

My work focuses on tissue regeneration in osteoarthritis (OA) and we've developed several new techniques for this. One of our first achievements was the unique canine osteoarthritis model, the 'Groove' model, which mimics the progressive features of human OA. The Groove model includes evaluation of gait (pain), cartilage, synovial tissue, synovial fluid and changes in the subchondral bone. This model is extended for use in sheep and goat. Moreover, I'm involved in joint distraction as treatment of knee osteoarthritis. Also, the importance of the mutual biochemical interaction between bone and cartilage, playing a potential role in the benefit of joint distraction, is subject of study. Simultaneously, we performed joint distraction on the knee in the Groove model. A next step is taken by studying the role of joint homeostasis in intrinsic cartilage repair under influence of joint distraction in the first pilot studies. Recently, I initiated the development of a whole-joint bio-mechano-reactor, which is currently at the level of a working prototype, enabling evaluation of many different pathways in the osteoarthritis process.

Harrie Weinans, PhD - *Professor*
Orthopedics & Rheumatology
UMC Utrecht
Technical University Delft

Mechanobiology in osteoarthritis
My group works on osteoarthritis (OA), a degenerative disease that leads to pain and deformity of the joints. The underlying biological mechanisms of OA are still unknown and through a joint position at the UMC Utrecht, I'm able to bridge the Rheumatology and Orthopedics departments. This allows us to integrate basic molecular and cellular science with emerging mechanical technologies. For example, we're examining how joint activity and inflammatory processes influence OA, and how these relate to tissue degradation of cartilage and underlying bone. In addition, we're working on new approaches for treating OA with medication released from gels that can be injected in the OA joint. For us, the proximity of basic scientists, clinicians and engineers is essential. We're all learning another language and trying to make significant contributions to solving disease.

Jos Malda, PhD - *Associate Professor*
Orthopedics
UMC Utrecht
Faculty of Veterinary Medicine, Utrecht University

Biofabrication
My research focuses on biofabrication and biomaterials design, in particular for the regeneration of (osteo)chondral defects. We're developing novel biofabrication strategies, as well, and "bioinks" for 3D printing. These hydrogel-based "inks" are both designed to drive specific differentiation of the embedded and/or endogenous cells, as well as to allow fabrication with high shape fidelity in order to generate constructs that further reflect the complexity of the real tissues. In addition, we're pursuing approaches towards the translation of the biofabricated constructs in veterinary (equine) and human clinics, including their use as an in vitro platform for testing. Finally, we're developing biofabrication strategies and making them available to other researchers through the recently established Utrecht Biofabrication Facility.

Tina Vermonden, PhD - *Assistant Professor*
Pharmaceutics
Utrecht University

Tissue engineering and drug/protein delivery
We focus on developing biomaterials for tissue engineering and drug and protein delivery. We design, synthesize and characterize polymers with special emphasis on cross-linking techniques to obtain advanced material properties for biomedical applications. For example, we study sustained protein release and degradation properties of nanospheres and hydrogels for pharmaceutical and biomedical tissue engineering applications.

Clinical Trial: IMPACT

Instant MSC product accompanying chondron autologous transplantation
A first-in-man clinical trial for cartilage regeneration was initiated at the UMC Utrecht in June 2013. This trial combines the novel approach of a single surgical procedure together with co-culture of allogeneic stem cells and chondrons. It has the potential to drastically improve cartilage regeneration efficacy; to significantly decrease the financial burden of the therapy; and to harness the natural capabilities of our own regenerative potential.

Treatment
Damage to articular cartilage of the knee may result from a variety of causes, such as sports injuries, trauma and normal wear and tear. While the pain and limited mobility are not life threatening, they do contribute to an immediate decrease in quality of life and may lead to osteoarthritis. Traditional treatments for articular cartilage damage include pain management, braces, and various surgical methods. Directly challenging the centuries-old dogma that cartilage does not regenerate, the first autologous chondrocyte implantation (ACI) treatment was performed in 1987 (published in 1994) by Brittberg et al in Sweden. With ACI, patients undergo a 2-step surgical procedure: an initial biopsy, where cartilage is harvested, and expanded in vitro, and a second surgery, where the cultured chondrocytes are implanted back into the patient, 6-9 weeks later. This treatment reports good results and clinical trials have been conducted of which the UMC Utrecht is one of the largest patient centers. However, this therapy is associated with high costs (over € 20,000 per treatment), two operations, and long recovery time.

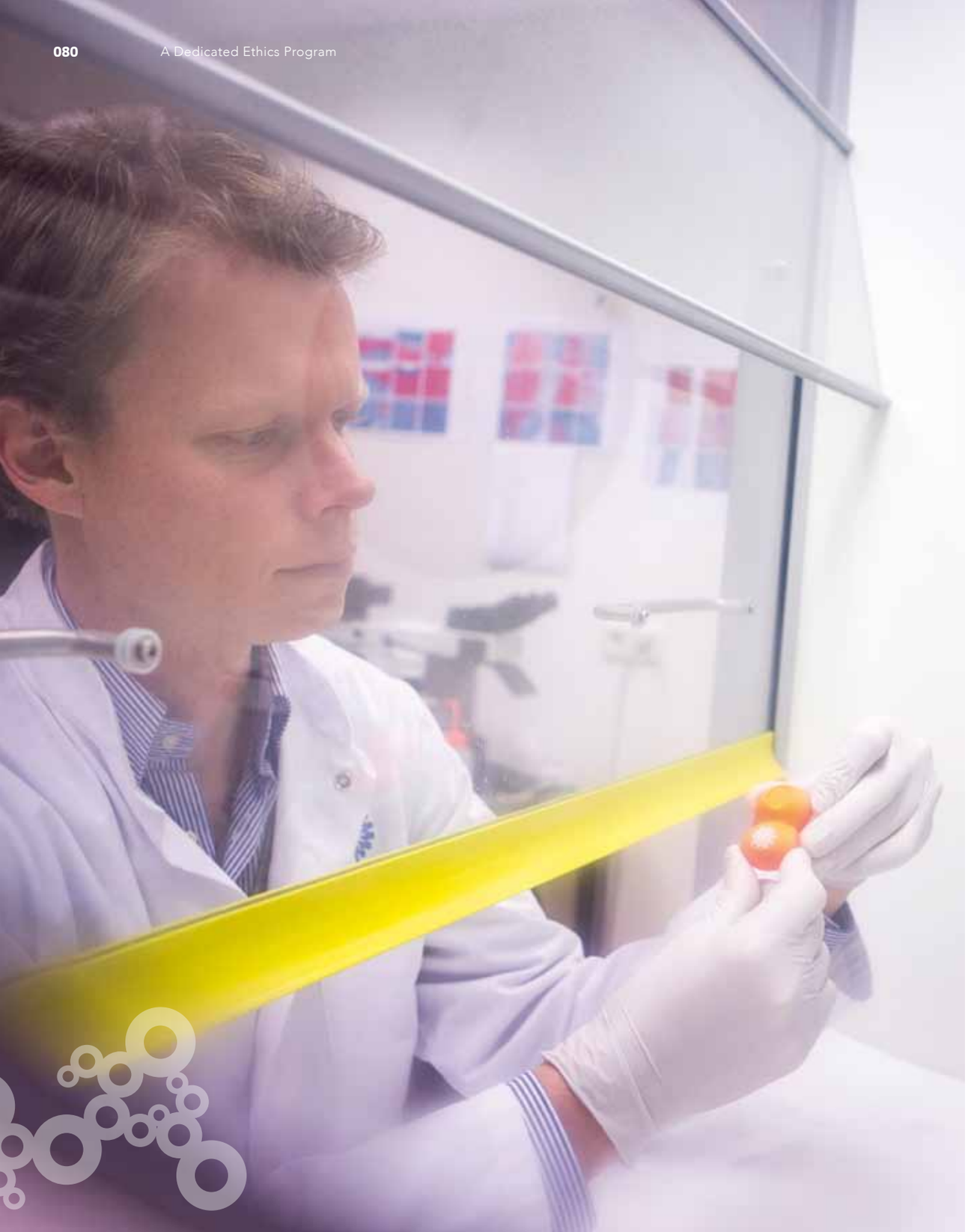
Traditional Surgical Therapy	IMPACT Trial
2 surgeries	1 surgery
Autologous transplantation (using cells from the patient)	Allogeneic transplantation (using donor cells)
Time in between surgeries until transplant: 6-9 weeks	Time during surgery until transplant: 75 minutes
Cost: > €20,000	Cost & recovery time may be significantly decreased

Novel findings

Within the patient-centered theme, musculoskeletal tissue regeneration of RMSC, Professor Daniël Saris and his group established the fundament for furthering the potential of cartilage regeneration as a clinical application. The Saris group and others have determined that a combination of chondrocytes with MSCs improves the chondrogenic phenotype of dedifferentiated articular chondrocytes. Pushing their findings further, Saris and his group improved cartilage regeneration in vivo in a goat model by co-culturing chondrocytes with MSCs. In addition, his group improved chondron isolation efficiency and time [chondrons are functional units of healthy articular cartilage consisting of a single chondrocyte with its surrounding pericellular matrix], by demonstrating that a 40-minute digestion with a Rapid Digestion Protocol was sufficient. The group also determined that a percentage ratio of 10:90 chondrocyte:MSCs, plus a fibrin glue hydrogel, is most effective for significant macroscopic regeneration of cartilage and postulates the idea that the MSCs, rather than re-differentiating into cartilage cells, excrete factors that stimulate existing chondrocyte growth. The allogeneic bone marrow-derived MSCs appear to have a immunomodulatory effect on Graft-vs-Host Disease, since they lack HLA2. These MSCs are cultured in the GMP-accredited Cell Therapy Facility at the UMC Utrecht and biobanked.

Clinical Trial

The UMC Utrecht is the only center in the world currently conducting such a single-step cell therapy trial for cartilage defects containing this cell combination approach. The goals of the trial, in addition to safety and feasibility, include: measurement of the level of the clinical improvement and quality of life; demonstration of cartilage repair; and cost measurement. The trial will be onducted with 35 patients with an 18-month follow-up. Patients in the IMPACT trial are 18-45 years of age with a 2-8 cm^2 defect in the femur condyle or trochlea of the knee. Patients will undergo a single surgery, where damaged cartilaginous tissue is removed, chondrons isolated, then assembled together with allogeneic MSCs from the Cell Therapy Facility within a fibrin glue hydrogel. A mere 70-90 minutes from the initial biopsy to injecting the construct into the patient is needed. Overall, this therapy has the potential to drastically reduce costs and rehabilitation time, due to the single-step surgery, thus having a large impact on quality of life and health related cost-effectiveness. The orthopedic RMSC group at the UMC Utrecht is the first group, worldwide, to safely and efficiently use a mixture of allogeneic stem cells and chondrons for the use of cartilage regeneration.



A Dedicated Ethics Program

A dedicated group of researchers within the RMSC program provides input from an ethics perspective in order to increase societal relevance and opportunities for future translation of research results. The contribution of the medical ethics team aims (1) to identify and evaluate the ethical issues raised by translational research, particularly in regenerative medicine, stem cells, genetics/genomics and biobanking and (2) to develop ethical guidelines for responsible innovation and translation in those fields. The Ethics Program is currently involved in projects on the ethics of translational pluripotent stem cell and the ethics of translational orthopedic regenerative medicine (the latter is described below).

More recently, a collaboration between the ethics group, Vascular Surgery and Nephrology & Hypertension departments at the UMC Utrecht was initiated. These departments have recently conducted a randomized, sham (placebo)-controlled trial (JUVENTAS trial) to investigate the safety and efficacy of a stem cell-based intervention for patients with critical limb ischemia. By comparing the ethical issues in cardiovascular RM with the orthopedic RM research field, this study aimed to find similarities and differences that can contribute to normative guidance for translating orthopedic RM into clinical trials. By evaluating the choices, considerations and experiences of the JUVENTAS team in retrospect, the trial identified several lessons for future stem cell trials, mainly randomized controlled trials (phase II and III).

Work in progress concerns the ethics of sham (placebo) interventions/surgery and the societal aspects raised by the translation of orthopedic RM interventions into the clinic.

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Annelien Bredenoord, PhD - *Associate Professor*
Medical Ethics
Julius Center, UMC Utrecht

Everbody has ethical intuitions about biomedical science

"We analyze the ethical issues raised by the rapid developments in translational medicine, particularly in regenerative medicine, stem cells, genetics, and biobanking. How can we translate basic research into the first small trials in humans and then to larger patient groups and ultimately to society? We examine ethics from 'bench to bedside', we usually say. We develop ethical guidelines for responsible innovation and translation, and try to raise ethical awareness in researchers, clinicians, students and society.

We look at new technologies at a very early phase and ideally start the ethical analysis before a medical intervention is used in patients – always in close collaboration with the disciplines and groups involved. Is it ethically acceptable to develop a new technology and under what conditions? Take novel stem cell interventions: when is this technology safe enough to apply in patients, and who decides this? Setting up a clinical trial involves many ethical decisions. Or take biobanks: not many people know that left-over material – human tissues, cells, DNA – is stored in biobanks for medical research. Suppose that researchers want to make an immortal stem cell line: what kind of consent is needed? Or suppose we find a gene in DNA material that is predisposing for breast cancer: should we inform the patient?

Biomedical science evokes all kinds of ethical intuitions in everybody. Novel biomedical technologies run through all domains of our existence: personal, professional, political, philosophical, economic, legal, and so on. Ethics is like football, everybody has an opinion about it. Finding and defining an ethical balance in regenerative medicine is delicate. Regenerative medicine and stem cell research are needed for progress in medical science, but we shóuld involve patients and society. If you don't engage society, you'll never have support for medical innovations."

Sophie Niemansburg, MD - *PhD candidate*
Medical Ethics
Julius Center, UMC Utrecht

Providing guidelines for ethical conduct

"Most research in regenerative medicine is still in the laboratory or animal experimental phase. Eventually that experimental work will be tested in patients in clinical trials. At the Julius Center, I try to identify the ethical issues surrounding such clinical trials. Interventions with living cells for example are more complex than common drugs, and often invasive. Can we ask healthy people for that? Or very sick patients, desperate for treatment? And how, for example, should we select the control group? Is a placebo intervention in their spine, or their heart acceptable? My goal is to provide guidelines for researchers and ethics committees that aim to set up clinical trials for RM interventions. I am working on a flow chart that can help them making decisions. It is an interdisciplinary, developing field I really enjoy working in, in particular because it is so relevant to society."

Michelle Habets - *PhD candidate*
Julius Center, UMC Utrecht

Value of regenerative medicine to society
"I examine the ethical issues that arise in human research using pluripotent stem cells. This is an exciting area, as worldwide there have only been a few trials with such cells. I have interviewed members of the International Stem Cell Forum, scientists, ethicists and policymakers, to learn about the major ethical problems they encounter. One of the aspects I am studying is the concept 'social value'. We want to create stem cell therapies for society; however, people may be harmed while developing them. How much social value is necessary to justify exposing research participants to risks? And how can we assess social value? I just love ethics, because I like thinking about problems that do not really have an answer."

Ethics of translational orthopedic regenerative medicine
The Biomedical Materials IDiDAS consortium develops regenerative medicine (RM) interventions for patients with early disc degeneration. The interventions will consist of injections into the spine of lower back pain patients by minimal invasive surgery, containing biomaterials with cells, growth factors and other stimuli. Early clinical trials are ethically challenging by nature and the addition of RM brings about new considerations: novel approaches (compared to drugs/devices); and invasiveness, combined with features of orthopedic patients (relatively healthy status, the availability of (end-stage) treatments, and strong influence of psychosocial factors). Based on this, we identified three sets of ethical issues that should be addressed when considering initiating early clinical trials: (1) assessment of risks and benefits, (2) designing a study in terms of endpoints and comparator (standard of care or sham intervention), and (3) participant selection.

To assess a physician's point-of-view, we performed in-depth qualitative interviews with 38 experts in the orthopedic RM field to identify the ethical issues they consider before translating RM interventions into clinical research and four themes emerged: (1) risks to study participants; (2) appropriate selection of study participants; (3) setting relevant goal(s) for measuring outcome, varying from regenerating tissue to improving well-being of patients; and (4) the need for evidence-based medicine and scientific integrity, which is considered challenging in orthopedics. The overall attitude towards the development of RM is positive, especially since current surgical treatments for spine disorders lack satisfactory effectiveness, however, respondents stressed that adequately addressing ethical and scientific issues in the translation of RM interventions into clinical research is critical. Incorporating ethical and societal considerations into RM provides an opportunity to stimulate evidence-based practice and to address hype- and profit-driven practices in orthopedics.

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Education

In 2009, we initiated a formalized education plan in the field of regenerative medicine with the establishment of a PhD program. Over the following five years, we developed additional degree programs, elective courses, and summer school courses. Today, education and training in RM is available to all levels of university education in Utrecht. All courses and programs encompass the diversity of this field, and provide a mixture of basic and translational research, novel technologies and clinical application with a focus on both human and animal patients. Courses include visiting (inter)national experts, hands-on practical activities, facilities tours, discussions and networking/social opportunities.

Education level	*Program/Course Name*	*Directors (D) / Coordinators (C)*
All	Lunch Seminar Series	Debby Gawlitta, Koen Braat, Joost Fledderus, Sarah Opitz (C)
PhD Progam	Regenerative Medicine Utrecht PhD Program	Wouter Dhert, Paul Coffer (D) Sarah Opitz (C)
PhD Program	NWO Graduate Program Grant	Wouter Dhert, Keita Ito (D) Debby Gawlitta, Joost Fledderus, Sarah Opitz (C)
Master's Program	RMT (RM and Technology)	Wouter Dhert, Keita Ito (D) Debby Gawlitta, Joost Fledderus, René van Donkelaar, Anita Driessen-Mol (C)
Master's Program	Biofabrication for future manufacturing *Expected start 2015*	Jos Malda, Juergen Groll (University of Wuerzburg), Dietmar Hutmacher (Queens-land University of Technology, Gordon Wallace (University of Wollongong) (D)
Bachelor Elective	Biomedical Sciences Program	Niels Geijsen (D), Joost Fledderus, Koen Braat, Simon Mastbergen (C)
Bachelor Elective	Medicine Program	Jacqueline Alblas, Joost Sluijter (D)
Bachelor Elective	Veterinary Medicine	Bart Spee (D)
Beginner Master	Regenerative Medicine Summer School Course	Bart Spee, Jos Malda, Koen Braat (D) Jetze Visser, Sarah Opitz (C)
Advanced Master	3D Printing & Biofabrication Summer School Course	Jos Malda (D), Jacqueline Alblas, Ferry Melchels, Jetze Visser Sarah Opitz (C)

RM Lunch Seminar Series

A monthly seminar series is open to the community and provides insight into the latest developments in this field. In addition to internal speakers, national and international guest speakers are invited to share their work.

Past invited guest speakers include, for example:

- Dietmar Hutmacher, Queensland University of Technology, Australia;
- Robert Chamuleau, Amsterdam Medical Center;
- Dennis McGonagle, University of Leeds, UK;
- Stuart Forbes, University of Edinburgh, UK;
- Vincenzo Cardinale, Sapienza University of Rome, Italy;
- Tonia Vincent, University of Oxford, UK;
- Ans van Pelt, Amsterdam Medical Center;
- Joyce Bischoff, Harvard Medical School, USA;
- Wayne McIlwraith, Colorado State University, USA.

PhD Program: Regenerative Medicine Utrecht

Graduate School of Life Sciences
Utrecht University

We're inspiring high-level multidisciplinary and translational education by integrating basic researchers and clinicians in human and veterinary medicine. PhD students are trained in the field of RM over a broad range of fundamental and translational research, underlying technologies, and clinical application. This program is a joint effort across Utrecht University, UMC Utrecht, and Hubrecht Institute.

Requirements

- BA/BS and/or MSc in Life Sciences; Medicine; Veterinary Medicine; Technical MSc program;
- Topic of PhD in the field of RM.

Program outline

- 4 years and start date is anytime;
- Courses;
- Seminar series;
- Theme days;
- Retreat.

Unique to program

- Home to the only veterinary medicine faculty in the Netherlands;
- Largest community of RM students in the Netherlands;
- Students are diverse: physicians, veterinarians, engineers, biologists, pharmaceutical scientists, informaticists, ethicists;
- All communication is in English.

NWO Graduate Program Grant

This new joint venture between Utrecht University/UMC Utrecht and Technical University Eindhoven (TU/e) was awarded in 2013. Funding from the Netherlands Organisation for Scientific Research (NWO) supports 4 outstanding PhD students for 4 years.

Requirements

- Master's students in their last year;
- Completed at least one internship;
- Motivation to conduct research in more than one discipline.

Program outline

Students are included in the RM PhD program with a specialized track for this program grant.

Unique to this program

- Students have the freedom of choice to select their PhD advisor and research topic (both must be within the scope of the advisor's current field);
- Students are required to write their own PhD proposal;
- Projects must integrate more than one discipline (sciences:technology: medicine);
- (Co)promotors must represent the vision of this program grant (eg, from two different disciplines).

Master's Program: Regenerative Medicine & Technology (RMT)

A joint degree program between Utrecht University and Technical University Eindhoven (TU/e).

This programs aims to train scientists at the intersection of biomedical science and technology, with a focus on clinical application. It combines the expertise and resources of both universities with particular attention to the application of new technologies in the field of RM.

Requirements

- Dutch or equivalent BSc in biomedical sciences or biomedical engineering;
- Explicit interest in the field of RM;
- Proficiency in written and spoken English.

Program outline

- Introductory course;
- Elective courses (eg, Mechanisms of disease; Image processing; Understanding drugs; bioinformatics);
- Minor research project;
- Writing assignment;
- Major research project.

Unique to this program

- Students enroll at either Utrecht University or TU/e;
- Students can take courses at both universities;
- Students can conduct research at both universities.

Master's Program: Biofabrication

The first formalized master-level degree program in the world is a joint effort between Utrecht University/UMC Utrecht; Queensland University of Australia; University of Wollongon, Australia; and University of Würzburg, Germany. Its aim is to train and education students in the emerging new field of biofabrication.

Program expected to begin in 2015.

Unique to this program

Students spend 1 year each in Australia and Europe, at two participating universities.

Bachelor Electives

Biomedical Sciences, Medicine and Veterinary Medicine Programs
These elective courses address the different aspects of the RM field, focusing on both fundamental research, as well as clinical applications. Topics discussed range from stem cells (embryonic and adult) to tissue engineering to ethical aspects of stem cell therapy. Courses include discussion-based lectures, practical activities, excursions, workshops, self-study, exams.

Summer School Courses

Regenerative Medicine and 3D Printing & Biofabrication Courses
The Utrecht Summer School is the largest summer program in Europe, with more than 2000 international students attending courses. The course in RM provides students with an overview of the field; in particular to current activities in Utrecht and afford students insight into the truly interdisciplinary arena of biomedical research, technology and medicine. The 3D Printing & Biofabrication course provides students with hands-on experience in 3D printing, and addresses different technologies and challenges in this emerging area.

For detailed information: www.utrechtsummerschool.nl

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Training the Next Generation

Education is a central focus of RM in Utrecht. We're fortunate to have the expertise and resources to teach, mentor and enable young investigators to develop into independent researchers and clinicians. With the patient as our end-point, we believe that significant steps forward are made when scientific research and clinical value flourish together.

The majority of members with the RM community in Utrecht actively volunteer their time for educational activities, through teaching, organizing, mentoring. We've highlighted a few examples of people who have integrated education into their daily routine.

Jos Malda, PhD - *Head, 3D Biofabrication Facility*
Orthopedics
UMC Utrecht
Faculty of Veterinary Medicine, Utrecht University

"Three-dimensional printing is a ground-breaking technology that's developing rapidly. We use it to create plastic pre-operative models that doctors can practice on, or patient-specific moulds that serve as a guide during operations. We can also print implants from plastics or metals, like a jawbone, or a hip.

Our research focuses on developing bio-ink that we can use to print living cells. We can create 3D constructs with different tissue types, layer-by-layer and in the future, we may be able to replace diseased tissue with biofabricated constructs.

As pioneers in this field, we're building a facility for 3D bioprinting, where we'll centralize our knowledge and the equipment for biofabrication. This facility will be a breeding ground for both research and education.

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I completed my post-doc at Queensland University of Technology in Australia, and have had a good working relationship ever since. Together with the University of Würzburg in Germany and the Australian University of Wollongong, we've received European and Australian grants to set up the first international master's degree program for biofabrication (awarded 2013).

The BioFab Master's Program will comprise two years and will be an innovation in global education. In the first year, students will attend basic courses and practical training at their host university. In the second year, they'll carry out a research project at one of the other universities. They'll receive a double master's degree from both universities.

These students will learn all aspects of biofabrication: biology, robotics, material science, and chemistry. There will be a strong need for people who excel in these different skills. In the next four years, we'll begin by enrolling 10 students in each of the four universities.

To make research viable for the long term it's important to educate the next generation of scientists. This will lead to better research, more grants, and better education. The UMC Utrecht and the three joining universities share the same philosophy. We all want to do excellent science, not solely focused on high impact scores, but even more so, on science that can make a difference for the patient."

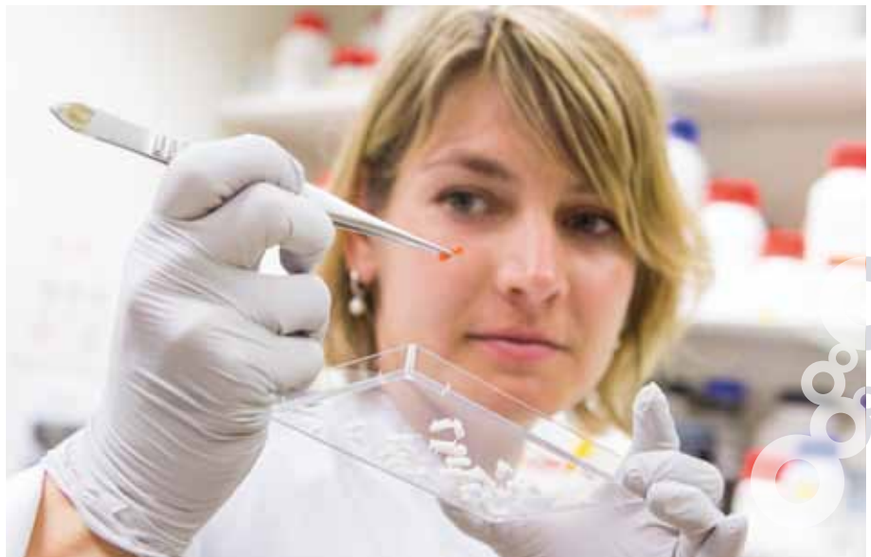
Debby Gawlitta, PhD - *Assistant Professor*
Orthopedics, moving to Oral-Maxillo-Facial Surgery
UMC Utrecht

Joost Fledderus, PhD - *Research Fellow*
Nephrology & Hypertension
UMC Utrecht

We coordinate the Master's Program, Regenerative Medicine and Technology, in collaboration with Eindhoven University of Technology. It's unique, because it focuses on both the biomedical and the biotechnical fields.

Regenerative medicine is becoming more technical every year, involving 3D-printers, bioreactors, biomaterials, and hydrogels. Therefore, students with biomedical or biotechnical backgrounds are encouraged to enrol. The program hosts a variety of experts who provide a broad overview of the entire field, and the students are required to write a research proposal in groups. The result is an attractive, coherent, high quality program.

The convergence of two fields will push each separate field forward. Our research interests are good examples. "As a biomedical engineer, I'm creating bone in the lab," says Debby, "and want to grow vessels in this tissue. Joost easily complements my research with his knowledge and experience." Joost agrees, adding, "I'm interested in mechanisms that improve vascular health. It's exciting to apply this to different areas of biomedical research."



We also organise lunch seminars for the RM community and we recently received a grant from the Netherlands Organisation for Scientific Research (NWO) to set up the NWO Graduate Programme in RM. This is aimed at recruiting four excellent PhD students from biomedical, medical or technical backgrounds. From all applicants, a committee with people from Eindhoven and Utrecht will select eight top students by the end of 2014. They'll meet the principal investigators within our program and "rotate" in three different labs. With the principal investigator of their choice, they'll write their PhD research proposal. The best four will be awarded funding in 2015. We've created an educational program that we, ourselves, would have wanted to follow. And now our own research benefits: the master's program attracts many students who want to do an internship, or a PhD. Ultimately, we want to train the best possible scientists to work in our labs.

Koen Braat, PhD - *Assistant Professor*
Cell Biology
UMC Utrecht

Bart Spee, PhD - *Assistant Professor*
Faculty of Veterinary Medicine
Utrecht University

Two years ago we started the Summer School program. In an intense week-long course, we give advanced bachelor and master students a broad overview of the field of regenerative medicine. We start with a topic that always leaves a big impression, called 'meet the patient'. Patients and their physicians tell their

story, for example someone who has received a life-saving bone marrow transplantation, or someone who was the first to receive an experimental stem cell-based therapy to regenerate damaged cartilage in his knee.

Students from all over the world come to Utrecht University to follow this course – and they're really enthusiastic. They learn about fundamental principles in the morning, and how this can be applied to the clinic in the afternoon. Invited lecturers and we, ourselves, teach about stem cells, tissues, organs, and we introduce them to practical work. In addition, we invite scientists from companies that make cells or scaffolds used in tissue engineering to come and tell what they do.

We both lead lab practicums, based on our own research. In the lab, we guide students through the process of designing and conducting experiments of making bone from mesenchymal stem cells and isolating cartilage to studying the effects of a particular factor, respectively. These hands-on activities are another highlight of the course.

We've also compiled three bachelor elective RM and stem cell courses, for veterinary students, for students in biomedical sciences, and for medicine students. The set-up is similar to that of Summer School.

We enjoy teaching a lot, especially when students are enthusiastic. It's contagious. The elective courses attract motivated students, so there are lively discussions. This is an important aspect for us - it sharpens our own minds, too. We can also quickly identify excellent students and can recruit them to do a master's internship or PhD in our labs.

Viability

We have, in a relatively short time span, grown tremendously - from non-existence in 2006, into a program with high earning capacity, scientific output, national and international visibility and campus-wide education and training. Our rapid growth and success builds upon the energy and enthusiasm of a relatively young group of PIs and their members dedicated to “making a difference” in scientific and educational innovation. In addition, our infrastructure is excellent and will be further strengthened with new investments by Utrecht University and the building of an RM Center with funding from the UMC Utrecht.

Our community and programs are thriving. Nationally, our community contains the largest critical mass in this field. We have partnerships and dynamic interactions with every Dutch University Medical Center and with all three technical universities, both at the scientific and educational levels. In addition, we have extensive industrial collaborations with SMEs and large pharmaceutical companies, for example CellCoTec (cellular regeneration of cartilage), DSM Biomedical (biomaterials), Philips Healthcare and Research (imaging), Progentix (osteoconductive materials and bone regenerative surgery), Sanofi/Genzyme (cellular regeneration of cartilage), Smith & Nephew (advanced healing technologies), SYMOCHEM (chemistry), Tigenix (cellular regeneration of cartilage), XelTis (biotoxicology and Quality control), and Xpand (biomaterials and bioreactors). We’re also members of many public-private partnerships and nation-wide consortia, such as the Biomedical Materials program (BMM), the Netherlands Institute for Regenerative Medicine (NIRM) and the SmartMix-program, Translational excellence in Regenerative Medicine (TeRM), and ZonMW Adult Stem Cell Program.

BM bone marrow **CLEM** correlative light electron microscopy **CLI** critical limb ischemia **EPCs** endothelial progenitor cells **ESCs** embryonic stem cells **HSCs** hematopoietic stem cells **HSCT** hematopoietic stem cell transplant **iPSCs** induced pluripotent stem cells **MSCs** mesenchymal stem cells **RM** regenerative medicine

Internationally, we coordinate and participate in large consortia, including EU-funded projects. Examples of European Commission FP7 projects include EU-AIMS (iPSC technology and neuroregeneration for autism), HydroZONES (bioactivated hierarchial hydrogels as zonal implants for articular cartilage regeneration), PRINTCART (bioprinting of novel hydrogel structures for cartilage tissue engineering), REBORNE (regenerating bone defects using new biomedical engineering approaches), SYSCILIA (study cilia within the context of genetic disease), and WntsApp (integrated approach to study Wnt signaling in stem cells and cancer). In addition, the BIOFAB (Biofabrication for future manufacturing) program was recently funded by the Life Long Learning program of the EU EACEA (Education, Audiovisual and Culture Executive Agency). On an individual basis, we're engaged in collaborations around the globe, from China and Singapore to Australia to the USA and Canada to Europe.

Talent

In 2013, we recruited five established investigators to Utrecht: Catherine Robin (Hubrecht), who developed a new technique for the first-time observation of the first blood stem cells in mouse embryo and Harrie Weinans (UMC Utrecht, joint position between orthopedics and rheumatology) brings expertise in mechano-biology and investigation into the etiology of osteoarthritis. In addition, three cardiovascular-based investigators: Caroline Cheng (UMC Utrecht, cardiology) focuses on vessel formation; Eric Duckers (UMC Utrecht, cardiology) brings extensive experience in the area of translating research findings into clinical trials; and Eva van Rooij (joint between UMC Utrecht, cardiology and Hubrecht), who studies microRNAs and heart disease.

Catharine Robin

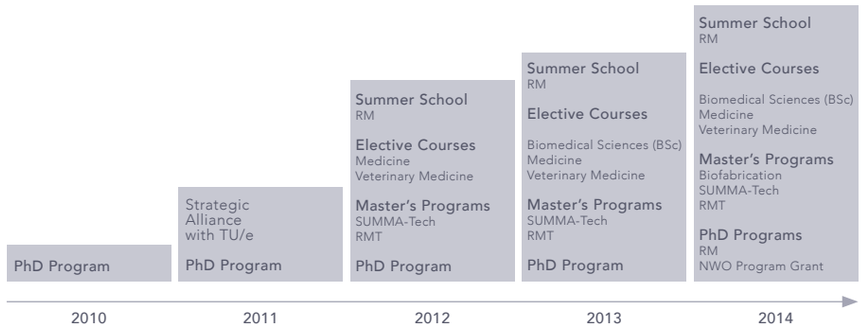
Harrie Weinans

Caroline Cheng

Eva van Rooij

Our educational programs have expanded considerably and are indicative of our investment in the next generation of investigators. In less than five years, we've created an environment that inspires and fosters young talent and enables them to pursue careers as independent researchers and clinicians.

Collectively, our diverse, far-reaching initiative in the field of regenerative medicine is flourishing in Utrecht: we're operating in the entire range from 'bench to bedside'; we're connecting basic scientists with engineers with physicians at early stages of research; and we're continuously striving to improve evidence-based medicine in order to capitalize on the potential of this very promising field.



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Center for Regenerative Medicine

In 2015, the Hubrecht Institute will double in size with the addition of a new research building. The UMC Utrecht will occupy two floors, with the intention of expanding the cooperation initiated in 2008 between the Hubrecht and the UMC Utrecht. In particular, the regenerative medicine program will open a new center in this space, which will house many researchers, shared equipment and the bio-fabrication facility. In Spring 2014, the first pile of the new building will be placed and we expect the building to be ready in August 2015.

This new center for regenerative medicine will bring together a majority of the investigators in this diverse community under one roof. We plan to operate with flex-space and with a culture of cooperation and openness. We anticipate that daily interaction between fundamental scientists, engineers and clinicians will stimulate creativity and new approaches to bringing regenerative medicine in the form of personalized care rapidly to our patients.

Image courtesy of OPL Architecten

Colophon

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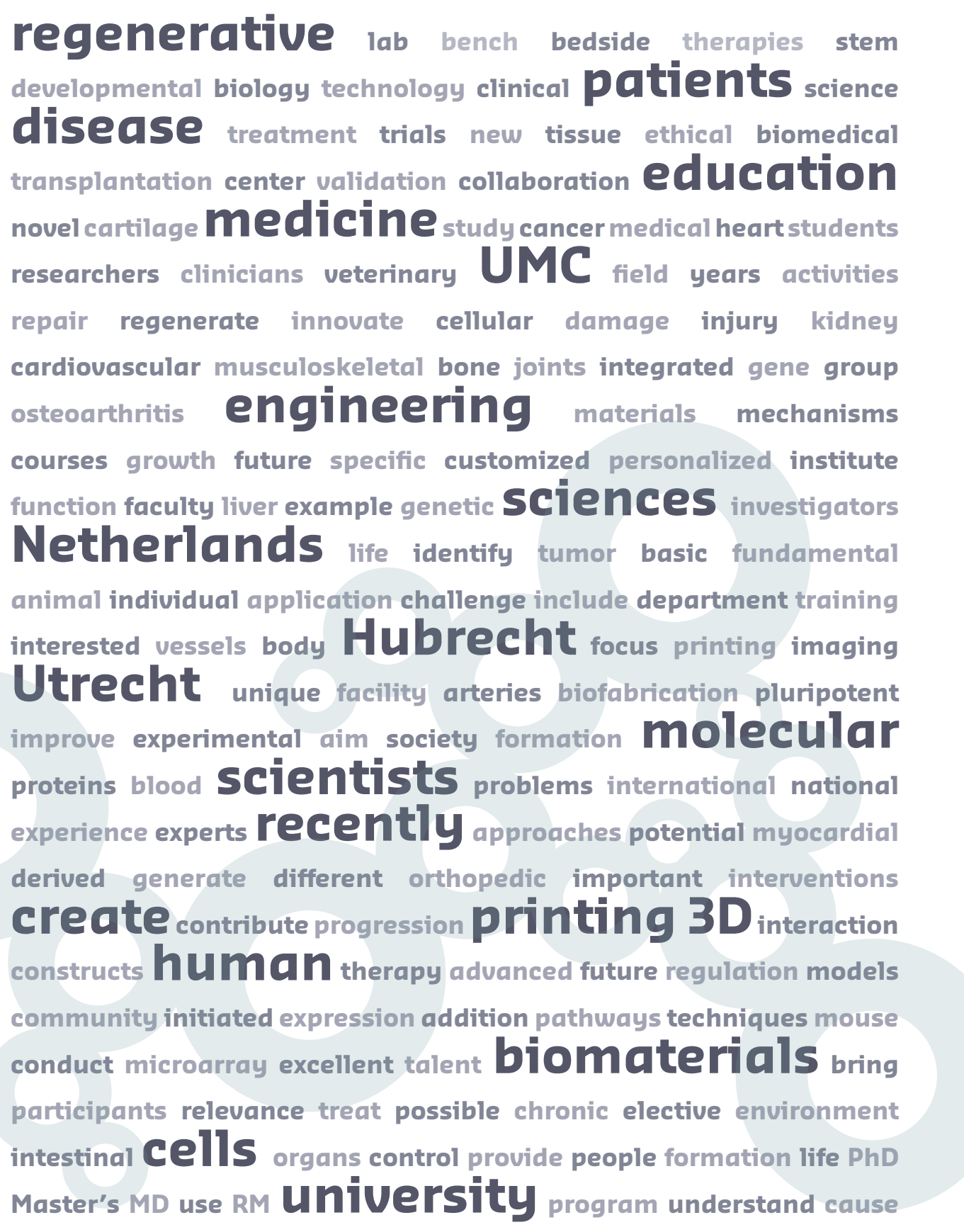
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Regenerative Medicine Utrecht

This publication aims to give you an overview of regenerative medicine, from bench-to-bedside, in Utrecht, The Netherlands. This diverse community cultivates a culture of innovation and excellence, inspiring talented scientists and clinicians. Most importantly, our efforts focus on translating biomedical research into clinical benefit for our patients and society.

This publication has been made possible by

regenerative medicine utrecht

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