University Medical Center of the University of Groningen

Research portfolio

Research Institutes and Research Programmes

UMCG's multidisciplinary Research Programmes are organised in five Research Institutes. Each Institute covers a specific part of the UMCG research area.
By establishing numerous international research projects and strategic alliances over the past, research within the Institutes bridged national boundaries. Especially for the UMCG focus "Active and Healty Ageing" international collaboration is required and prepares the UMCG to contribute to this global challenge. For every UMCG Research Programme the relevance for Healthy Ageing is defined.

Regarding the training and education of future scientists (MSc and PhD) the five Research Institutes collaborate in the Graduate School of Medical Sciences assuring the incorporation of state of the art scientific know-how.

1. **GUIDE Institute**: Chronic Diseases and Drug Exploration
2. **BCN-BRAI**N Institute: Behavioural and Cognitive Neurosciences
3. **SHARE Institute**: Health Research and Epidemiology
4. **W.J.Kolff Institute**: Biomaterials
5. **CRCG Institute**: Fundamental, Clinical and Translational Cancer Research

Some of the Research Programmes are ***Platform Programmes***, embedded in and supporting all five Research Institutes.

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RESEARCH INSTITUTE GUIDE:
Chronic Diseases and Drug Exploration

1. Biopharmaceuticals, Discovery, Design and Delivery (GUIDE-BDDD)

Programme leaders: prof. dr. H.W. Frijlink, prof. dr. K. Poelstra

Mission

The BDDD Division explores innovative approaches oriented towards the early phase of drug development up to the use of these approaches in practice. The focus is on fundamental research towards the discovery and design of bio-pharmaceuticals that over the past decades have grown enormously in importance as medicinal products. Moreover research is performed on the design and administration of small molecular entities. The division uniquely combines (translational) research on drug targeting, drug delivery, biopharmacy and pharmacokinetics, from bench to bedside. Furthermore, fundamental aspects of biotechnological production processes and the design, application and production of dosage forms are studied.

Description of the Programme

The sub-programme Pharmaceutical Biology has as its central aim the study of the living cell as a source of pharmaceutically important products. Natural and directed diversity of micro-organisms, plants and plant cells are explored as a source of natural products, including protein therapeutics.
The attention of the group has shifted from natural product analysis to natural product synthesis with a strong focus on enzymes as biocatalysts. Prof. Poelarends is studying enzyme promiscuity and he has demonstrated that this property can be explored to evolve novel biocatalysts with unique synthesizing capabilities. During the last reporting period a unique TBOA biosynthetic route consisting of only 3 steps was invented as an alternative to the 15 steps classical chemical synthesis pathway.

The sub-programme Pharmaceutical Gene Modulation focuses on the development of systems for the specific delivery and regulation of genes. These systems should lead to totally new therapies treating the fundamental cause of a disease and not only the symptoms.
The subprogram gene therapy (Haisma) focusses on the application of (viral) vectors for gene therapy of cancer and inflammatory disease. First, TRAIL and derivatives thereof are used for selective destruction of cancer and inflammation-inducing cells. Second, prodrugs in combination with targeted enzymes are explored for selective cancer chemotherapy.
The subprogram chemical biology (Dekker) involved the chemistry-based development of small molecule inhibitors and detection methods of cellular enzymes to study their functions. Ultimately, this research will open up opportunities for drug discovery and diagnosis aimed at epigenetic regulation and lipid signalling in inflammatory diseases.

The sub-programme Pharmacokinetics, Toxicology and Targeting explores innovative drug delivery tools for the cell-specific targeting of drugs and therapeutic proteins. Specific peptides and protein fragments are studied as homing devices and tools for improving pharmacokinetics. This is combined with research on the in vitro prediction of drug metabolism, transport and toxicity, as well as with pharmacokinetic modelling and simulation.

The incorporated discipline of Pharmaceutical Immunology (Melgert) explores the pharmacokinetics and toxcicity profiles of therapeutic proteins and explores the immune system for novel therapeutic proteins and drug targets. In addition, the study of metal-based compounds with possible therapeutic applications or as chemical probes to investigate protein functions in biological systems is explored in a new research line within the Department. With these new disciplines, the focus of the subprogramme PTT fully lies on the development of innovative drugs (small molecules and biopharmaceuticals) and the development of new pharmacological tools to study the pharmacokinetic and toxicology profiles of drugs in vitro, in vivo and in silico.

In order to guide the early stage drug research towards patient therapies a crucial contribution comes from the sub-programme Pharmaceutical Technology and Biopharmacy that performs research in the field of dosage forms and their interaction with the living organism. Basic research on the design and development of novel and improved drug delivery systems is combined with research on new processes, equipment and technologies for the production of (biopharmaceutical) dosage forms and their performance. The position of the BDDD programme within pharmaceutical research is schematised below.
With the appointment of Dr. Olinga a new line focusing on the translational aspects of drug research is added to the scope of activities. With this addition the group will strengthen its capacity to bring new drug products from the laboratory into the clinic. Already now the sugar glass technology and the oral targeting research lines of the group are benefiting from this activity.

Relevance for Healthy Ageing

Research on new drugs is by definition highly relevant to the aging population. On average more than 70% of the drugs used in society are used by the elderly. Moreover, many of the diseases that are the focus of the research in the programme are age-related; examples are cancer, COPD, fibrosis, Parkinsonism and influenza, all examples of diseases that become more and increasingly problematic in an aging population.

Principal Investigators

Prof. dr. GMM Groothuis
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2. Center for Liver, Digestive and Metabolic Diseases (GUIDE-CLDM)

Programme leaders: prof. dr. H.J. Verkade, dr. S.C.D. van IJzendoorn

Mission

The increasing prevalence of obesity, diabetes, dyslipidemias, (non-alcoholic) liver diseases and other metabolism-related disorders, particularly with increasing age, is emerging as a major burden on public health care. These disorders may have an extended subclinical course, before the actual diagnosis is made, and they are an important cause of morbidity due to their causal role in liver, digestive and cardiovascular diseases, cancer, and other age-related chronic diseases. Understanding the (patho-)physiological and developmental basis of these diseases and, reciprocally, defining interventional targets to maintain health, is necessary for designing novel strategies to combat or deal with the consequences of these diseases. The aim of the research group is to better understand, diagnose, and treat acquired and inborn diseases that are related to the perturbation of metabolism and/or flow of metabolites.

Description of the Programme

Because of the complexity of (chronic) diseases that involve metabolism, the programme takes a multidisciplinary approach that integrates (computational) systems biology with basic and clinical research at the (inter-)organ, (sub)cellular, and molecular level. Relevant mechanisms will be studied during life span, including prenatal life, to understand the contribution of metabolic programmeming to these diseases. Relevant mechanisms will be studied that control the transport and processing of proteins, lipids and metabolites, how these contribute to health or, when perturbed, human disease. Cellular mechanisms will be investigated to prevent and/or treat digestive (liver and intestine) organ damage in acute and chronic disease. Novel approaches will be provided to prevent and treat age and obesity related metabolic disorders. Novel hypotheses will be generated using human genetics and systems biology and validated with advanced mouse models. The programme PIs contribute the necessary variety of complementary methodology and expertise.

Relevance for Healthy Ageing

A healthy metabolism is important for healthy ageing. Metabolism and the ageing process are tightly correlated: metabolism affects the ageing of an organism, while the metabolic system declines with increasing age. The prevalence of metabolic syndrome, of which obesity, hyperglycemia and dyslipidemias are core components, increases strongly with age. Metabolism-related and chronic diseases often display a significant period of mostly asymptomatic or non-specific presentation and may easily go undiagnosed. A better understanding of the pathogenesis of metabolism-related diseases and an early detection, intervention and prevention leads to a prolonged healthy life span.

Principal Investigators

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Prof. dr. F Kuipers

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Dr. AJA (Bart) van de Sluis
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Prof. dr. MH Hofker
Prof. dr. AK Groen
Prof. dr. AJ (Han) Moshage
Prof. dr. DJ Reijngoud
Prof. dr. UJF Tietge
Prof. dr. KN Faber
Dr. HM van Dullemen
Dr. DPY Koonen

3. Critical Care, Anesthesiology, Peri-Operative and Emergency Medicine (GUIDE-CAPE)

Programme leaders: dr. A.M.G.A. de Smet, prof. dr. M.M.R.F. Struys

Mission

For poorly understood reasons vulnerable patients (such as the very young and the elderly) have marked susceptibility to pathological conditions (such as infection, trauma and cancer) and to the adverse consequences of the process, which are required to manage these problems. To optimize the possibilities of 'Healthy Ageing' in these vulnerable groups, much further research is required. Our desire is to focus on restoration and maintenance of vital homeostatic functions by studying the pathophysiology underlying life threatening events and the consequences of pharmacological and other interventions during emergency care, surgical procedures and critical care. This requires a multi-system approach, since aging, disease, drugs and surgery appear to result in interacting (and mutually amplifying) impairments in the function of the cardiovascular (heart, large and small vessels), respiratory, central and peripheral nervous, renal, endocrine and immune systems.
CAPE members have clinical interactions with a large proportion of all the patients treated at the UMCG. The departments of emergency medicine ("CSO" and "MMT"), anesthesiology and pain management, Operating room organization ("OZO" and "ODBC"), critical care and the planned acute care department are relevant clinical partners for CAPE. To promote translational science we plan to nurture existing links with research groups in vascular medicine, neuroscience, pain medicine, medical microbiology, pharmacology and pharmaceutical science (Figure 1). Essential national and international collaborations are also in place.

Description of the Programme

The purpose of CAPE research is to reduce mortality and especially morbidity among high-risk patients undergoing emergency care, major surgery and critical care. This requires an improved understanding of the pathophysiology and pharmacology of the altered body homeostasis resulting from the primary acute problems and from the adverse consequences of the interventions required for the primary problem. Optimizing the restoration and protection of the homeostasis will allow patients suffering from injury or disease to overcome this critical episode

with fewer long-lasting sequelae that could negatively influence the natural progress of their healthy aging. Consequently, CAPE will focus on three main strategies:

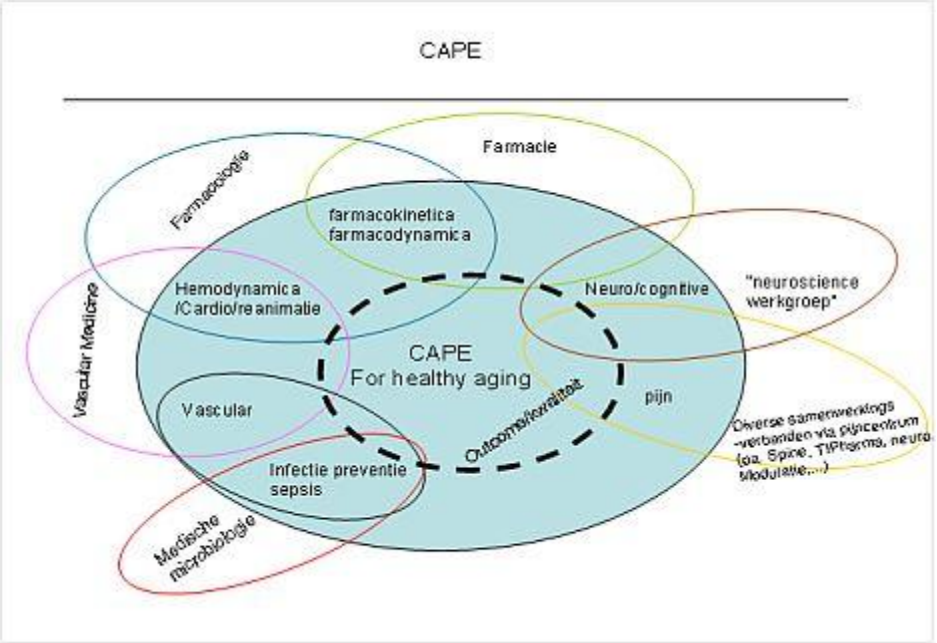

Figure 1: CAPE structure including established projects and collaborations.

1. Understanding the pathophysiological changes occurring during emergency, perioperative and critical care treatment.
2. Understanding the pathophysiological consequences of different interventions (such as drug treatments) used during emergency, perioperative and critical care; and identifying and validating new pharmacological and interventional therapeutic strategies.
3. Finding drugable targets is the main purpose.
   To realize these goals, CAPE will continue and co-ordinate existing preclinical, translational and clinical research programmes within the emergency medicine, anesthesiology, and critical care departments at the UMCG. A common, overarching and critical theme is the multiple harmful immunological, metabolic and inflammatory changes caused by and/or amplifying the impaired homeostasis. Most of these changes are induced and/or manifest in organ dysfunction. Therefore, CAPE will also study the alterations of vascular physiology and tissue oxygenation with a focus on cardio-respiratory, cerebral, endocrine (glycometabolic) and renal function (electrolyte imbalance and lactate).

   In parallel with studies of the underlying mechanisms, we will study pharmacological treatments and targets for organ support, restoration of homeostasis and optimal long-term outcomes. Practically, CAPE will focus on the targets of hypnosis and sedation and the long-term consequences thereof, the balance between nociception and antinoception and the influence of this balance on acute and chronic pain, improved monitoring of organ function, improved glycemic control and optimization of organ perfusion by cardiovascular support (drugs and fluids), and the control of life-threatening infectious diseases (prevention/treatment).
   To achieve these goals, CAPE will apply existing expertise, strategies and methodologies. Mathematical and computer modelling expertise (pharmaco- and physiometrics) are required to support the understanding of organ function, and pharmacological behaviour. Preclinical work and animal research is ongoing in collaboration with other UMCG research schools (e.g. Vascular Medicine, Clinical Pharmacology, Nuclear Medicine, Imaging). Using new and existing

ideas, translational projects will investigate therapeutic targets in patients and volunteers. For volunteer research, CAPE will benefit from established relationships with local Phase I units (PRA and QPS) and various (inter-)national collaborations. For patient studies, observational and interventional studies will apply sophisticated technologies available to the departments connected to CAPE. CAPE has developed a professional GCP-level computer-based data management system to collect and time-synchronise high-frequency datastreams from multiple high-end monitors of organ function.

Finally the structure and composition of CAPE facilitates outcomes research. The members come from various UMCG clinical departments involved in the care of large numbers of patients. For much of this care, large amounts of data are recorded in electronic databases, facilitating studies of the quality of patient care and correlations with outcome. The leadership roles of the members in their own departments makes it easier to implement new findings in routine clinical practise, and then study the influence of these practice changes on important outcomes, as well as providing a means to screen for rare, unexpected unwanted sequelae.

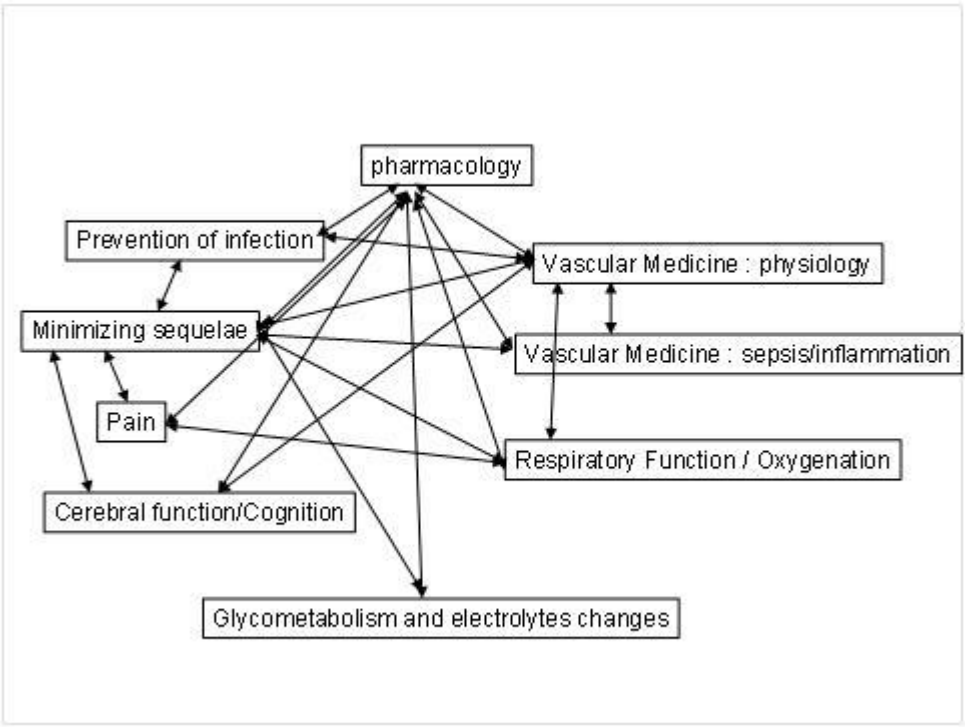

Figure 2 : multiple cross links exists between the CAPE projects.

Relevance for Healthy Ageing

The goals of CAPE match perfectly with the research theme “Healthy Aging” that has been selected by the University Medical Center Groningen and University of Groningen. On average, Dutch people are living longer; but an increased lifespan does not imply a prolonged “healthspan” as ageing is associated with chronic, slowly progressing degenerative diseases, and also with increased risks of acute changes in health. Many patients presenting to the UMCG require intensive care, and/or anesthesia for surgical procedures to treat acute and chronic problems, presenting our group with challenges and opportunities to influence outcomes and improve the chances of healthy aging. Until a few decades ago, the focus of much anesthesia and intensive care research was on short-term outcomes such as survival beyond an acute illness or procedure. As a result, short-term outcomes have generally improved

significantly (an exception is survival after severe sepsis). Recent research indicates that choices made during acute care, critical care and anesthesia for surgery, may have a significant impact on important long-term outcomes, such as long-term survival, cancer recurrence, cognitive function, post-traumatic stress disorder, renal function, and the incidence of chronic pain. Thus, our goals fit in well with the 'Healthy Aging' theme, since our aims are to maintain and extend wellbeing and welfare by limiting the impact of interventions for acute and chronic problems.

Principal Investigators

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Dr. MWN Nijsten
Prof. dr. TWL Scheeren
Prof. dr. JG Zijlstra
Dr. MCJ Kneijber

4. Groningen Institute for Gastro-Intestinal Genetics and Immunology (GUIDE-3G)

Programme leaders: prof. dr. R.K. Weersma, prof. dr. C. Wijmenga

Mission

Our mission is to build an interdisciplinary research group and to develop a framework integrating clinical data and knowledge on environmental risk factors, genetics, genomics, computational sciences and functional studies. The framework we propose here could be applied to any common complex disease and will transform the process of investigating the mechanisms underlying many common diseases. Our focus is on diseases of the gastrointestinal (GI) tract, which has already been the subject of successful multi-disciplinary research within the UMCG/RUG. Hence the current interdisciplinary research group will consist of PIs from different departments, with different areas of expertise, and with a proven and excellent track record in the field of GI diseases.

We will build on previous work in which we have identified genetic risk factors for celiac disease, Crohn's disease and ulcerative colitis by genome-wide association studies (GWAS). These GWAS loci are key signposts pointing to systems and pathways that, when altered, can result in disease. Yet the nature of many of these disease risk genes and their function is so far unknown. We have to take the next step which will move the research field in an entirely new direction: we aim to investigate the fundamental disease mechanisms using predisposing genetic variations as crucial starting points. We will take advantage of unbiased high-throughput technologies to develop an understanding of the underpinning of the genetic susceptibility, by

translating genes to function and placing them in functional 'networks' and to perform functional studies to elucidate how genetic risk variants will lead to disease.

Description of the Programme

Our mission is to build an interdisciplinary research group and to develop a framework integrating clinical data and knowledge on environmental risk factors, genetics, genomics, computational sciences and functional studies. The framework we propose here could be applied to any common complex disease and will transform the process of investigating the mechanisms underlying many common diseases. Our focus is on diseases of the gastrointestinal (GI) tract, which has already been the subject of successful multi-disciplinary research within the UMCG/RUG. Hence the current interdisciplinary research group will consist of PIs from different departments, with different areas of expertise, and with a proven and excellent track record in the field of GI diseases.

We will build on previous work in which we have identified genetic risk factors for celiac disease, Crohn'sIn this programme we aim to make major breakthroughs in our understanding of GI diseases by bridging the gap between the disease genotypes and the disease phenotypes. The chronic inflammatory intestinal diseases celiac disease and IBD (Crohn's disease and ulcerative colitis) are both characterized by a dysregulated immune system in response to gluten or to the intestinal flora in a genetically predisposed host. We will work on the crossroads of three of the major research topics in science at the moment namely:

1. the genetics of complex GI diseases
2. the immunology of GI diseases, and
3. the role of the microbiome and of infectious diseases on disease development and progression, and
4. the interaction between these above mentioned components.

For the genetics and the immunology of the immune mediated GI diseases the PI's have an excellent track record. For the analysis of the microbiome strong collaborations are established both local, at a national level (Wageningen University) and at the international level (Harvard Medial School/Massachusetts General Hospital/Broad Institute Cambridge, USA). The study of infectious diseases is taking place in collaboration with national (Nijmegen Radboud University) and international collaborators (Harvard Medial School/Massachusetts General Hospital/Broad Institute Cambridge, USA).

All the computational and bioinformatics knowledge for integration of these data are available within the groups and through collaboration with Harvard Medial School/Massachusetts General Hospital/Broad Institute Cambridge, USA.

The programme will entail different aspects:

1. A comprehensive assessment of both the patients and their affected cell populations (i.e. T cells) will lay the foundation for the path from genetic association to molecular phenotype. This will mainly entail different levels of omics data.
2. We will perform genetic risk modeling to define individual risk profiles in patients and populations (LifeLines)
3. We will study the role of the gut microbiome (as the host immune system closely interacts with the microbiome). Since we can obtain reliable genetic risk profiles from all the individuals studied, this will also give us the opportunity to study the relationship between genetics and the gut microbiome.

4. An analysis of various risk genes together, rather than as single entities, in relation to immune cell behavior.
5. Functional studies based on perturbed genes or genetic pathways.
6. Functional studies on the role of environmental factors like smoking in disease development.

Relevance for Healthy Ageing

The diseases under study (celiac disease, Crohn's disease, ulcerative colitis) are chronic diseases often start at young age with normal life expectancy, but require life-long treatment. Genetic risk factors for these diseases are multiple and commonly present in the "healthy" population. Understanding how genetic variations and the interaction with an individual's environment leads to disease development will have major implications for healthy aging of the patients, but even more so to prevent the diseases.
Understanding of the disease pathogenesis will eventually lead to better treatment options of chronic diseases which improves quality of life and promotes healthy life. An active part of the new programme will be our focus on the gut microbiome and the interaction with both the environment and the genetic background. A "healthy gut" contributes to a healthy life.

Principal Investigators

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Drs. LH Franke
Dr. E Brouwer
Dr. ir. HJM Harmsen
Dr. SCD van IJzendoorn
Prof. dr. KN Faber
Dr. A Zhernakova
Dr. MA Swertz

5. Groningen Institute for Organ Transplantation (GUIDE-GIOT)

Programme leaders: dr. H.G.D. Leuvenink, dr. S.J.L. Bakker, prof. dr. R.J. Porte

Mission

Mission: To provide a platform for multidisciplinary fundamental and clinical research with the aim to improve outcome after solid organ transplantation.
Aim: To strengthen and expand the leading position of the UMCG in the field of solid organ transplantation.
Rationale: Transplantation is a life saving therapy for patients suffering from end stage organ failure. The UMCG is the most prominent transplant center in the Netherlands and is the only

center licensed to perform all forms of solid organ transplantation. Transplantation is a multidisciplinary treatment in which specialists work closely together. To ensure optimal outcome, organ specific knowledge both in terms of physiology and anatomy is essential. In addition, knowledge about donor management and optimization, donor organ preservation and post-transplantation management of issues such as ischemia/reperfusion injury, rejection and infections, long-term quality of life are relevant aspects that require continuous research and development.

Integration of experience and knowledge into a program will lead to better understanding the chain of events during transplantation, improvement of translation of basic research to clinical applications, and will increase the visibility of the UMCG as top institute providing high quality care for patients in need of and organ transplant.

Description of the Programme

The program aims to increase knowledge required to achieve improvements in 1) management of the donor and optimization of donor organ quality, 2) preservation of the organ, 3) early organ damage following implantation (by for example ischemia-reperfusion injury), 4) chronic graft dysfunction, and 5) long-term quality of life. These topics cover all important aspects in the chain of events in solid organ transplantation.

Donation: The increasing need for transplantable organs forces transplant professionals to accept organs from suboptimal donors (so called extended criteria donor or ECD). Preserving or even improving organ quality during the pre-donation phase by evidence based donor management, donor pre-conditioning, and optimization of retrieval techniques is an essential part of organ transplantation. More research in this area will be needed to increase outcome after transplantation of organs from ECD and to stimulate wider usage of such organs.
Preservation: Static cold storage is currently the most widely used method of organ preservation. Although this method is sufficient for organs from low risk and optimal donors, it is insufficient for organs from ECD. More sophisticated techniques such as cold and normothermic machine preservation will be needed to improve functional quality of ECD organs. A benefit of normothermic machine preservation is that it allows functional testing and pharmacological conditioning of the organ. The UMCG is a world leading institute in the development of methods for preservation of heart, lung, liver, kidney and small bowel. It is expected that these research programs will benefit from centralization with one Groningen Transplant Institute.
Short-term effects: Graft reperfusion is a critical part of the chain of events during transplantation. Reperfusion injury may negatively affect organ quality and function, which adds to any pre-existing injuries, especially in ECD organs. Novel strategies to decrease the injurious processes as well as to improve repair processes will be examined and developed with this research theme.
Long-term effects: Even after a successful transplantation, there is no guarantee for good long-term function. Various processes may affect organ function and survival, including graft rejection, recurrent disease, and graft fibrosis leading to decline in function. In addition, recipients long-term after transplantation may suffer from the side-effects of immunosuppression. Research in these areas will aim to improve long-term graft and patient survival and to improve quality of life.

Relevance for Healthy Ageing

Organ transplantation has many aspects that have a strong and prominent link with healthy aging. First, organ transplantation is a life saving therapy for several types of organ failure. Due to the increasing success rates of organ transplantation, more and older patients are being accepted for transplantation. In addition, organs from older donors are increasingly accepted for transplantation because of the widening gap between donor organ demand and supply. Some recipients are living with a donor organ that is much older than the recipient him/herself. This makes organ transplantation a very interesting “model” to study aging of solid organs. On the other hand, the chain of events in transplantation, leading to an accumulation of injuries of various origins also results in accelerated aging of the donor organ. These aspects make organ transplantation a clinically relevant, but also scientifically very interesting subject in the field of healthy aging.

Principal Investigators

Dr. HGD Leuvenink
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Dr. EAM Verschuuren
Prof. dr. H van Goor
Prof. dr. E Heineman
Dr. MAJ Seelen
Prof. dr. W van Son
Prof. dr. JA Lisman

6. Groningen research Institute for Asthma and COPD (GUIDE-GRIAC)

Programme leaders: prof. dr. H.M. Boezen, prof. dr. G.H. Koppelman

Mission

The mission of Groningen Research Institute for Asthma and COPD (GRIAC) is the multidisciplinary study of all aspects of obstructive airway and pulmonary diseases through interaction between clinicians and fundamental researchers. Research takes place at the interface of fundamental and applied patient-related research. The main theme is unravelling the underlying mechanisms of the development and progression of airway obstruction, allergy, and airway hyperresponsiveness, and their mutual interactions. These phenomena constitute, in interaction with environmental factors, risk factors for the development of asthma and COPD and are crucial characteristics in their clinical pictures.

Research is aimed to stretch from bench to bedside and back with feedback loops. Central to the research is the goal to translate fundamental findings into the clinical situation and vice versa, i.e. translational medicine. Questions that are generated, but unanswered by clinical research, are approached using in vitro cellular systems and in vivo animal models. The other way around, hypotheses generated from in vitro or in vivo research are translated to the clinical human situation.

To this aim GRIAC focuses on the following main topics related to asthma and COPD:

- Identification of risk factors for development, progression and remission of disease
- Identification of disease related genes and their functionality
- Unravelling the pathophysiology of allergen-, environment- and smoke- induced disease, in both humans and animal models
- Unravelling the effects of disease related inflammation on lung function, hyperresponsiveness and remodelling of large and small airways
- Defining new targets for intervention and evaluation of intervention strategies
- Development of non-or minor invasive tools to assess severity of disease and (side) effects of treatment.

Description of the Programme

The research programme involves the following sub-programmes:

1. *Epidemiology* - Epidemiological studies on endogenous, environmental and lifestyle risk factors, both in general and patient-based populations, from prenatal onwards to old age.

2. *Genomics* - Studies on genes, gene expression and function, molecular mechanisms and gene-gene and gene-environment interactions in disease development, progression, remission, and severity, as well as disease intervention (pharmaco- genomics).

3. *Pathophysiology and pathogenesis of allergen, smoking and other lifestyle factors, and environment-induced diseases* - In vivo studies in humans and animal models using mice and guinea pigs. Investigations include lung function techniques and studies of blood, tissues and/or cells derived from airways or lungs. Furthermore, in vitro studies assess cellular activation and interaction as well as signalling pathways in cells and tissue explants (e.g. lymphocyte subsets, epithelial cells, fibroblasts, intact airway, and smooth muscle preparations). Interactions of different cell types are studied in cells obtained by sputum induction as well as airway and lung tissue obtained by bronchoscopy, by surgical biopsy or autopsy.

4. *Assessment, modulation and intervention in disease severity, progression and remission* - Disease outcome assessment is being studied with techniques such as exhaled breath analyses and small airway function. In addition, validated questionnaires on Quality of Life, drug side effects, hyperresponsiveness and symptoms are developed for diagnostic purposes as well as outcome assessment. Interventions are investigated at the level of cell cultures, animal models and clinical studies with targeted therapy.

Relevance for Healthy Ageing

"Healthy Aging" has been adopted as the main theme for research and clinical profile of the UMCG. An important long term project within this theme is "LifeLines" a planned 30-year survey on risk factors (obtained by questionnaire, objective physiological data and biological and

genomic markers) for disease development, COPD being one of the leading themes. This fits very well with the research agenda of GRIAC, including co-morbidity and systemic manifestations of COPD. We are and will be actively participating in the development of this programme within the UMCG.

After consultation of the programme leaders and all PIs of the participating departments in GRIAC and additional discussions in the board, GRIAC has explicitly incorporated healthy ageing into its mission: The mission of GRIAC is the multidisciplinary translational study of obstructive airway and pulmonary diseases and healthy ageing.

Principal Investigators

Prof. dr. HM Boezen
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Dr. JNG Oude Elberink
Prof. dr. DS Postma
Prof. dr. W Timens
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Dr. HI Heijink
Dr. NHT ten Hacken
Dr. MN Hylkema
Prof. dr. JGR de Monchy
Prof. dr. AJM van Oosterhout
Dr. JM Vonk
Dr. R Gosens
Prof. dr. H Meurs
Prof. dr. M Schmidt
Dr. BGN Melgert

7. Kidney Health Institute (GUIDE-KHIS)

Programme leaders: prof. dr. C.A.J.M. Gaillard, prof. dr. H. van Goor, dr. H.J. Lambers-Heerspink

Mission

The overall mission of the Groningen Kidney Center is to promote research leading to a finer comprehension of the functional renal decline caused by an underlying renal disease or the physiologic process of aging. This takes place through the identification of the underlying pathophysiological mechanisms leading to progressive loss of renal function in renal disease patients and in the experimental setting. In this respect the importance loss of renal function for the function of other organs such as the heart is acknowledged. Consequently, the bi-directional

interaction of the kidney with the heart is designated as an area of focus.
The Groningen Kidney Center aims to function as a catalyst in the field of renal diseases for undergraduate students, graduate students, PhD students and postdoctoral fellows. Well equipped clinical and research core facilities are available for that purpose. The strength of the interdepartmental participation in our center is reflected by an atmosphere of scientific collegiality, which allows all participants to gain from the rich scientific resources available in the clinic and the research facilities. The renal programme becomes effective through the development of various clinical pharmaceutical and life-style intervention trials aiming at the reduction of functional and structural renal deterioration in renal disease and aging. Basic research in experimental and patient-based conditions allow for deepening of the understanding of the molecular basis of renal disease through the use of genetics, molecular biology, biochemistry, imaging and pharmacology. The overall objective of the research programme is to acquire knowledge of the devastating process of renal disease through interpretation, translation, prevention and intervention all in all leading to the coveted improvement of prognosis and well-being of patients with a (cardio)-renal disease.

Description of the Programme

Progressive renal function loss is a chronic process that typically evolves over decades, ranging from mild, asymptomatic loss of function associated with normal ageing, to progressive decline associated with a high morbidity and mortality, eventually necessitating renal replacement therapy by dialysis or renal transplantation. Effective targeting of chronic renal function loss and its complications therefore essentially requires a lifetime perspective, to be able to account for the specific characteristics of each of the subsequent stages of the lifeline, with its associated determinants of renal health and disease, as well as for the longitudinal perspective, where each stage also carries the heritage of the preceding stages.

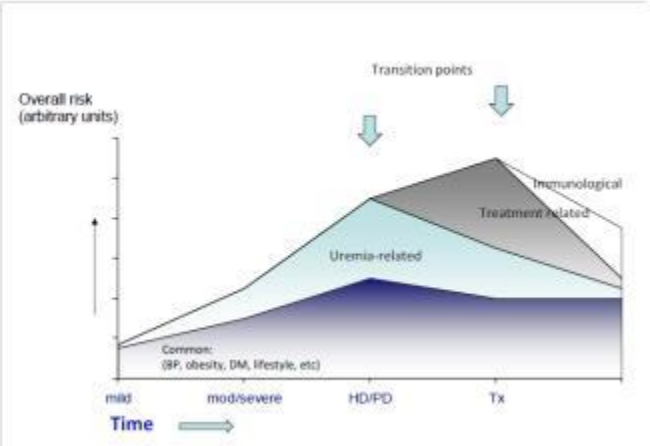

Figure 1: Overall risk (renal and cardiovascular morbidity and mortality) in patients with progressive renal function loss over time, illustrating change in contribution of different types of risk factors over time.

Within this context, the main aims of the programme are to:

- Identify the pathophysiological mechanisms of progressive renal function loss and its complications
- Develop and improve strategies for prevention of progressive renal function loss and its complications

To this purpose the programme includes experimental, clinical and epidemiological studies, covering the full spectre from basic science, via experimental and clinical intervention studies to clinical implementation, and dissemination in clinical care and society. The programme includes:

1. Cohort studies: identification of prognostic factors in general population, populations at high risk for renal disease such as diabetes, and (cardio)-renal patient populations, including native renal disease, transplant recipients and former kidney donors. Serve to identify high risk populations as well as targets for intervention. Cohorts from routine care are also used to identify targets for improvement of clinical care
2. Intervention studies in patient cohorts, including pharmacological intervention, lifestyle intervention and their combination. Intervention studies include relatively small dedicated pharmacological / lifestyle intervention studies to study the specific pharmacological effects on renal function as well as involvement in large scale phase 3 clinical trials to examine the effects on long-term renal disease progression.
3. Experimental studies aimed at dissecting underlying pathophysiological mechanisms in animal studies, and in vitro cell culture studies , and in the human experimental set-up.
   To account for the close interaction between progressive renal damage and cardiovascular disease, the Groningen Kidney Center has strategic collaborations with CVC and VAS.
   To account for the role of immunological factors in progressive renal damage in native and transplanted kidneys, the Groningen Kidney Center has strategic collaborations with the Centre for Translational immunology and the Transplantation Centre.

Relevance for Healthy Ageing

As noted above, a longitudinal, lifelong approach, spanning different stages of the lifeline, is at the core of research on progressive renal function loss and its complications. The data, resources, and concepts originating from such a lifelong longitudinal approach will be of great value for healthy ageing research in a broader sense.

Moreover, renal health is an important prerequisite for healthy ageing. Lifestyle factors contributing to accelerated ageing, including nutritional factors, weight excess, lack of physical activity and environmental toxins, have enhanced impact in patients with renal impairment, by the poor homeostatic and buffering capacity of the kidney, with often easily apparent adverse clinical consequences. Hence, lifestyle-monitoring and lifestyle management, with emphasis on dietary intervention, has traditionally been a main focus in nephrology, with a strong tradition in secondary and tertiary prevention in patients with advanced renal disease where rigorous lifestyle management is a prerequisite for survival.
Over the last years, the value of this expertise for application in larger populations, including earlier stages of renal impairment, patients with heart failure, high risk groups with diabetes and/or primary cardiovascular disease, and hypertension and overweight in the general population has been increasingly recognized. Thus, nephrology serves as a resource for expertise on lifestyle-monitoring and -management, that has immense innovative potential for elaboration outside the domain of advanced renal disease, into the domain of healthy ageing for larger populations.

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8. Microbes in Health and Disease (GUIDE-MHD)

Programme leaders: prof. dr. J.M. van Dijl, prof. dr. A.W. Friedrich, dr. Y. Stienstra

Mission

The mission of the 'Microbes in Health and Disease' (MHD) programme is to define the detrimental and beneficial roles of microorganisms in human health and disease, and to exploit this knowledge in the fight against infectious diseases and the promotion of healthy ageing. This will be achieved through the integration of fundamental, translational, and clinical application- and behaviour-oriented drug research.

The main aims are (i) to obtain a Systems-level understanding of microbial epidemiological principals, (ii) to develop novel approaches and drugs for the prevention or treatment of infections caused by important bacterial, fungal and viral pathogens that are especially threatening to very young, frail elderly, immune-compromised or critically ill individuals as well as individuals living in less affluent regions of the world, (iii) to pinpoint and exploit beneficial effects of the human microbiota to promote healthy ageing, and (iv) to translate the gathered knowledge and results into clinical applications, and to implement them in the education and training of doctors and healthcare workers.

Description of the Programme

The **prevention of infectious diseass** is an important integrative element in the research on bacterial, fungal and viral pathogens. This is achieved through pre-clinical and clinical research with the objective to prevent the emergence of highly-resistant microorganisms, and to validate the influence of measures for infection prevention.

The **bacteriological research** addresses the mechanisms that lead to virulence and antibiotic resistance of a variety of dangerous human pathogens, as well as their (molecular) epidemiology and risk profiles. The investigated pathogens include Staphylococcus aureus, Streptococcus pneumoniae, Porphyromonas gingivalis, mycobacteria, bacteria expressing extended spectrum β-lactamases (ESBL) or carbapenemases (CPE), and highly pathogenic and zoonotic enterohemorrhagic Escherichia coli. The anticipated deliverables of this research are novel targets for fast diagnostics and preventive or therapeutic interventions with novel anti-microbial agents, human monoclonal antibodies or vaccines. A fundamental aspect of the bacteriological studies is the analysis of the secretome, which includes all proteins exported to the cell surface and host milieu. This is important, because the secretome is a major reservoir of compounds that directly interact with the human host thereby influencing health in negative or positive ways. To obtain deeper insights in the roles of the secretome in bacterial fitness, growth, survival and antibiosis, the bacteria S. aureus and Bacillus subtilis are studied using **Systems Biology** approaches. The transmission dynamics of bacterial pathogens are analysed by modern network analyses and mathematical modelling to understand their global distribution and to pinpoint the most effective intervention possibilities. Transmission and immunological aspects of bacterial colonization are also studied in close collaboration with dermatologists focusing on the genetic blistering disease Epidermolysis bullosa. The research in oral microbiology is focused on the role of anaerobic bacteria in oral diseases, such as periodontitis, peri-implant infections and endodontic infections, as well as non-oral diseases such as rheumatoid arthritis and the chronic destruction of hard and soft tissues. Related to bacterial infections afflicting less privileged populations, our research addresses tuberculosis and Buruli ulcer in several different regions around the world and with different partners, including WHO. In ecological studies the dynamics of the human gut microbiota and interactions between bacteria are investigated, not only in relation to diseases like type I diabetes or Crohn's disease, but also in response to interventions with antibiotics or prebiotics and probiotics. In this context, the beneficial gut microbe Faecalibacterium prausnitzii is studied as a model for the promotion of gut health.

The **virological research** addresses viral infections that represent major threats to human health. These include flaviviruses (dengue virus, West Nile virus) and other vector-borne viruses (Chikungunya virus), influenza and other respiratory viruses (respiratory syncytial virus [RSV], rhinovirus), tumor-associated viruses (human papilloma virus [HPV], hepatitis C virus [HCV]), and hepatitis E virus (HEV). The research activities range from unravelling virus-host cell interactions, and development of prophylactic and therapeutic vaccines, to the establishment of new diagnostic tools and studies on virus epidemiology. State-of-the-art technologies (single-virus tracking, siRNA screens, systems immunology approaches, multiplex PCR etc.) and sophisticated technical equipment are employed to better understand disease pathogenesis, to improve diagnostic possibilities and to identify possible targets for antiviral therapy, new vaccines and improved vaccination modes. This will enable timely diagnosis, and effective prophylaxis and/or therapy of viral infections in the future.

The **epidemiological research** investigates and predicts the behaviour of bacterial and viral pathogens with special focus on their transmission, interactions between viruses and bacteria (primary and secondary infections), drug resistance and virulence. Mathematical modelling and network analyses are used to integrate the biological information with transmission dynamics in patient populations and the community. Ultimately, this will yield predictive models of patho-adaptation, as well as the local (nosocomial), cross-border and global spreading of infectious diseases.

Relevance for Healthy Ageing

Europe and other developed countries have ageing societies that are increasingly susceptible to bacterial, fungal and viral infectious diseases. At the same time, antibiotic resistance, enhanced by insufficient antibiotic stewardship and drug abuse in the veterinary practice, is developing fast and catching up with formerly effective measures to prevent or fight infections. Consequently, completely untreatable microbial infections and conditions like those in the 'pre-antibiotics era' are rapidly emerging. In developed countries, this is an increasing threat for very young, frail elderly, immune-compromised and critically ill individuals. In less privileged parts of the world untreatable infections, such as multidrug resistant tuberculosis, are a serious threat also for healthy individuals. To meet this major societal challenge also in the decades to come, it will be of crucial importance to fight the emergence of untreatable infections and to develop new preventive or therapeutic measures that are fast and (cost-)effective. It is the central aim of our research programme to contribute to an improved control of infectious diseases in the future. A better understanding of disease epidemiology and the availability of rapid diagnostic tests will facilitate early disease control and timely interventions in terms of quarantine and treatment. The on-going identification and in-depth characterization of drug targets will contribute significantly to the development of new antimicrobial therapies that are urgently needed to combat emerging infections with drug resistant pathogens. Especially the development of smart vaccines and human monoclonal antibodies will serve in the provision of adequate care for frail and elderly individuals with immature, compromised or ageing immune systems.

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9. Preservation of Cardiac Function over Time (GUIDE-CVC)

Programme leaders: prof. dr. R.A. de Boer, dr. J.A. van Kuivenhoven

Mission

Despite extensive treatment modalities, heart failure related morbidity and mortality remain extremely high – heart failure has a worse prognosis than most common types of cancer. It is our duty to strive for better understanding of the disease leading to better treatment.
The CardioVascular Center (CVC) aims to improve care for patients with heart disease and to prolong heart disease free interval in healthy aging subjects. We envision to work along the translational axis, i.e. from experimental work into the clinics or vice versa, from clinical observations back to mechanistic insights.

Our Mission

The CardioVascular Center (CVC) is dedicated to preserve cardiac function over time.
We strive to:

1. Gain better understanding of development and progression of cardiac disease
2. Lower burden of cardiac disease and associated morbidity and mortality
3. Improve treatment and outcome of cardiac disease
4. Develop patient tailored therapy

Our aims

Through close interaction between clinics and preclinics, participation in large national and European consortia, cutting-edge methodology and a lean organization we aim to:

1. Describe the natural course of heart diseases and describe correlates of CV disease; prevent heart disease (life style modifications, risk factor management, and drugs);
2. Intervene in established disease, with life style modifications, drugs, interventions, and devices, prevent consequences of cardiac diseases.
3. Describe and prevent cardiac dysfunction over time, with emphasis on aging and co-morbidities.
4. Discover novel targets, pass such targets through the translational axis within short time span, develop new therapies aiming at patient tailored therapy, or involve parties who do this, conduct proof-of-principle clinical trials, and apply/protect IP around our enterprises.

Description of the Programme

To enable our mission to preserve cardiac function along the lifeline, several research lines work closely together. The central theme is protected by including the time interaction and modelling in all research activities.

1. To study the dynamics of heart disease and its development, our research group will make use of a large biobanks, comprising several cohorts of subjects from the general population (PREVEND, LIFELINES) with long term folllow-up. This will allow to study elements and risk factors of heart disease development.
   Furthermore, we have created large databases of high risk patients, e.g. patients with new onset atrial fibrillation, that allow early intervention studies.
2. Our research group has a longstanding history of elucidating specific mechanisms that might contribute to the onset and progression of heart failure, leading to targeted randomized intervention study as a proof of concept. Examples are erythropoietin, the cardiorenal

syndrome, the influence of vitamin D deficiency n heart failure, the role of advanced glycation end products in the progression of heart failure, and rate versus rhythm control in atrial fibrillation. We will continue developing these experimental en clinical research lines in clinical heart failure, pulmonary hypertension, pregnancy and heart disease, atrial fibrillation, and acute myocardial infarction: pharmacological studies, disease management studies and device therapy.

3. Heart failure is a typical disease of the elderly patient. The mean age of a patient with heart failure in the Netherlands is currently 77 years. Moreover, patients with heart failure have more co-morbidities than non-cardiac patients with a similar age. This implies that heart failure might cause these co-morbidities. Our research group will continue to conduct research on the prevalence, predictive value, and cause of these co-morbidities, and therefore contribute to healthy ageing of this population. Examples are diabetes and heart failure, liver function abnormalities, renal dysfunction, cognitive dysfunction, and atrial fibrillation.
4. We lead several large scale heart failure biomarker studies that are expected to uncover several novel markers that may be pursued (COACH, BIOSTAT-CHF, BENEFICIAL, PROTECT) that allow the study of genetic and plasma biomarkers. These biomarkers are of clinical use for the diagnosis of heart failure, for identifying patients at higher risk, and for targeted treatment of patients with heart failure.
5. Through the study of genetic and plasma biomarkers, we aim to identify novel targets for heart failure treatment. We envision to work along the translational axis, i.e. from experimental e experimental work into the clinics or vice versa, from clinical observations back to mechanistic insights.
6. Large scale atrial fibrillation studies are expected to uncover mechanisms associated with the induction and maintenance of atrial fibrillation, the association between heart failure and atrial fibrillation and the discovery of new therapies directed at the underlying mechanisms (‘patient tailored therapy, RACE 3, RACE 5, AF RISK and PASTA).
7. In patients with congenital heart disease abnormal loading conditions commonly result in heart failure. The Center of Congenital Heart Disease of the UMCG conducts research in children and adults with congenital heart disease, focusing on lifetime myocardial and pulmonary vascular adapatation to abnormal loading conditions. Our major research subjects are pulmonary hypertension and pulmonary vascular remodeling; right ventricular adaptation and failure; and pregnancy in women with congenital heart disease.

Relevance for Healthy Ageing

"The heart is a tough organ: a marvelous mechanism that, mostly without repairs, will give valiant pumping service up to a hundred years." Willis John Potts, MD, 1895-1968

Our mission to preserve cardiac function over time has important relevance to the general theme healthy aging. Heart disease is a disease primarily of the elderly, and therefore the study of heart disease will involve mostly elderly patients. The CVC has participated and initiated several projects with a primary focus on aging: telomeres in cardiovascular disease (which has led to the discovery of two genes that accelerate biological aging); the SENIORS study (Study of the Effects of Nebivolol Intervention on OUtcomes and Rehospitalisation in Seniors With Heart Failure), the first heart failure trial exclusively aimed to study the elderly. We have an interest in the study of heart failure patients with co-morbidities, which by default involves elderly. This has resulted in well recognized research lines on cardiorenal interaction, heart failure and anemia, and atrial fibrillation and cerebrovascular morbidity.
Furthermore, it should be noted that the treatment of congenital and acquired cardiovascular disease has contributed to an increased life span, more so than treatment of any other disease. Patients with congenital heart disease nowadays survive well into adult age, but the majority

faces lifetime abnormal loading conditions which often result in heart failure. The research of the congenital heart centre contributes to increased knowledge on risk factors and treatment outcomes in pulmonary hypertension.
All of this should be regarded as clear valorisation of research money and has directly benefited the population as a whole. Several key publications from the CVC have changed the global guidelines, e.g. the treatment of atrial fibrillation (RACE1&2, NEJM 2002/2010), acute myocardial infarction (TAPAS, NEJM 2009) and pediatric pulmonary hypertension (TOPP, Lancet 2012), helping to further lower morbidity and mortality and to better utilize scarce resources.

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10. Translational Immunology (GUIDE-TRIGR)

Programme leaders: prof. dr. A.M.H. Boots, prof. dr. P. Heeringa

Mission

To understand how the immune system in an individual develops and interacts with the environment along the Life Line resulting in: “healthy immune ageing” or development of chronic diseases, such as cardiovascular diseases, neurodegenerative diseases, autoimmune diseases and cancer.
The research programme aims to unite immunological concepts and expertise and to seek an integrated approach towards translation of basic immunological concepts into clinical practice (and vice versa).

Description of the Programme

Age is a intrinsic risk factor for the development of immune mediated, chronic disease and cancer. Many chronic diseases are TRIGeRed by an aberrant immune response to environmental challenges. Thus, understanding how the immune system dynamically develops along the Life Line of an individual is of major importance in terms of health and disease. TRIGR presents an integrated, multidisciplinary approach in which clinicians and basic researchers join forces and define research themes based on the following research questions.

1. How can normal immune-aging be evaluated and which factors accelerate age-related changes in the immune system.
2. Can patients potentially at risk be identified, e.g. what are the indicators/biomarkers that predict disease development, disease activity and treatment outcome.
3. What age-related molecular mechanisms underlie the development of chronic diseases.
4. How can we expand immune-longevity and prevent the development of chronic diseases.

Relevance for Healthy Ageing

An initiative to gain knowledge on fudamental aspects of immune-aging in relation to chronic disease development with an emphasis on translation into clinical practice. TRIGR provides a platform for research dedicated to improve our understanding of age-associated alterations of immune function along the life line of a given individual and thus gain fundamental insight into (patho)physiological aspects of immune-aging in relation to chronic disease development. As such, it is anticipated that TRIGR will substantially contribute to the concept of “healthy aging”. It is our objective to integrate our research with ERIBA and LifeLines.

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11. Vascular Ageing Programme (GUIDE-VAP)

Programme leaders: dr. M.C. Harmsen, prof. dr. C.J.A.M. Zeebregts

Mission

The Vascular Ageing Programme (VAP) Groningen is a collaborative and interdisciplinary initiative of several clinical and pre-clinical departments within the University Medical Center Groningen that have established research lines and collaborations on vascular medicine already. Our joint mission is to understand the pathophysiological mechanisms of the development of vascular disease in the ageing population, to find therapeutic targets and to develop novel treatment modalities that successfully combat these diseases. The participants within VAP form a platform i.e. task force for fundamental, translational, and clinical research that focuses on the major aspects of vascular damage and its treatment in the ageing patient. The strength of this UMCG consortium is the wide expertise in vascular medicine, including basic vascular biology, biochemistry, molecular biology, pharmacology, various types of '-omics', imaging and patient-based research, which enables a translational approach to tackle vascular diseases.
The overall objective is to improve preventive, diagnostic, and therapeutic possibilities in the ageing patient with vascular disease using both a bed-to-bench and bench-to-bed approach.

Description of the Programme

Main themes/tasks within VAP are:

1. Mechanisms of the ageing vessel: from molecule to system. This involves the dissection of the dysfunction, (epi)genetics and (patho)physiology and underlying mechanisms of the ageing vascular system ranging from microvasculature to macrovasculature including the role of platelets and coagulation.
2. Vascular targets of the ageing vessel: from imaging dysfunction to adjustment. This involves target finding which includes imaging of the vascular anatomy, function, biology and dysfunction.
3. New therapies to treat and/or prevent ageing-induced vascular disease. This involves development of targeted drug- and cell-based therapeutic interventions in animal models and clinical trials.

Within this programme, vascular diseases will cover a broad area of vascular disease states ranging from presymptomatic micro- or macrovascular endothelial dysfunction, fibroproliferative vascular disease and diabetic angiopathies, vasculitis, and end-stage atherosclerotic diseases such as arterial occlusive disease and aneurysm formation. To address the aforementioned tasks both (animal) experimental and clinical set-ups (including trials) will be used in which specific inflammatory, fibrotic, angiogenic, ischaemic and age-related pathways will be evaluated. Existing patient cohorts will be employed (Parelsnoer, PREVEND, LifeLines – frequently in collaboration with other research programmes), while new cohorts will be recruited and studied as well. Results obtained will form the basis of drug- and cell-based therapy including targeted regenerative medicine-based approaches that may employ biomaterial-based delivery of stem cells or their products. To reach these goals various specific techniques will be applied including a wide range of organotypic cell culture assays, molecular analyses (such as gene expression and microRNA arrays as well as (micro)vascular lasermicrodissection/qRT-PCR technology), genomics, proteomics, metabolomics, pharmacolomics, kinomics, overexpression and knock down (shRNA lentiviral) systems, small animal models, various

molecular imaging techniques such as spectroscopy, BioOptical Imaging, (micro)PET-CT and (micro)SPECT-CT (PET-MRI applied), and human tissues collected in a new Vascular Tissue Bank. Ample experience with these techniques is available within the various research groups of the participating (affiliated) PIs. Using this approach, new medical treatments and (endo)vascular treatment techniques, some of which are already under investigation, will be further developed and will be brought from bench to bedside.

Relevance for Healthy Ageing

During ageing, the vasculature becomes more prone to damage and disease. Important risk factors for vascular disease include obesity, diabetes, metabolic syndrome and chronic kidney disease. All of these risk factors are negatively affected by ageing. Aging can be seen as an accumulation of major and minor insults. Acute illnesses e.g. sepsis can cause organ damage due to vascular injury. For that reason patients after severe insults have high risk of premature terminal organ failure later in life. Minimization of insults (infectious or operative) might lead to preserved organ function and longer well-being. Another important age-related factor that promotes vascular disease is inflammation. The elderly population is immunocompromised. For reasons not yet understood (investigated in the adjunct Translational Immunology programme of GSMS) this 'inflammageing' may cause endothelial dysfunction and leads to microvascular disease such as vasculitis, enhanced microvascular responsiveness to e.g., conditions such as sepsis, or to arterial disease such as atherosclerosis. Aging is associated with various changes in the vascular system at differing structural and functional levels. At the macroscopic level, an increase in arterial lumen size and arterial wall thickening, mainly of the intima, are observed. In addition, increased vascular calcification and a generalized stiffening of the arterial tree lead to increased arterial wave reflectance, increased systolic blood pressure, decreased diastolic blood pressure, and a widened pulse pressure. Especially atherosclerosis is an age-related disease, affecting an essential part of adults over the age of 60 years and increasing over time. But already at age 40, the lifetime risk is around 40% and hence a considerable health care burden. Atherosclerosis is a slowly developing vasculo-inflammatory disease which already starts during adolescence and may cause plaque formation and thrombo-embolic events later in life. Among the multiple risk factors established for cardiovascular disease, age remains one of the strongest predictors for a cardiovascular event. Early identification of patients at risk is of the utmost importance and fits precisely in the goals of Healthy Ageing. The novel strategies that will be developed by VAP to combat vascular disease and atherosclerosis progression have direct effects on both quantity and quality of life. Treatment of atherosclerosis to prevent vascular complications is associated with massive financial expenses. Understanding the genetics and pathogenetic mechanism(s) that underlie the development of atherosclerosis and other vascular diseases as well as associated vascular complications will help to identify new therapies which will reduce costs and increase quality of life. VAP will establish contacts with relevant investigators of ERIBA once this institute comes into function, but also outside the UCMG.

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RESEARCH INSTITUTE BCN-BRAIN:

BEHAVIOURAL AND COGNITIVE NEUROSCIENCES

1 Molecular Neuroscience and Ageing research

Programme leader: prof. HWGM Boddeke

MISSION
The programme 'Molecular Neuroscience and Ageing Research' addresses research on ageing and related neurodegenerative disease in perspective of susceptibility that comes with ageing. The aim of the programme is to elucidate the process of brain ageing and to explore preventive and putative therapeutic, neuroregenerative approaches at the level of dietary additives, drug development and development of biotechnological tools (e.g. cell based therapy). In support of this programme, we also develop novel imaging techniques that support long-term monitoring and prognosis of age-related neurodegeneration and putative repair processes. The level of research within the programme ranges from basic neuroscience up to the applied clinical level and seeks to apply novel knowledge from bench to bedside. This is achieved by extensive collaboration between the departments of Neuroscience, Cell biology, Genetics, Pathology, Neurology, Neurosurgery, the department of Nuclear Medicine and Molecular Imaging and with the 'Healthy Ageing' institute ERIBA.
The programme is firmly based in the 'Healthy Ageing' consortium 'Ageing Brain' and thereby warrants close collaboration with clinical partners in the UMCG.

DESCRIPTION OF THE PROGRAMME
The main research lines concern:
1. Neurodegenerative diseases
2. Neuro-repair strategies
3. Imaging of neurodegenerative diseases

1. Neurodegenerative diseases
Three aspects of neurodegenerative disease are being studied: 1) toxicity of aggregation-prone proteins, 2) neurodegeneration associated with metabolic abnormalities and 3) neuroinflammation.
Studies on protein aggregation and metabolic disorders are primarily focused on Alzheimer's disease, Parkinson's (and Parkinson's related) diseases, Huntington's disease and various ataxias. This research line aims at understanding disease mechanisms and the identification of quality control systems involved in protection against aggregation-prone disease proteins. The studies make use of advanced genetics, cell biology, and biochemistry using cell-based models and D. Melanogaster, C. Elegans, and mouse disease models. This is sometimes is combined with immuno-histo-pathological analyses on post-mortem brains of the respective patients.
Neuroinflammation is tightly related to protein toxicity-mediated neurodegenerative diseases. Neurons suffering from protein aggregates transmit stress signals to the surrounding glia cell population. The neuroinflammation research is focused on microglia and astrocytes, particularly addressing neuroglia signaling, glia phenotypes and glia ageing. These studies make use of advanced microscopy and genetics in primary cultures, Drosophila models, and transgenic senescence accelerated mouse models.

2. Neuro-repair strategies
Research on neuro-repair strategies primarily address the chronic demyelinating disease multiple sclerosis (MS). An essential part of the research line is focused on promoting remyelination by stimulation of endogenous oligodendrocyte progenitors. This includes myelin biogenesis and identification of essential axon-derived signalling cues. Furthermore, we aim at revealing environmental restrictions in MS lesions that underlie remyelination failure. Secondly, we are developing strategies for cell based remyelination therapy. An optimal procedure has been developed to induce specific differentiation of iPS cells into functional oligodendrocytes. The functionality of these oligodendrocytes was demonstrated in mouse models for MS. Currently, a collaboration with the BPRC Institute is ongoing to establish biological validity of iPS-derived oligodendrocytes in marmosets.

3. Imaging of neurodegenerative diseases
Research within this unit is focused on development and evaluation of novel radiopharmaceuticals for visualization and quantification of biochemical processes in intact organisms and the application of novel and existing radiotracers to basic and clinical research questions in neuroscience. Tracers have been developed for quantification of CNS receptors, assessment of P-glycoprotein function in the blood-brain barrier, visualization of activated microglia, cyclooxygenase-2 expression, active herpes virus within the brain, etc.. Particularly compounds such as 11C-verapamil and 11CPK11195 have been applied in many human studies, e.g. for examining changes of blood–brain barrier (BBB) function and microglia activation in several psychiatric (e.g. schizophrenia, depression) and neurodegenerative disorders (e.g. Parkinson's disease). For basic research in experimental animals, the department has microPET and microCT cameras at its disposal.

RELEVANCE FOR HEALTHY AGEING
Brain ageing is intrinsically related to the susceptibility for specific neurodegenerative and neuroinflammatory processes that are major hallmarks of neurodegenerative diseases. In order to pursue healthy aging of the brain and preservation of cognitive capacity and appropriate motor behaviour the basic mechanisms of neuroinflammation and the basic pathology of neurodegenerative diseases need better understanding. In addition, better diagnostic tools are needed to recognize neurodegenerative diseases at the earliest possible state. These goals are pursued by the following programmes:
1. Neurodegenerative diseases: toxicity of aggregation-prone proteins and related neuroinflammation
2. Neuro-repair strategies
3. Imaging of neurodegenerative diseases

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2 Translational Neurosciences

Programme leaders: prof. N.M. Maurits, dr. J. van der Naalt

MISSION
There is a clear gap between clinical and basic neuroscience, and there is a need to bridge this gap in the expanding field of translational neuroscience. Within the research programme 'Translational Neuroscience' (TN) the aim of research will be on (1) non-clinical (fundamental) studies - both in healthy volunteers, as well as in model systems - that have the specific intent to discover mechanisms, biomarkers, pathogenesis or treatments of nervous systems disorders, and (2) clinical studies, to provide a foundation for the development of, or that directly test, novel diagnostic and therapeutic strategies for patients with nervous system disorders.
The research program aims to study specific aspects of healthy aging across the life span, from initial development and healthy functioning of the nervous system to neurodegenerative diseases. Its mission is to enable optimal participation in daily life activities such as school and work, but also to improve quality of life in its last stages. It covers the age span extending from conception up to old age.

DESCRIPTION OF THE PROGRAMME
'Translational Neuroscience' will harbor two main research lines:
1) Motor control and movement disorders
2) Neurological damage: long-term outcome and its determinants

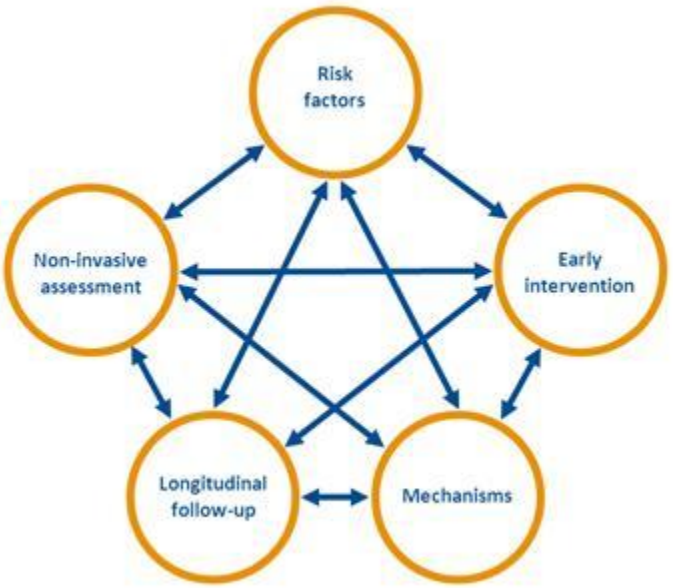
1) Motor control and movement disorders
Within research line 1) motor-related interactions between parietal, premotor and prefrontal cortical regions will be investigated in healthy subjects, providing information on how visuomotor functions are embedded in parietal-premotor circuitry, ranging from basic sensorimotor transformations to free-choice selection. Besides these studies of the motor system on brain level that employ neuroimaging techniques such as fMRI or PET, behavioral aspects of (supra)normal motor performance across the life span will be studied as well, employing kinematic and muscle measures in controlled or real-life circumstances and even in virtual reality. The resulting knowledge on normal cerebral motor control, peripheral aspects of motor functioning and gait and balance, will be applied in studies of patients with movement disorders or motor problems such as Parkinson's disease, ataxia, dystonia or limb amputees, to improve our understanding of neuro-pathophysiology, neuroplasticity and provide possible targets for treatment. With this goal in mind, genetic studies will also be undertaken.

2) Neurological damage: long-term outcome and its determinants
After acute treatment of neurological diseases has been successful, long term neurological and cognitive outcome becomes of importance, particularly from the point of view of healthy ageing. Long term effects of traumatic brain injury, cerebrovascular accidents, (juvenile) epilepsy but

also of preterm births and birth-related neurological deficits such as cerebral palsy (and their treatments) have major personal and societal impact. In research line 2, to improve quality of life, starting at birth, but also across the lifespan, clinical studies will be executed in patients with neurological damage, to evaluate long term outcome and to determine predictors for outcome. Employing this knowledge, randomized controlled intervention studies will be set up to find out how to optimize both short- and long-term outcome.

Studies in the programme employ several key approaches (see diagram):
1. Non-invasive assessment of the nervous system
2. Determination of mechanisms of typical and pathological neurological functioning
3. Early intervention
4. Longitudinal, long-term follow-up
5. Assessment of risk factors (for neurological/neurodevelopmental disorders and for worse outcome after neurological events)

The studies that are performed within this programme typically have their roots in at least two of these components. This resulting integral approach is effective and fruitful to elucidate key elements of typical and pathological neurological development and functioning.



RELEVANCE FOR HEALTHY AGEING

Evidence accumulates that conditions during early life, both prenatally and postnatally have life-long consequences for the health status of the individual. Knowledge of early risk factors for neurodevelopmental and neurological disorders, for mechanisms of typical and atypical development and for worse outcome after neurological events and treatment, offers the opportunity for prevention and early intervention of neurological, cognitive and psychiatric disorders. Typically, these disorders are chronic and treatment is only symptomatic, underlining the importance of the development of new interventions to improve efficacy and outcome. Most neurodegenerative diseases (such as Alzheimer's disease or Parkinson's disease) are diseases of old age; their incidence and prevalence sharply increase after the age of 60. Any improvement in understanding these diseases, in (early) diagnosis or in treatment, will therefore have huge impact on the quality of life and therefore contribute to healthy ageing.

PRINCIPAL INVESTIGATORS
Prof. dr. ir. NM Maurits
Dr. J van der Naalt
Drs. AF Bos
Prof. dr. RJM Groen
Prof. dr. M Hadders-Algra
Dr. BM de Jong
Prof. dr. MAJ de Koning-Tijssen
Dr. T van Laar
Prof. dr. OF Brouwer
Prof. dr. PP de Deyn
Prof. dr. HPH Kremer
Dr. GJ Luijckx

3 Abnormal Neurological Development, Early Diagnosis and Intervention

Programme leaders: Prof. dr. CMA van Ravenswaaij-Arts, **Prof. dr. TJ de Koning**)

MISSION
The program aims to study early diagnosis and intervention in children with abnormal neurological development in a multidisciplinary setting and covering all aspects including aetiology, pathogenesis, epigenetics, diagnostic applications, accurate phenotyping (dysmorphology, neuroradiology, orthopedagogy) and intervention (diet, medication, etc.).
New techniques to efficiently screen the complete genome for alterations that are responsible for diseases, either directly or by increasing the susceptibility, are rapidly evolving (next generation sequencing, NGS). The clinical applicability of NGS is currently being tested for large sets of genes with a known function. In the group of children with abnormal neurological development most genes involved in the pathogenesis are still unknown and NGS in this heterogeneous group of disorders offers enormous opportunities (1) to detect thus far unknown causes of developmental delay (DD), (2) to unravel susceptibility and epigenetic factors and, (3) by a better understanding of the pathogenesis, to develop early intervention and treatment.
The prerequisites for this program are available within the UMCG. The NGS techniques (dept. Genetics) and bioinformatics tools are at hand (Genomics Coordination Centre). More importantly, large well-characterised patient collections are available through specialised multidisciplinary clinics, for studying new genetic causes in selected patient groups (microcephaly, movement disorders, speech delay(CSK/KNO)), for studying the application in routine diagnostics (TDO), for studying epigenetic effects (PKU), and for studying the natural course and effect of intervention (CHARGE clinic and clinic for rare chromosome disorders).

DESCRIPTION OF THE PROGRAMME
Untargeted genome-wide studies are needed to find new causes for developmental delay (DD). Such studies will reveal many new genomic variants and the challenge will be to unravel the pathogenicity (disease-causing ability) of these variants. This can be done, amongst others, by

looking at the expression patterns and function of the genes in animal models. More informative, however, is comparing the phenotypes of children with variations in the same gene. For this, detailed and accurate phenotyping is a must. Dysmorphology, neuroradiology and developmental and behavioural assessments adapted to the patient group under study are important phenotyping tools. Whenever the genetic aetiology is known, the gene function can give clues for intervention. It will also be possible to study why intervention is more effective in some patients than others, e.g. by looking at concomitant genetic variants or environmental/epigenetic factors. Early diagnosis is important in order to enable early intervention. This is especially true in the prenatal situation. With the increasing possibilities of early prenatal imaging and screening techniques, it becomes more and more important to gain insight in the aetiology and course of structural aberrations of the nervous system in the foetus.

The program will comprise studies on 4 different levels:

I. Improvement of diagnostics in children with abnormal neurological development using next generation sequencing techniques. Starting point of these studies are the phenotypically well-characterised patients of the TDO-clinic (>800).

II. Identifying novel genes involved in abnormal neurological development in selected patient groups: primary microcephaly, movement disorders, hyperketotic hypoglycaemia, cleft palate combined with DD. Followed by sophisticated phenotyping using dysmorphology, neuroradiology, movement disorder recordings and developmental and behavioural assessments adapted to the patient groups under study.

III. Studying the effect of treatment and epigenetic influences in well-characterised patient cohorts, already available in the UMCG: CHARGE syndrome, Phelan-McDermid syndrome (intranasal insulin), PKU (epigenetic effects on the efficacy of the diet).

IV. Implementation of new early prenatal diagnostic techniques for the identification of structural aberrations of the fetal cerebrum and studying the relationship with underlying causes and outcome.

RELEVANCE FOR HEALTHY AGEING

Early diagnosis is important in order to enable early intervention and prevention of secondary developmental, behavioural and health problems. An illustrative example of this principle is the Phelan-McDermid syndrome. This syndrome is due to a deletion of the SHANK3 gene and characterised by severe behavioural and developmental problems. Knowledge of the underlying cause and function of the gene involved, coding for a protein that interferes with the intracerebral insulin receptor, suggests a positive effect of intranasally administered insulin on behaviour and development of these patients and thus a better long-tem outcome. A study to proof this will start in 2012. Another example is the study of the effect of diet in PKU patients. Understanding the underlying causes for the differences in diet-effectiveness between PKU patients may result in a more personalised life style advice and thus better long-term well-being. The overall objective of the program is to facilitate collaboration between different research groups in order to strengthen our knowledge needed for an optimal care of children with a neurological developmental disorder. The combination of multidisciplinary care (specialised multidisciplinary outpatient clinics) with translational and clinical research offers the opportunity to improve diagnostics, to add to the knowledge on natural course, as well as to perform research on new treatment modalities in order to contribute to a better Healthy Aging of these vulnerable patients.

PRINCIPAL INVESTIGATORS
Prof. dr. CMA van Ravenswaaij-Arts
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Dr. PJ Hoekstra
Dr. FJ van Spronsen
Prof. dr. OF Brouwer
Prof. dr. RJ Sinke
Prof. dr. MAJ de Koning-Thijssen

4 Perceptual and Cognitive Neuroscience

Programme leaders: prof. FW Cornelissen, prof. D. Baskent

MISSION
The programme 'Perceptual and Cognitive Neuroscience' focuses on research on human sensory systems, and the processing of the sensory information in the nervous system. Our perceptual and cognitive abilities are what make us human. They determine how we perceive the world around us, how we interact with our physical, social and cultural environment, and whether we make sense or non-sense of it. These are some of the key features of our conscious brain. They enable us to respond and act adequately, adapt to a changing environment, communicate with others, and maintain our social abilities. Understanding perception and cognition, and in particular the different ways in which we use these functions in our daily life, is of utmost importance for the quality of life, but in some cases even for survival.

DESCRIPTION OF THE PROGRAMME
Research within the research programme 'Perceptual and Cognitive Neuroscience' will focus on unraveling of normal and/or impaired functioning of the human sensory systems and processing of the sensory information by the nervous system, i.e. cognition. This scientific challenge of understanding perceptual and cognitive (dis)functions can be faced best by multidisciplinary teams of experts integrating expertise from various disciplines within one project.
Using their expertise and working in collaboration in multidisciplinary projects, researcher within PCN will target questions such as:
- How do we maintain healthy perceptual and cognitive systems and function?
- How does the brain serve our perceptual and cognitive functions?
- How do the complex interactions between sensory and cognitive systems change with ageing?
- How do these interactions change with disorders and illnesses?
- How do such changes affect the way humans interact with their physical, social and cultural environment?

'Perceptual and Cognitive Neuroscience' will harbor two main research lines:
1) Sensory and cognitive systems throughout the lifetime
2) Disease or disorder-related changes in sensory and cognitive systems

RELEVANCE FOR HEALTHY AGEING
Human perceptual and cognitive abilities are closely tied to ageing. The maturation of these systems may follow vastly differing timelines, continuously changing the interactive nature of these systems. Age-related declines are observed in human sensory and cognitive systems, even in the absence of accompanying diseases and dysfunctions. These alone indicate a complexity that needs a multi-disciplinary approach to fully tackle the questions at hand.

In addition to age-related changes, neuro-degenerative diseases such as glaucoma, parkinson and alzheimer's disease affect our sensory and cognitive functions. Such diseases, but also brain injury, psychiatric disorders such as depression, schizophrenia, and stress-related diseases, and their perceptual and cognitive implications, have far-reaching consequences for functioning in our society.

PRINCIPAL INVESTIGATORS
Dr. FW Cornelissen
Prof. dr. D. Başkent
Dr. R Bruggeman
Prof. dr. P van Dijk
Prof. dr. NM Jansonius
Prof. dr. A Aleman
Dr. ADJ Martens

5 ICPER: Interdisciplinary Center Psychopathology and Emotion Regulation (BCN-BRAIN/SHARE)

Programme leaders: prof. AJ Oldehinkel, prof. P. de Jonge)

MISSION
The Interdisciplinary Center Psychopathology and Emotion regulation (ICPE) aims to perform high-quality psychiatric research at the crossroads of various disciplines, including Psychiatry, Epidemiology, Social Sciences, Neurosciences, and Internal Medicine. The program focuses on common mental health problems, with a special emphasis on affective disorders. Main goals are to unravel psychobiological processes involved in the onset and course of affective disorders, and to develop and evaluate personalized interventions to improve mood-related problems and social-emotional functioning. Affective problems account for a large proportion of the burden of disease throughout the life span. Apart from being a cause of suffering on their own, they are also highly prevalent in somatic and psychotic disorders, and interfere with their course. Affective problems are often rooted in early life, with diverging expressions and consequences in subsequent phases of life. These characteristics render affective disorders particularly relevant for healthy ageing.

DESCRIPTION OF THE PROGRAMME
The interdisciplinary nature of the ICPE is reflected in both the research themes and the methods used. Large longitudinal epidemiological surveys (e.g., TRAILS, NESDA, LifeLines) are complemented with studies involving more, or more in-depth, measurements in smaller groups to elucidate underlying endophenotypes and temporal patterns. The study designs are

both observational and experimental, and involve a variety of (neuro)psychological, social, and biological measures, including neuroimaging techniques.
Specific research themes include questions regarding trajectories of mental health, person-environment transactions and interactions, emotion regulation in psychotic disorders, and psychopathology in the context of somatic conditions. The ultimate goal is to identify high-risk groups and causal risk or protective factors in order to develop more effective, personalized prevention and intervention strategies for mood and mood-related problems and social-emotional functioning.

RELEVANCE FOR HEALTHY AGEING
The ICPE has adopted a lifecourse perspective on the development of mental health problems, implying that they are the consequence of a continuous interplay of genetic or acquired person characteristics and environmental factors. Besides having a major impact on quality of life, mental health problems also mark an increased risk of future physical health problems and aggravate disabilities, and are thus of crucial relevance for (un)healthy ageing.

PRINCIPAL INVESTIGATORS
Prof. dr. AJ Oldehinkel
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Prof. dr. A Aleman
Dr. R Kortekaas
Prof. dr. WA Nolen
Prof. dr. J Ormel
Prof. dr. RC Oude Voshaar
Dr. H Riese
Prof. dr. RA Schoevers
Dr. S Sytema
PFM Verhaak
Dr. H Burger
Dr. CA Hartman
Dr. ADJ Martens
Prof. dr. JGM Rosmalen

RESEARCH INSTITUTE SHARE

1 Health Psychology Research (SHARE-HPR)

Programme leader: prof. dr. M. Hagedoorn

Mission
The Health Psychology Research program (HPR) aims to gain insights that will be useful in resolving the psychological problems experienced by people with chronic somatic illness and that will add to the body of knowledge on those psychological and social processes that enable or impede people's adaptation to chronic somatic illness. This knowledge can be used to develop and provide adequate psychosocial care for people who experience difficulties in adapting to a chronic somatic disease. In pursuing these objectives, the programme aims to uphold the highest standards of scientific research and to share its knowledge through publications of its findings in renowned international journals. The training of junior researchers, both at MA and PhD level, constitutes an essential part of the program.

Description of the Programme
The Health Psychology Research program focuses on the adaptation of patients to the diagnosis of a chronic somatic disease and its treatment. The program covers two major research lines:

· Research aimed at gaining insight into the course of outcomes of adaptation, including quality of life, depression and distress, and the role of psychological and social predictors herein, taking into account medical factors; and

· Research aimed at developing and evaluating psychosocial screening programs and psychological interventions for patients in need of psychosocial help, and identifying psychological and social mechanisms underlying the effectiveness of interventions, taking into account medical factors.

Psychological and social factors can influence the adjustment to chronic illness, while at the same time they too can be influenced by the disease as well.
Insights from the theoretical research line are used in the development of interventions. Diseases of interest include cancer, cardiovascular disorders, diabetes and COPD; specific treatments include organ transplantation, focusing on renal and liver transplantation. The psychological factors under study include individual characteristics with a strong focus on perceived control, mindfulness and goal adjustment and social factors with a strong focus on partner relationship and dyadic coping.

Relevance for Healthy Ageing
Our focus is on chronic somatic diseases that to a large extent can be considered as diseases of old age. It is expected that the prevalence of chronic somatic diseases among the elderly will increase even more as a result of improved medical treatments, resulting in increased survival, and the ageing of the population. This means that an increasing number of elderly will have to live with a chronic disease, of which the long-term consequences are not yet fully understood.

At the same time, the elderly also experience a decline in physical, psychological and social resources that are needed to deal with chronic disease. This double-edged sword may have a major impact on their quality of life, which can be considered as an essential part of healthy ageing. To design effective interventions for the elderly, it is important to gain insight into this dual influence of psychological and social factors, and how they affect their quality of life.`

Principal Investigators
Prof. dr. M Hagedoorn
Prof. dr. JC Coyne
Dr. JEHM Hoekstra-Weebers
Prof. dr. R Sanderman
Prof. dr. AV Ranchor

2 Public Health Research (SHARE-PHR)

Programme leaders: prof. dr. SA Reijneveld, prof. dr. U. Bültmann

Mission
The mission of the Public Health Research (PHR) program is to contribute to healthy ageing. It does this by research on the prediction and (early) detection of adverse health and disease, and on social participation in chronic diseases. These research themes are part of prevention and societal participation, that is, of core domains of public health. They are also pivotal parts of the mission of the entire University Medical Center Groningen that is to contribute to healthy ageing, to which graduate school SHARE contributes by health research.

Description of the Programme
The PHR program aims to contribute to the knowledge on public health: community medicine and occupational health. Its research focuses on two themes with high relevance for public health i.e. the prediction and (early) detection of adverse health and disease, and social integration in chronic disease. This especially concerns musculoskeletal and mental disorders. Much of the research of the PHR programme on prediction and (early) detection of adverse health and disease, and social participation in chronic diseases occurs in two public health settings, i.e. preventive child healthcare and occupational healthcare. However, it is not limited to these settings, because of two reasons. First, the ambition of the programme is to study chains of care that are connected to these themes, i.e. to extend to for instance clinical care and social care. Second, the programme aims to provide evidence that is internationally generalisable, whereas these settings are partially country-specific. This implies a necessity to include other settings as well. In addition, PHR has mainly focussed on health problems with a high public health impact, in particular on musculoskeletal and mental disorders. Topics of research conducted in PHR are for instance community-based early identification of psychosocial problems in children, factors that influence work participation in young disabled, and improvement of societal functioning and participation following knee replacement.
To reach its aims, the PHR team has a multidisciplinary composition in which public health physicians, social scientists and health scientists cooperate with clinical groups like orthopaedics & sports medicine, and psychiatry, and with allied health professionals like

physiotherapists. Members as well as the total programme maintain very close links with public health and occupational health organisations, and other organisations that should employ the evidence obtained by the programme. This collaboration also provides input to the programme regarding priorities within the central research themes.
Most research is conducted in close cooperation with organizations such as occupational healthcare providers such as Arbo-services, UWV and public (child) health services such as GGD'en and well-child clinics. Increasing, research also comprises prevention among and participation of the elderly, partially instigated by the healthy ageing theme of the entire UMCG. Moreover, the program conducts research jointly with several international partners, in particular in Central Europe, Canada and Denmark.

Relevance for Healthy Ageing
The central themes of the PHR program, prediction and (early) detection of adverse health and disease and social participation in chronic diseases, are pivotal for the central mission of the entire University Medical Center Groningen that is to contribute to healthy ageing. In fact, PHR aims at the start of healthy ageing, that is the prevention of disease, and at its end, maintaining healthy ageing by social participation if health deteriorates and health problems have occurred. Early detection and subsequent treatment of behavioral problems in preterm children is an example of the former, reintegration in the work setting after a major depressive episode or cancer is an example of of the latter. The program currently hosts projects concerning both topics. In short, PHR is at the core of the mission of the UMCG.

Principal Investigators
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Drs. I van den Akker-Scheek
Prof. dr. PJ Coenraads
Prof. dr. RL Diercks
Prof. dr. JW Groothoff
Dr. LJ Middel
Dr. M Stevens
Dr. S Brouwer
Prof. dr. SK Bulstra

3 Extremities, Pain and Disability (SHARE-EXPAND)

Programme leaders: prof. dr. JHB Geertzen, prof. Dr. CK van der Sluis

Contents
Our research improves the participation and quality of life of patients with musculoskeletal disorders and musculoskeletal pain and individuals who have undergone amputations of one or more extremities. Our research is of the highest quality and is tied in with our mission. It focuses on two priority areas; the first is disorders and amputations of the extremities, the second is pain. Naturally, our research falls within the UMCG-wide theme of Healthy Ageing. We have decided to integrate the two priority areas in the coming years, with a specific focus on research questions spanning both areas. Integration of research will result in even more specialization

and deepening of knowledge. We have a high profile, which is visible in our collaborations with national and international organizations working in our field. In addition, we actively disseminate our knowledge through publications in prominent journals and presentations targeting wide audiences. We make new insights into rehabilitation available so that patients may optimally benefit from them. We embed our knowledge by training new generations of medical and paramedical students and providing refresher courses for professionals already working in the field.

Description of the Programme

Clinical rehabilitation commonly deals with complex cases with multiple co-morbidities and complications rather than with single pure pathologies. Treatment is concentrated on enduring disabilities of patients with multiple problems, for which there is no single curative intervention. Multidisciplinary and multimodal interventions characterise most treatment programmes in clinical rehabilitation.

Rehabilitation programs explicitly aim to improve patients' mobility, independence in self-care, ability to communicate, and ability to live independently and engage in productive activities. Consequently, a biopsychosocial rather than a biomedical model has been put forward as the underlying model.

The mission of the Department of Rehabilitation Medicine, Centre for Rehabilitation of the University Medical Center Groningen (UMCG) is to bridge the gap between theory, research and practice in the various treatments of patients with disabilities due to accidents or diseases. Dissemination of knowledge and training of professionals and (potential) researchers has been stimulated. Moreover, multidisciplinary collaboration has been facilitated, as developments of knowledge of disablement and treatment processes need a multidisciplinary orientation.

We decided to primarily restrict the scope of clinical problems and treatment programs, which are object of study:

1. Extremities: amputation, prosthetics and orthotics (lower and upper extremities) and arm and hand problems.
2. Specific and a-specific (low back) pain syndromes.

In the years to come, the research will become even more focused and the two priorities will be linked even more closely through the selection of research themes incorporating aspects of both.

In the near future, the 'extremities' research will focus on disorders of the hands and feet and amputation of extremities, more specifically on impairments, activities and participation.

The 'pain' research will focus on chronic pain and work participation. In new research projects, the two areas will be joined more explicitly.

Relevance for Healthy Ageing

EXPAND research is a part of the main theme of research of the University Medical center Groningen: "Healthy Ageing". In our field, Rehabilitation, we have to deal with patients with restrictions/limitations in the field of Activities or Participation (ICF model). The group of persons with chronic pain is only increasing as is the group of persons with a disability or handicap due to the ageing in general. We are collaborating with 2 groups, "Active Ageing" and "Healthy Ageing at Work".

Principal Investigators

Prof. dr. JHB Geertzen
Prof. dr. CK van der Sluis
Prof. dr. PU Dijkstra
Prof. dr. K Postema

Prof. dr. MF Reneman
Prof. dr. CP van der Schans

4. Methods in Medicines Evaluation and Outcomes Research (SHARE-M2O)

Programme leaders: dr. P. Denig, prof. dr. MJ Postma

Mission
The overall mission is to collect relevant data and develop and apply advanced methods to expand knowledge on determinants and consequences of treatment and other medical interventions in daily practice, and support decision making and optimal use of (pharmacotherapeutic) interventions. This is done through interventional, observational and epidemiological studies, economic evaluations, health technology assessments (HTAs), development of tools and methods to support the quality of therapy decisions and implementation.

Description of the Programme
The emphasis is on pharmacotherapy and other treatments for multi-factorial diseases (cardiovascular diseases/diabetes/mental diseases), reproduction and prevention (screening, vaccines). The focus is on prevention of disease, prevention of complications, medication therapy management, and medication safety, all explicitly as part of healthy aging. Various outcome measures are applied, including intermediate and hard endpoints, adverse events, safety outcomes, health-related quality of life, organisational aspects, costs and quality of care. There is particular interest to develop and use advanced methodologies to measure health outcomes in specific subpopulations.
Constituting elements of M2O are two units form the department of Pharmacy and two from the UMCG, respectively: PharmacoEpidemiology & PharmacoEconomics (PE2), Pharmacotherapy & Pharmaceutical Care (PPC), Clinical Pharmacology (Drug Utilization Group) and the Health Technology Assessment (HTA) unit of the department of Epidemiology.
The main research fields are: Drug Utilization, Pharmacoepidemiology, Pharmacotherapy/pharmacovigilance, and Health Economics & Health Outcomes Research. Within these fields the following themes are currently distinguished:

(a) Health economics in vaccinology,
(b) Personalized and targeted (monitoring of) treatment in elderly, patients with multi-morbidity, children and newborns, pregnant women and individuals with psychiatric disorders,
(c) Epidemiological methods using observational treatment and outcome data (making use of databases such as IADB, Eurocat, GIANTT, Lifelines, Lareb, PHAMOUS, VIPP, GPRD),
(d) Investigating multi-factorial disease, in particular diabetic, cardiovascular and nephrological diseases with a focus on drug utilization and pharmacoepidemiology
(e) Monitoring and management of medication safety and medication errors in vulnerable patient groups (a.o. elderly, psychiatric patients),
(f) Quality of prescribing, adherence to clinical guidelines, identifying (determinants of) suboptimal treatment and development/evaluation of interventions to counter suboptimal treatment.

Relevance for Healthy Ageing
Regarding Healthy Aging, the cooperation between Pharmacy and the UMCG provides unique opportunities. In particular, the aging of the population and the vast and accruing possibilities for pharmacotherapy – both curative and preventive – poses challenges that include a broad range of sectors, even beyond pharmaceutical and medical sciences. This requires cooperations even beyond the M2O internal structure, for example, with demographics, economics and psychology. Such cooperations are already functioning.
Focus points of the M2O program fit well into the Healthy Aging concept. In particular, the program comprises the whole range of safe and (cost-)effective treatment and prevention from pregnancy and birth to old age. For example, safety of medicine use durinf pregnancy, cost-effectiveness of infant vaccinations and observational studies in childhood pharmacotherapy all involve the healthy start of the aging process. During midlife, our program focusses on continued preventive interventions, personalized medicine and (cost-)effective early treatments of incident diseases (for example, diabetes). For elderly, M2O-studies are a.o. directed at quality of life in aging, medication safety in health-care institutions (for example, nursing homes), elderly vaccinations and secondary prevention in diabetes.

Principal Investigators
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Prof. dr. MJ Postma
Prof. dr. FM Haaijer-Ruskamp
Prof. dr. E Buskens
Dr. TL Feenstra
Dr. H Groen
Dr. PFM Krabbe
Drs. HJ Lambers Heerspink
Prof. dr. E Hak
Prof. dr. LTW de Jong-van den Berg
Prof. dr. AC (Kees) van Grootheest

5. Ethical, Legal, Social Issues in Genetics (SHARE-ELSI)

Programme leaders: prof. dr. IM van Langen, dr. E. Birnie

Mission
Our mission is to build an interdisciplinary research group from researchers experienced in studying the ethical, legal, social impact (ELSI) of changes in health care as well as specialists in the fields of genetics and other medical specialties currently involved in Mendelian genetics, aiming at fast and continuous translation of genetic research findings into optimal clinical applications in the above mentioned fields.
Our aim is innovation and improvement of clinical genetic patient care as well as the application of new genetic knowledge in other medical specialties, primary care and in genetic population screening. Innovation and improvement of clinical genetic patient care not only consists of the

development or adjustment of genetic counselling techniques but also addresses the process and organization of genetic care and the related societal aspects, e.g. informed consent procedures.

Description of the Programme

Continuous technological progress and new developments in the field of clinical genetic care offer opportunities for large-scale disease prevention strategies, based on stratification of (pre)clinical, genetic risks and the early detection and treatment of disease. They directly lead to the unraveling of the cause of many Mendelian diseases and, in the near future, also to the understanding of the genetic causes of prevalent complex diseases, e.g. diabetes, hypertension, dementia, and congenital malformations. However, these new techniques also create confusion in medical professionals as well as in patients and in the general public. This is because the massive detection capacities –effective and efficient as they may be– not only generate the wanted and clinical useful findings, but also information that is unsought (but sometimes clinically important!) and/or unwanted and/or not understood yet. Hastily introduction without proper guidance may lead to potentially dangerous medical and ethical, legal and psychosocial situations, like breaching of autonomy, genetic discrimination, decisional conflict and improper use of health care resources.

Appropriate handling of these aspects is challenging for the professionals, patients and public involved since practice guidelines are still lacking worldwide. The results of research in our program will certainly add to these new practice guidelines.

The proposed interdisciplinary research group will consist of PIs from different departments, with different areas of expertise and with a proven track record in the fields of ELSI-studies, (clinical) genetic research or applied genetic medical research (see appendix for an overview of the composition of the proposed group). In addition, the PIs of proposed group will continue to acquire research funding for these activities.

Relevance for Healthy Ageing

New genetic findings and their applications in health care are increasingly facilitating a more risk oriented (preventive) instead of disease (complaint) oriented style of health care provision. Healthy aging is stimulated if patients and 'the public' can be encouraged to profit from these developments, not only by using certain predictive tests but also by adjusting their behavior based on the test-results. Research is for instance needed to answer questions on patient autonomy related to the above and on best practices to motivate people to adopt a healthy lifestyle. Additional research will be aimed at behavior of professionals who are confronted with this paradigm shift.

Principal Investigators

Prof. dr. IM van Langen
Dr. E Birnie
Prof. dr. MA Verkerk
Prof. dr. MP van den Berg
Prof. dr. AV Ranchor
Prof. dr. CMA van RavensWaaij-Arts
Prof. dr. RH Sijmons
Dr. JP van Tintelen
Prof. dr. RJ Sinke

6. Reproductive Health Reproductive Origins of Adult Health and Disease

Programme leaders: SHARE-ROAHD; dr. H. Groen, dr. A. Hoek

Mission
1. Investigating preconceptional, preimplantation and pregnancy-related **determinants and predictors** of health and disease of the future child and mother.

2. Investigating **screening and diagnostic procedures** before conception and during pregnancy to identify diseases in the future child and mother.

3. Exploring **interventions** before conception and during pregnancy to promote the health for the future child and mother.

4. Conducting **implementation** research for evidence based optimal perinatal care.

Description of the Programme
The purpose of the theme **"Reproductive Health"** is to bring together preclinical, clinical and epidemiological investigators to investigate, *in vivo* and *in vitro*, embryonic, fetal and early neonatal determinants in the preconceptional period and during pregnancy that are pivotal for health and disease later in life, to develop diagnostic procedures for the mother and the future child, and to develop interventions to enhance health in the fetus and the mother. Moreover, to investigate and implement evidence based perinatal care for pregnant women.

Current research activities:

Preconception:
1. Investigating the influence of preconceptional lifestyle factors in the general population on the outcome of pregnancies in terms of growth, development and health of neonates and mothers.
2. Investigating preconceptional lifestyle, medical, and psychiatric interventions within the population with one or more known risk factors for adverse outcome: men and women with chronic diseases as well as men and women with genetic diseases who wish to conceive, in order to optimize pregnancy outcome. Investigate early determinants, diagnostic tests and interventions for women with chronic psychological stress or psychiatric diseases with a focus on the risks and benefits for mother and child.
3. Investigating determinants and effects of the deliberate postponement of childbearing in men and women. Investigate determinants of "social freezing" in women (cryopreservation of oocytes).
4. Investigating the effect of ovarian surgery on the risks on fetal aneuploidy.

Preimplantation:
5. Investigating optimization of cryopreservation of gonadal tissue or gametes in patients with irreversible damage of their gonads due to chemotherapy, radiation or surgery, as well as optimization of culture techniques of embryo in vitro.

Pregnancy:
6. Investigating determinants of pregnancy associated diseases such as hypertensive disorders

(preeclampsia), diabetes gravidarum, and placental disorders. Development of techniques for early diagnosis and intervention, in animal models as well as in man.
7. Exploring the drug use in pregnancy e.g. the FA-intervention in community pharmacies and pregnancy prevention programs in place for teratogenic drugs.
8. Investigating pregnancy-induced adaptations in immunology and the role of aberrant adaptations in immunology in the development of pregnancy complications.
9. Development of techniques for early detection of chromosomal and structural birth defects both on the level of a screening program. The development of chip-based methods for next generation sequencing.

Perinatal care:
10. Health technology assessment (HTA) and implementation research addressing the optimization of antenatal care in the Dutch health care system for pregnant women, such as implementation research after perinatal audit.

Projects currently within GROningen Unit for Perinatal Studies (Groups), and Groningen expert center of perinatal mortality(GECPM) will be positioned within this theme.

Relevance for Healthy Ageing
"Healthy ageing is a lifelong process that starts even before conception, with parents who pass on their genes and with them the risks and opportunities for a healthy life course, or the occurrence of illness later in life". This quote from the UMCG website epitomizes the importance of reproductive health for healthy ageing. Indeed, healthy ageing starts before conception and is further determined during embryonic and fetal life. Growth and development of the future adult is affected by genetic and epigenetic programming of gametes and pre-implantation embryos. These processes are still poorly understood in vivo, but evidence exists that they are influenced in vitro by assisted reproduction technologies. Maternal factors determine the metabolic and endocrine environment in utero during pregnancy, and also influence the growth and development of the fetus. The so-called "Barker Hypothesis" suggests that several diseases in adulthood such as cardiovascular diseases, diabetes, lung diseases and possibly psychiatric vulnerability find their origin during pregnancy. An unfavorable intra-uterine environment can be caused by lifestyle factors such as drug exposure, alcohol consumption, smoking, unhealthy diet, overweight and chronic psychological stress and may lead to changes that can have a permanent impact on the structure, function, physiology and metabolism of the placenta and the fetus. Eventually, this unfavorable environment affects fetal organ development and gene expression and results in an adult with a greater susceptibility for the development of the chronic diseases later in life. Not only the future child has an increased risk for health problems, but also the mother who has pre-existing diseases or who develops pregnancy related diseases such as preeclampsia has an increased risk for health problems in her future (i.e. hypertension, diabetes cardiovascular- and renal diseases). Investigating mechanisms and factors that are responsible for changes in placenta function and maternal physiology can help to understand the changes that occur in the fetus and the "future adult", and the mother.

Principal Investigators
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Dr. H Burger
Dr. ir. E Corpeleijn
Dr. MM Faas
Dr. MN Hylkema
Prof. dr. IM van Langen

7. Smart Movements (SHARE-SMART)

Programme leaders: prof. dr. C. Visscher, prof. dr. LHV van der Woude

Principal Investigators
Prof. dr. C. Visscher
Prof. dr. LHV van der Woude
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Dr. CJC Lamoth
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8. Life Course Epidemiology (SHARE/GUIDE-LCE)

Programme leaders: prof. dr. RP Stolk, prof. dr. ER van den Heuvel

Mission
Life course epidemiology can be defined as the study of long-term effects on chronic disease risk of exposures during gestation, childhood, adolescence, young adulthood and later adult life. In epidemiological practice this means longitudinal follow-up research. Since ageing starts at fertilization, these studies should not be limited to the elderly.
LifeLines is a prospective population-based study among ultimately 165.000 inhabitants from the three northern provinces of the Netherlands, using a three-generation family design. The overall aim of LifeLines is to unravel the interaction between genetic and environmental factors in the development of multifactorial diseases.

Description of the Programme
This program focuses on the epidemiological approach of healthy ageing: longitudinal observational cohort studies. The common interest and expertise is the methodology to analyze data from these, often large scale, datasets. Medical statistics is included, as well as genetic epidemiology, both important methodological disciplines in Life Course Epidemiology. The program contains the vast long lasting experience of population cohort studies at the UMCG, ranging from the oldest population study in the Netherlands (Vlagtwedde-Vlaardingen study) to the largest (LifeLines). Other important cohort studies included are TRAILS, Prevend and GECKO.
Research themes include 1) methodological approaches for healthy ageing research in a population setting, and 2) etiology and prognosis of chronic age-related diseases, in multidisciplinary collaboration of methodological experts within LCE and disease-specific clinical

experts.
Members of the program are primarily based in the Department of Epidemiology. Therefore the proposed program director is Ronald Stolk. When the Scientific Board of LinesLines has been established, the board members will be added to the LCE programme.

Relevance for Healthy Ageing
Life Course Epidemiology is the core of Healthy Ageing research. Following groups of unselected individuals over the life span, and investigate the risk factors for incidence of disease (or absence of disease) will identify relevant risk factors and predictors for Healthy Ageing.
An important aspect of the LCE program is the inclusion of non-clinical, that is societal, research groups. Healthy Ageing is more than the absence of disease. Social capital, informal care, distance to health care facilities and other societal factors do contribute to health and well being at older ages.

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Dr. CA Hartman
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RESEARCH INSTITUTE CRCG:

CANCER RESEARCH CENTER GRONINGEN

1. SALL: Stem Cells, Ageing, Lymphoma and Leukemia

Programme leaders: prof. A. van den Berg, prof. JJ Schuringa

MISSION
The research program “Stem cells, Aging, Leukemia and Lymphoma” coordinates research programs in the field of basic, translational and clinical research in an attempt to better understand the molecular mechanisms regulating hematopoietic stem cell functionality, how these are perturbed in the development of leukemia and lymphoma and can be translated into improvement of treatment and late sequelae of these diseases.

DESCRIPTION OF THE PROGRAMME
The PIs and other members of the SALL program are appointed at various departments, i.e. ERIBA, Haematology, Pathology, Paediatric Oncology and the Stem Cell Biology group. The main topics that are studied include stem cells, leukaemia and lymphoma with a focus on both translational and clinical research topics.
The Stem Cell research is focused on how blood cell development is regulated during normal hematopoiesis. Most studies are aimed at identifying mechanisms and genes that specify hematopoietic stem cell self renewal, using the mouse as a model system. Also the flatworms are used as a model to understand the fundamental mechanisms underlying regulation of stem cell activity during aging. Stem cell purification, transplantation, genetic perturbation, transcriptional profiling and epigenetic screenings are key instruments in our studies. The leukemia research line focuses on leukemia in children and adults and has a clear focus on the leukemic stem cells. Primary human hematopoietic stem/progenitor cells and leukemia cells are manipulated by a variety of cell biological and molecular techniques to deepen our insights in the development of human leukemia’s and in which way normal young and old stem cells are affected by intervention of chemotherapy and transplantation. In addition, there is a second focus on VEGF signaling and angiogenesis especially in relation to leukemic progression and resistance and the results are translated to clinical studies.
The Lymphoma research is focused on the most common B cell lymphoma types and aims to deepen our insight into the pathogenetic mechanisms of lymphoid malignancies. In Hodgkin Lymphoma a main research focus is on the relationship between the tumor cell and its microenvironment, the role of Epstein Barr Virus, HLA expression, genome wide association studies, miRNAs and (serological) biomarkers. In non-Hodgkin lymphoma a main focus is on primary and secondary genetic hits and on noncoding RNAs. Results from these fundamental studies are translated into clinical studies such as testing their value as diagnostic criterion for classification, biomarker for treatment response and prognostication and late treatment-related toxicity in close collaboration with the HOVON and EORTC lymphoma groups.

RELEVANCE FOR HEALTHY AGEING
Appropriate functioning of the immune system is essential for healthy aging, and stem cell renewal & differentiation play crucial roles in this process. Aging affects stem cell self-renewal

and may result in enhanced or reduced stem cell renewal capacity. Accumulation of genetic and epigenetic aberrations in time may lead to the formation of leukemic stem cells and the subsequent development of leukaemia. Studying stem cell renewal and leukemic stem cell renewal will reveal the mechanisms that lead to inappropriate functioning and leukaemia. Lymphomas develop from B or T lymphocytes that escape from apoptosis due to accumulation of genetic and epigenetic aberrations over time. Thus, aging is also a crucial factor in lymphoma development. Of interest in this respect is that some lymphoma subtypes occur both in young and elderly individuals, whereas other lymphomas are specific for either young or old individuals. In general age is an important prognostic factor. Unravelling the genetic and epigenetic aberrations in lymphoma will increase our insight in the pathogenetic processes and will help to improve current treatment regimens, predict prognosis and response to therapy.

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Dr. F Foijer
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Dr. GW van Imhoff
Prof. dr. JC Kluin-Nelemans
Prof. dr. E Vellenga
Prof. dr. ESJM de Bont

2. Targeted Gynaecologic Oncology

Programme leaders: prof. HW Nijman, prof. dr. S. de Jong

MISSION
Mission: to stimulate, integrate and optimize excellent translational and clinical research that has an impact on overall survival and quality of life in patients with (pre)malignant gynaecologic neoplasia.
Aim: Excellent translational and clinical research in (pre)malignant gynaecologic neoplasia by bringing together supplementary knowledge from a multidisciplinary team.
Rationale: The UMCG is the tertiary referral center for the North-east of the Netherlands (catchment area ca. 3.5 million people). Within the UMCG longstanding bilateral collaborations have been established on improving, prevention, early diagnosis and treatment strategies in patients with(pre)malignant gynaecologic neoplasia. In this programme, we will broaden and intensify these collaborations by bringing together gynaecologic oncologists, medical oncologists, radiotherapists, clinical geneticists, epidemiologists, psychologists, sexologists, pathologists, biologists, pharmacists, nuclear medicine specialists and immunologists. We will further intensify preclinical and clinical research based on our large number of patient referrals and clinical databases together with PBMC-, DNA-, paraffin- and fresh frozen tumor tissue- and

serum sample-bank, collected over a period of more than 25 years. Next, we can benefit from our innovative in vitro and in-vivo tumor models. All of this will allow us to perform research from lab to clinic and vice versa. By fostering education and the exchange of knowledge, we will expand multidisciplinary collaborations. These collaborations will ultimately raise the quality of research, publications, and grant proposals. This will also attract biological and medical students to be trained in the various aspects of translational research.

DESCRIPTION OF THE PROGRAMME

The main focus of our programme is the translation of basic and preclinical research to clinically relevant settings by taking advantage of our large number of referrals of patients with (pre)malignant gynaecologic neoplasia and our unique databases consisting of clinical, genetic and pathological characteristics of the majority of patients treated at our university medical center. The supplementary knowledge within the programme will not only stimulate basic research but also translational and clinical research, enabling us to perform research from bed-to-bench and vice versa.

To intensify our collaborations while maintaining the scope of our research focussed, we will specifically stimulate areas of already existing collaborations on the various patient categories and tumor (sub)types:

1. Regarding hereditary cancers we focus on ovarian and breast cancer (*BRCA1 & BRCA2* mutation carriers) and endometrial cancers in women with Lynch syndrome. Research includes establishing preclinical disease models, identification of risk modifiers and targets for treatment, and the development of strategies to target and prevent hereditary tumors. Research findings can be immediately applied in genetic counselling and prevention strategies to the large population that is being referred to and screened in our departments.

2. Cervical cancer is the primary focus for research on (i) prevention and early diagnosis (eg using DNA methylation markers), next to new treatment strategies including (ii) therapeutic vaccination strategies. Ad (i) We search for specific and sensitive methylation markers by several genome-wide approaches resulting in the identification of a methylation panel of genes, which might improve population-based cervical cancer screening. In addition, the role of these genes in cervical carcinogenesis will be analyzed to identify novel targets for treatment. Ad (ii) we are developing innovative immunization strategies against HPV induced neoplasia (e.g. cervical cancer). Several approaches in the area of the activation of the innate and adaptive immune system are being pursued including genetic immunization with recombinant suicide viral vectors based on Semliki Forest virus and protein/virosome-based immunization strategies. For valorization of this strategy a company (VICINIVAX) has been established.

3. Multimodality treatments are explored to improve anti-cancer treatment e.g. in ovarian cancer histiosubtypes. The multimodality treatments are based on tumor characteristics of chemoresistant ovarian cancer, derived from transcriptome, kinome, methylome and immune profiles to target pathways related to apoptosis, survival, oncogene activation and DNA methylation as well as enhancing anti-tumor activity of the immune cells. Efficacy of treatments is tested in cell lines and xenograft models, ex-vivo patient living explants, and in-vivo patient derived xenotransplants in mice. The patient-derived primary models are essential to study the interactions between tumor cells and microenvironment, including immune cells.

4. Clinical research focus on exploring novel anticancer therapies and surgeon assisting technologies for sensitive detection of (local) metastases in cervical, ovarian and vulvar cancer. Imaging guided development of novel anticancer therapies and the detection of sentinel nodes or metastases are extensively explored. Therapeutic cancer vaccination clinical trials are in development to be added to the multimodality treatment strategies.

The next step is to translate the knowledge to the other fields within our programme or outside.

RELEVANCE FOR HEALTHY AGEING

Cancer is the most important cause of death in the Netherlands. Improved prevention and early detection of gynaecologic cancers will have a major impact on healthy aging of women. With the development of preventive and novel treatment strategies we will reduce overall cancer-related kill and short and long term morbidity induced by the current treatments. We will focus on extensive collaborations with ERIBA and Oncolife programme to further contribute to the healthy aging programme.

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3. Cellular Damage and Repair in Cancer and Cancer Treatment

Programmeleaders: dr. M. van Vugt, prof. GH de Bock, prof. R. Coppes

MISSION

The aim of the "*Cellular Damage and Repair in Cancer and Cancer Treatment*" programme is to coordinate research activities on the mechanistic insight and clinical implications of short- and long-term effects of anti-cancer treatments. The activities are focussed on three levels:

1. Genetic and chromosomal damage in tumorigenesis and ageing.
2. Short- and long-term responses to anti-cancer treatments in normal and cancer tissues.
3. The short- and long-term effects of cancer, anti-cancer treatments and preventive strategies on health related outcomes and quality of life in cancer survivors.

This research programme brings together scientists that investigate treatment consequences in cancer (stem) cells and normal (stem) cells, both at a basic mechanistic level and in (pre)clinical studies. In large cohort studies, the short-term effects of cancer and its treatment, as well as the incidence and prevention of long-term adverse effects of cancer and its treatment, will be investigated in cancer survivors on health related outcomes and quality of life in cancer survivors.

Our goal is to study different aspects of cellular and DNA damage, its repair and the clinical consequences thereof. We will do so by bringing together basic, translational and clinical researchers, and thus creating a scientific atmosphere that inspires (PhD) students, stimulates scientific collaboration and encourages cooperative research projects. By coordinating research activities of fundamental to clinical content, we aim to better understand the molecular and cellular mechanisms of cellular damage repair and translate these findings into improved

selection of cancer patients that benefit best from DNA-damaging treatment modalities, and improved management of short- and long-term consequences of cancer and anti-cancer treatment in cancer survivors.

DESCRIPTION OF THE PROGRAMME

The research programme “Cellular **Da**mage and **Re**pair in Cancer and Cancer Treatment” coordinates both basic research as well as translational and clinical studies in the field of cancer (treatment) related cellular and DNA damage in tumor and healthy tissue, as well as the short- and long-term consequences of cancer and anti-cancer treatment in cancer survivors.

1. The role of chromosomal and genetic defects in tumorigenesis and ageing

Cancer is a genetic disease. Epidemiological studies as well as studies in model organisms have shown that mutations in our DNA lead to accelerated cellular and organismal ageing and cancer. Within this programme we investigate which gene mutations interfere with genomic maintenance and predispose to accelerated ageing and cancer development. In addition, we use novel single cell DNA template strand sequencing techniques to study genetic variation between cells as a function of age and differentiation stage as well as genome instability in cancer (stem) cells

2. Responses of normal and cancer cells to genotoxic agents

Successful response of cancer patients to (genotoxic) therapies relies on multiple and diverse factors. Within this research programme we study how DNA damage repair, pro-apoptotic signalling and pro-survival signalling are involved in response to commonly used and experimental anti-cancer therapeutics. Moreover, specific subsets of treatment-responsive and treatment-resistant cancer cells and normal tissue cells are studied to ultimately identify mechanisms of treatment response. In addition, within our programme, analyses of patient-derived material are used to identify and validate predictive and prognostic markers in several tumor types and in normal tissues.

3. Long-term effects of anti-cancer therapeutics

Increasingly, better treatment results in more cancer survivors. Unfortunately, cancer and anti-cancer therapeutics also affects normal tissues, which may lead to profound adverse effects. These adverse effects include altered metabolism, cardiovascular events, normal tissue dysfunction and secondary cancers, many of which can be denominated as accelerated ageing. In addition, these adverse effects also clearly adversely affect health related outcomes and quality of life. Within this research programme, basic cellular studies aim to identify effects of radio/chemotherapy on normal (stem)cells and their regenerative potential. Also the effects of multimodality treatment, including surgery and anaesthesia, will be studied on cognitive functioning. In addition, clinical studies are performed to investigate prediction, short- and long term effects on health related outcomes and quality of life of screening and preventive strategies in individuals at increased risk of cancer (due to a mutation), and repair of late-stage adverse effects of cancer-therapies.

The “*Cellular Damage and Repair in Cancer*” programme organizes monthly meetings in which PhD students, post-docs, undergraduate students, technicians and PI’s discuss research progress. These cross-disciplinary and inter-departmental meetings are aimed to create an atmosphere, in which scientific insight and techniques are exchanged to optimally stimulate interaction and collaboration.

RELEVANCE FOR HEALTHY AGEING

Cancer is a genetic disease. Epidemiological studies as well as studies in model organisms have shown that mutations in our DNA lead to cancer. The process of tumorigenesis, however, is a multistep process that may take years to decades until cancer clinically manifests. For this reason, cancer risk rises with age and clearly prevents healthy ageing.

Paradoxically, whereas DNA damage causes cancer, also the treatment of cancer classically depends on DNA damaging agents. Unfortunately, these treatments are often not sufficiently effective. Efforts to improve these therapies and to identify those patient subgroups that benefit most from treatment, will ultimately help to increase the percentage of cancer survivors and their quality of life.

Improved cancer therapies and early-detection screening programmes have resulted in increased numbers of cancer survivors. These individuals have often undergone intense genotoxic therapies resulting in cellular depletion, inflammation and adverse metabolic and cardiovascular effects, resulting in normal tissue hypo-function. Strikingly, these effects significantly resemble accelerated ageing effects of non-cancer patients. Insight into how therapy-induced damage to and repair of normal tissues results in accelerated ageing will improve mechanistic insight into physiological processes of ageing and will clarify how we can improve anti-cancer therapy to secure healthy ageing of cancer survivors.

PRINCIPAL INVESTIGATORS

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Prof. dr. JA Langendijk
Prof. dr. MG Rots

4. Guided treatment in optimally selected cancer patiens: Translational and clinical research in oncology

Programme leaders: prof. dr. JA Gietema, dr. GM van Dam

MISSION

To improve outcome of cancer treatment with better guided therapy in optimal selected cancer patients while reducing collateral damage and unintended late effects.
Current classification of cancer is still based largely on the morphology of tumor cells, while current cancer diagnostics (e.g. CT/MR/PET) are primarily based on visualization of the size and shape, and to a lesser extent, the molecular composition and heterogeneity of tumors. The identification of more cancer-specific dynamic cell biological changes in tumors and/or body fluids and their visualization will improve detection, classification, characterization and imaging of cancer. By combining current and novel state-of-the-art imaging and -omics modalities, tumor heterogeneity will be acknowledged and tackled. In addition, these cancer-specific cell biological changes can also be exploited to identify unique targets for innovative guided therapy, to better select cancer patients to be treated, and to advance early identification of treatment efficacy, to adapt treatment to changing tumor characteristics, with the ultimate aim to improve outcome. This will improve and support our strategy to personalize patient tailored treatment of cancer. Furthermore, if successful these interventions should result in as minimal as possible harmful immediate and late side effects that would hamper quality of life and jeopardize healthy cancer survivorship.

DESCRIPTION OF THE PROGRAMME

A major challenge in current cancer research is the translation of promising preclinical data on more specific dynamic changes in cancer cells and its microenvironment into successful interventions. The tumor heterogeneity within and between patients hampers improvement. An important focus of research is the development and use of molecular imaging tools -both radioactive and optical- for drug development, patient and target selection and for monitoring of treatment effects including serial tumor biopsies, resulting in spatiotemporal information on tumor heterogeneity. Smart and small early clinical studies are considered to be the basis for successful translation. In addition, phase II studies followed by phase III studies will finally give a true evaluation of diagnostic accuracy of dynamic monitoring modalities and novel treatment options. Often, more detailed cellular mechanistic information is required to understand the nature of the different early changes in tumor lesions, their microenvironment and the response patterns seen in patients. This requires studies with a broad variety of techniques to define pharmacodynamic behavior of a systemic treatment with more detail on tumor pathology, -omics, imaging techniques and pharmacokinetics.
Positioned in a horizontal matrix structure, this programme by nature will interact and receive scientific input from the translational findings and developed tools from high output foci within the **GUTS** programme and from early level of translation from the other programs from the NNOC **“DARE”**, **“TARGON”**, and **“SALL”**.
With the improving results of anti-cancer treatments and the increasing numbers of long-term survivors, the relevance of and knowledge about the pathogenesis of treatment-induced long-term (and short-term) morbidity is also increasing. Improving knowledge about the occurrence of side-effects will provide opportunities for tailoring potentially toxic treatment and/or guiding primary and secondary prevention strategies for serious side effects of cancer treatment on an individual patient-basis.

Translational research
Objectives

- To develop and explore new tools for innovative classification, diagnosing and staging of cancer to tackle tumor heterogeneity.
- To identify and evaluate new targets for innovative cancer therapy.
- To develop markers and tools for early detection of cancer therapy response.

Clinical studies
Objectives

- To evaluate newly developed tools for innovative classification, diagnosing and staging of cancer in order to improve treatment outcome and understand treatment failure.
- To combine imaging and -omics in different relevant tumor and treatment groups in order to optimize selection of individual treatment options in view of tumor heterogeneity.
- To perform smart and small, marker guided early phase studies in patients with solid tumors in order to improve the treatment outcome.
- To detect and develop prediction models for early and late effects of cancer treatment, that can be used for primary and secondary prevention programmes.

Setting of investigations in the programme (horizontal matrix)

- Studies of relevant and informative oncological disease models i.e. ovarian cancer, neuroendocrine tumors, lung cancer, testicular germ cell tumors, head and neck cancer, GE-tumors, breast cancer, brain tumors.
- Studies in role models for relevant pathways e.g. DNA damage and repair.
- Studies on screening, inherited cancer predisposition, premalignant lesions, susceptibility for cancer or late effects, therapeutic drug monitoring, multi-morbidity, physical activity, health related quality of life and palliative care.
- Prospective follow-up of cancer patients from their initial treatment at our cancer center.

RELEVANCE FOR HEALTHY AGEING

An important objective of this program is to improve the understanding of cancer biology and to improve the outcome of cancer treatment based on a tumor- and patient-tailored approach. Better staging and selection of patients prior to their treatment will improve outcome and reduce unwanted sequelae. Adoption of a healthy lifestyle also during and after cancer treatment together with better handled multi-morbidity will lead to improved treatment outcome and thus contribute to healthy ageing.

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RESEARCH INSTITUTE WJK: W.J. Kolff Institute

1. Bioadhesion, Biocompatibility and Infection (KOLFF-BIOBI)

Programme leaders: prof. dr. HJ Busscher, dr. PC Jutte

Mission

Healthy ageing with a high quality of life is a general desire. Ageing starts with birth and no matter how well we adapt our life styles in an attempt to age in a healthy way, sooner or later the human body will become beyond natural repair. Sometimes severe trauma causes the human body to become damaged beyond natural repair. Often, oncological removal surgery creates irreparable damage while not seldom the results of wear cannot be repaired by natural processes.

Nowadays irreparable damage to the human body needs not necessarily be associated with loss of function and quality of life. Numerous permanent biomaterials implants or temporary devices are available for the restoration or temporary support of function. Whereas the implants and devices may differ widely (e.g., artificial hearts, prosthetic joints, vascular prostheses, dental implants, surgical meshes, breast implants, sutures, urinary and intravascular catheters, voice prostheses, contact lenses), all biomaterials implants and devices will attract microorganisms that interfere with their intended function. Biomaterials implants for permanent applications share the same two barriers with respect to their extended use: “the possibility of biomaterials-associated-infection and the lack of tissue integration”.

Although the programme focusses on the prevention of biofilm formation on all biomaterials implants and devices, its aims are formulated with respect to the infection prevention of permanent implants and devices:

1. To determine physico-chemical and biological mechanisms for the (simultaneous) interaction of microorganisms, mammalian cells and immune system components with biomaterials surfaces yielding tissue integration over biofilm formation to protect an implant.

2. To design new multi-functional coatings that can be applied to discourage microbial adhesion and growth and at the same time stimulate mammalian cell adhesion and growth on totally internal, permanent biomaterials implants.

To develop new *in vitro* and *in vivo* evaluations methods to substantiate biomaterials-related claims with respect to reduced infection risks of different implants and devices currently used in modern medicine.

Description of the Programme

Biomaterials implant surfaces in the human body are prone to infection, as can develop through three distinctly different routes. Peri-operative contamination is the best documented route and usually causes early implant-related infection. Also immediate post-operative contamination can be a cause of early failure of a biomaterials implant. Late post-operative infections by spreading of organisms from infections elsewhere in the body, have been described as well to be a cause for implant-related infections and failure of the implant. Since a biomaterial-associated infection (BAI) is difficult to treat with antibiotics due to the protection offered by the biofilm mode of

growth and intra-cellular sheltering or microorganisms, the fate of an infected implant often is removal, at great discomfort to the patient and costs to the healthcare system. Frequently even, the condition of a patient does not allow replacement surgery or removal of the implant or device. BAI can even be lethal when bacterial spreading throughout the body occurs. Whereas the infection rate of primary implants may be considered low (4-6% on average, depending on the implant type), infection rates in revision surgery are much higher and around 15% with huge discomfort to the patients and much higher costs than of primary placement.

Although mechanisms of bacterial and mammalian cell adhesion have been studied for decades, no ubiquitously accepted mechanism has been forwarded, and research is ongoing. An important general conclusion is, however, that bacteria often use the same adhesive sites in adsorbed protein layers on biomaterials implants and devices, than do mammalian cells. In order to put mammalian cells at an advantage in their attempts to integrate a biomaterials surface in the body versus microbial biofilm formation, we need a shift in paradigm for the development of biomaterials coatings from mono-functional (only non-adhesive to bacteria OR only adhesive to cells) to multi-functional (non-adhesive to bacteria AND adhesive to mammalian cells) ones. New insights in mechanisms of microbial and mammalian cell adhesion will be applied to develop multi-functional biomaterials coatings in combination with the Zernike Institute for Advanced Materials, Groningen, The Netherlands and Stevens Institute of Technology (Hoboken, USA) and other industrial and academic partners. Importantly, methods to evaluate biomaterials coatings, have only focussed on measuring one aspect of the coating performance at a time, while the shift in paradigm toward multi-functional coatings requires methods by which mammalian cell interaction on a biomaterial can be evaluated simultaneously with biofilm formation and the reaction of immune components.
Such studies not only attempt to find solutions for the current problem of BAI, but also prepares for the future problem of infections related to porous, biodegradable scaffold materials as used in tissue engineering.

Relevance for Healthy Ageing
Modern health care is greatly dependent on the use of biomaterials implants and devices for the restoration of function, after trauma, (oncological) intervention surgery or simply wear due to old age. This means that sooner or later, everybody in an aging society will have to rely on biomaterials implants or devices, either temporary or permanent. Therewith, biomaterials are indispensable for healthy aging.
Dental implants and total joint arthroplasties form the majority of all implants clinically applied, requiring tissue integration over biofilm formation. In dental implants, tissue integration is stimulated by creating a tight fit between the bone and the implant surface, but reportedly up to 15% of all implants fail due to peri-implantitis. In orthopaedics, joint arthroplasties are fixed with antibiotic-releasing bone cements, but there is a strong preference developing in the field for uncemented prostheses. Therewith the protection offered by antibiotic-releasing cements disappears and the clinical situation becomes very similar with dental implants.
The program focusses on the design of multifunctional coatings that can be applied for clinical applications as described above, requiring tissue integration. However, the programme is not limited to these application as the design phase will also yield opportunities to prepare non-adhesive, contact-killing and antimicrobial-releasing coatings that can be applied on temporary implants and devices like dental abutments, contact lenses, voice prostheses and intravascular or urinary catheters, as used extensively (but not exclusively) in the elderly.

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2. NanoBioTechnology and Advanced Therapeutic Materials (KOLFF-NanoBioMat)

Programme leaders: prof. dr. A. Herrman, dr. P. van Rijn

Mission
Nanobiotechnology is a highly interdisciplinary research area. It is based on the interplay of contributions from chemistry, physics, biology, pharmacology, materials science, medicine and several forms of engineering. The integration of disciplines is exploited to generate structures with dimensions on the nanometer scale originating from biological or bioinspired components such as oligonucleotides, proteins, other (bio) polymers, viruses and cellular components. Equally important as nanotherapeutics is the utilization of synthetic nanomaterials to manipulate and follow biological processes as well as developing analytical tools based on nanosystems applied in biology and medicine. The impact of nanobiotechnology on the medical field can be divided in two areas. On the one hand, it is the enabler for new therapeutic modalities and advances in the field have the potential to revolutionize the way the medical community approaches modern disease management. On the other hand, inorganic nanoparticle probes are powerful tools for signal amplification in the context of DNA and protein detection systems and some assays are already commercialized.
Within this program we will employ tools from nanobiotechnology to fabricate powerful drug carrier systems and nanoscale surface coatings. These systems will be composed to a great extend on oligonucleotide and peptide scaffolds or their hybrids with other materials like synthetic polymers since these materials allow best the design of nanoobjects with predefined and programmable size, shape and functionality. Starting out from such materials, the efforts and mission of the program can be summarized as follows:

Fabrication of multifunctional drug carrier and coating systems exhibiting nanometer-sized dimensions or features.
Delivery of biologicals (nucleic acids and proteins) since those entities have the greatest future therapeutic potential and their success heavily relies on formulation and stabilization by nanosystems. Another class of compounds on which we will focus are pharmacologically highly potent drugs/new chemical entities that have a toxicity profile that limits their further therapeutic application in free dosage forms.
Development of new in vitro and in vivo methods to investigate and prove the efficacy of

(targeted) drug delivery systems with an emphasis on spatial resolution in the nanometer regime.

Description of the Programme

Nanotechnology is defined as the “intentional design, characterization, production, and applications of materials, structures, devices, and systems by controlling their size and shape in the nanoscale range (1-100 nm).[British Standards Institute 2007] And indeed this new field of science has undergone explosive growth in the last 10-15 years, whereby the subfield known as Nanobiotechnology holds some of the greatest promise.

In this context it is planned to construct novel carrier systems based on DNA, proteins, peptides and hybrids of these materials with other synthetic moieties. The reason for employing these biological building blocks as scaffolds is that they allow the fabrication of nanostructures with predefined size, geometry, surface functionality and payload. Excellent examples for such a way of DNA nanoconstruction are the so called DNA origami approach or the self assembly of 3-D objects from DNA tiles. In this program similarly defined nanoobjects are envisaged for the utilization as delivery vehicles including DNA block copolymer micelles, virus capsids, polymeric micro/nanospheres (D. Grijpma) and liposomes with DNA amphiphiles (A. Herrmann) or engineered channel proteins incorporated into the membrane (A. Kocer).

These carriers will be equipped with targeting functions especially peptides recognizing PDGF-receptors (K. Poelstra) on cancerous cells/tissue and epitopes on endothelial cells being part of the blood-brain barrier (BBB) to induce carrier transport across the BBB (I. Zuhorn). The lab of Molema and Kamps at UMCG will focus on harnessing these delivery systems with ligands specific for endothelial cells in tumor and inflammatory microvasculature. Their lab has furthermore unique read-out systems of pharmacological activity in the complexity of tissues as a prerequisite for P-O-C of targeted delivery success. In particular, targeting of the nanoobjects will greatly benefit from the use of the novel carrier systems since the targeting units can be introduced at specific sites with controllable spacing and density. Due to the fact that the fabrication of the delivery vehicles relies on self-assembly many different structural features can be realized in short time allowing to apply a combinatorial approach for their testing.

Targeting the right type of cells or tissue is just the first step that needs to be mastered for successful delivery of a drug. After internalization of the carrier the pharmaceutically active ingredient must reach its intracellular target. For that purpose laser scanning confocal imaging and life-cell imaging will be employed. These techniques will be supported by approaches to optical sub-diffraction resolution imaging (“super-resolution”) providing us with unique insights into un-synchronized intracellular processes and dynamics with high temporal (down to nanoseconds) and spatial resolution (down to nanometres) (A. van Oijen). In this way, we will be able to study up-take mechanisms, to follow the fate of carriers, to observe release of payload and to localize drugs.

All these techniques and carrier systems will be employed for the delivery of nucleic acid and protein drugs. Since such drugs are very prone to degradation and suffer from poor cellular uptake we will, in the era of synthetic biology, employ protein engineering to overcome some of these obstacles (apoptosis inducing anticancer drug, W. Quax; supercharged proteins, A. Herrmann) or use the sugar glass technology (W.L.J. Hinrichs) for further stabilization. Since several of the carrier systems are based on biomacromolecules they might elicit immune responses. Therefore, ophthalmic drug delivery plays an important role in this program due to the immune privilege of the eye.

Relevance for Healthy Ageing

Cancer is the leading cause of death in economically developed countries and its global burden

is expected to increase one reason being an aging population. Several efforts within this program are directed towards developing novel carriers for the delivery of anticancer drugs. The nanomaterials are designed to target tumors in vivo and when infused into the blood stream lead to accumulation of the drug in the tumor tissue. In the future cancer patients might strongly benefit from the advanced therapeutic materials developed in this program because appropriate ways of surface functionalization of the carrier increases their half-life in the blood circulation, prevent opsonising proteins from adhering and reduce rapid metabolism and clearance. Moreover, adverse side effects that especially affect elderly patients are minimized by preventing nonspecific uptake of toxic therapeutic agents into healthy tissue.
Besides in cancer treatment, elderly patients will also greatly benefit from drug carriers being employed in the context of ophthalmic delivery. Eye-related diseases are usually cured by local treatment with eye drops or intraocular injections. Diseases regarding the anterior sections of the eye like infections of the cornea or the conjunctiva can nowadays only be treated with the very frequent application of highly concentrated antibiotic eye drops. Almost all intraocular tissues are not reached by surface applied therapies. Only 1% of the drug remains at the eye while 99% of the pharmaceutically active ingredient is washed away by tear flow and eyelid movement, which can lead to systemic side effects when getting in contact with nasal mucosa and oral cavity. It is even more difficult to achieve effective levels for treatment of diseases of the retina like age related macular degeneration (AMD) making regular intraocular drug injections necessary. With the novel carrier systems the amount of injections might be minimized or even completely avoided.

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3. Maintaining Oral Health and Oral Function (KOLFF-MOHOF)

Programme leaders: prof. dr. HJA Meijer, dr. PK Sharma

Mission
Mission: to provide new tools for prevention of oral health disorders to occur and to produce new strategies to restore and maintain oral health and function during life with minimal costs and efforts.

Aim:
1. to improve understanding of the mechanisms of biofilm formation and manipulation and to better understand the role of saliva. The focus is:
1a. physico-chemical factors involved in salivary protein adsorption, oral lubrication, prevention of biofilm formation to hard and soft oral surfaces, and surfaces of restorative and orthodontic materials
1b. new oral health care measures for the control of oral biofilms, including toothpaste formulations, more effective toothbrushes, coatings and other modifications of dental materials used for the restoration of oral function.
1c. clinical evaluation of oral health care products and dental materials applications and further explore the relation between oral health and the human health status in general.

2. to improve understanding of behaviour of indirect restoration materials and dental implants and to explore new strategies to restore function. The focus is:
2a. evaluation of indirect restoration materials
2b. evaluation of dental implants in the aesthetic region
2c. evaluation of dental implants to improve retention of full dentures
2d. evaluation of short dental implants
2e. exploring new possibilities with dental implants, as well intra-orally as extra-orally

3. to improve understanding and to explore new materials for fixation systems in maxillofacial traumatology

Rationale: Maintaining oral health and restoring function is important for quality of life. Laboratory models of oral ecosystems and manipulation of essential parameters in these systems are studied *in vitro* and tested *in vivo*. Therefore this programme requires a multidisciplinary research approach in which both clinical research scientists and laboratory scientists in microbiology, physics and material science corporate.

Description of the Programme
A healthy oral cavity, acceptable aesthetics and a functional dentition contribute to quality of life. Oral health facilitates eating, drinking, speech and therefore plays an essential role in healthy aging. The oral cavity is the main portal of entree of the human body and therewith the first defence line against disease. The balance between oral health and disease involves predominantly chemical and microbial surface phenomena. One area involves the role of saliva in oral homeostasis. With aging the balance shifts gradually toward a more diseased state. All surfaces in the oral cavity are covered with an adsorbed salivary protein film to provide sufficient lubrication and to allow mastication and speech. Particularly in the elderly, decreased salivary lubrication often needs treatment including artificial saliva's. Salivary conditioning protein films on oral hard and soft surfaces facilitate microorganisms to adhere and to form oral and dental biofilms. Dental plaque is essential in the etiology of dental and periodontal diseases. Inhibition and manipulation of biofilm formation is an essential strategy to prevent chronic oral infectious diseases to develop. A variety of oral health care products and measures is currently available. However, especially in the elderly and children receiving orthodontic treatment effective control of the oral biofilm needs further improvement. Chemical plaque control is also essential in periodontics and implant dentistry where they support both preventive measures as well as treatment interventions. If the preventive measure fails, cavities will appear.
The restoration of cavities can be done with composite biomaterials, requiring optimal adhesion between enamel or dentine surfaces and the composite. In cases of tooth loss, rehabilitation through dental implants is one treatment option. This requires favorable interaction with bone

cells and the implant surface and a repulsive one with oral microorganisms. Next to establishing and maintaining osseointegration of dental implants, also aesthetics of the restoration, function and patient satisfaction are part of the evaluation. Applying biomaterials in fixation of bones and covering of defects after trauma must help in quickening the healing process. In vitro and in vivo evaluations of new materials are carried out to explore properties and possible complications. The programme is characterized by multidisciplinary research including clinicians, microbiologists and material scientists.

Relevance for Healthy Ageing

Oral disorders are often cumulative, i.e. destruction of oral tissues and loss of function accumulate in time. Therefore, aging is positively associated with reduced oral functions. Oral diseases have great impact on mastication, lubrication, speech, taste and aesthetics. Maintaining or restoring oral health and function have therefore a significant impact on quality of life parameters. Oral diseases, e.g. periodontitis is not only a local chronic inflammatory oral infectious disorder but the disease has systemic effects. Positive associations have been established between oral health and cardiovascular diseases and auto-immune diseases notably diabetes, rheumatoid arthritis and thyroid disorders. Oral diseases can have an impact on the onset and progression of these diseases. Also, treatment of these diseases can be hampered in subjects with oral infections. Reduction of the total inflammatory status including reduction or elimination of chronic oral infections in susceptible individuals can therefore contribute to reduction of medical and economic burden.

Tooth loss still increases with age, and demographic trends indicate that the population of older individuals is increasing in size. As a result, the number of edentulous people and the demand for complete dentures will continue to be high for several decades. Edentulous patients often experience problems with removable complete dentures. Lack of stability and retention of their dentures, together with pain, decreased chewing ability, and speech problems, are common obstructing complaints reported by these patients. Clinical studies revealed that these denture-related complaints seriously affect the patients' quality of life. For example, masticatory performance in complete denture wearers is less than 20% of masticatory performance in subjects with a natural dentition. As a result many denture wearers face problems when eating food, and particularly when eating hard or tough food. This inconvenience forces patients to change their diets, often resulting in poorer nutrition compared with patients who have their natural teeth. Therefore, it is not uncommon for many denture wearers to report gastrointestinal problems. Implant-retained overdentures improve edentulous patients' nutritional status, general health, and quality of life.

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4. Restoring Organ Function by Means of Regenerative Medicine (KOLFF-REGENERATE)

Programme leaders: prof. dr. RA Bank, prof. dr. SK Bulstra

Mission

Mission: To realize the re-establishment of tissue and organ function by means of biological or engineering intervention strategies based on an understanding of the determinants of cell plasticity, in particular the role of micro-environment and extracellular matrix, thus enabling to manipulate the structure-function-environment relationship in an integrative fashion.
Aim: The central aim of regenerative medicine is the functional repair of damaged or diseased tissues and organs by application of modulating molecules and/or (stem) cells with the guidance of polymeric scaffolds.
Rationale: Regenerative Medicine is a promising and rapidly developing multidisciplinary research area. Most regenerative medicine approaches currently deal with the repair of tissues rich in extracellular matrix. A main problem in these approaches is the establishment of a functional collagen network. We here investigate the homeostasis of collagen in normal and fibrotic tissues, tissue repair processes (with a focus on inflammation), and the use of materials to restore organ functions (with a focus on the foreign body reaction).

Description of the Programme

Regenerative medicine aims at the generation of functional biological tissues for the replacement of diseased or impaired tissues. To do so, often (stem) cells are used in combination with a degradable biomaterial that serves as a temporary scaffold and which is replaced by the tissue in question. Tissue damage and biomaterials implanted into the body invariably evoke an inflammatory response, which sets the stage for tissue repair. Normally, the progression from inflammation to repair is regulated in such a way that tissue repair is adequate. Aberrant inflammation will lead to fibrosis.
The research programme focuses various aspects of tissue (re)generation, repair and remodeling, including inflammation. Our main research questions are:
1. What is the role of key cellular and molecular players in maintaining the balance between inflammation, physiologic repair and aberrant repair (fibrosis)?
2. How can we orchestrate the tissue microenvironment in order to promote repair and/or prevent fibrosis?
3. How can we translate basic insight into above aspects into new therapeutic approaches (e.g. by means of biomaterials)?

Organ and tissue repair

Organ and tissue damage invariably leads to inflammation, which makes way for tissue repair. The interplay between inflammatory cell subsets dictates the outcome of inflammation, but is poorly understood mechanistically. Some of the research topics are:

- What is the cellular composition of inflammatory processes in settings of organ damage and *in vivo* foreign body reactions?
- What regulates the cellular plasticity of macrophages?
- How do macrophage subsets (M1, M2) determine the outcome of inflammation and tissue repair?
- How is the transition from inflammation to repair modulated?

- How can the local inflammatory microenvironment be modulated by local drug delivery, in order to achieve reparative outcomes?
- In what way differs fetal wound healing from adult wound healing?

The foreign body reaction

This response towards implanted materials by the non-specific immune system is known as the foreign body reaction (FBR). Macrophages are key players in the FBR, as well as the giant cells that are formed by means of fusion of macrophages. Controlling the activation of macrophages and the formation of giant cells are powerful tools to modulate the FBR, thereby improving regenerative strategies to repair tissues. For this we want to obtain insight in:

- The respective role of macrophage subsets in the foreign body reaction;
- The molecular basis of macrophage fusion and molecular basis of collagen degradation by macrophages and giant cells;
- The way macrophages communicate with fibroblasts and *vice versa*;
- The role of fibroblasts in collagen deposition (capsule formation; stromal formation);
- The role of physical and chemical parameters of biomaterials on the onset and evolution of the foreign body reaction.

Fibrosis

A pathological outcome of wound healing processes in a variety of organs (e.g. heart, liver, lung, kidney, skin) is the deposition of an excessive amount of collagen, being the hallmark of fibrosis. The pathogenesis of fibrosis remains poorly understood, mainly because it is unknown what subsets of fibroblasts are involved in collagen deposition, and where these subsets originate from. In addition, we know little about the role of certain collagen-modifying enzymes in fibrosis. Understanding the pathways leading to an excessive accumulation of collagen is not only of help to define intervention points for novel therapeutics to prevent fibrosis, but will also benefit regenerative medicine approaches (one of main problems in tissue engineering is the limited deposition of collagen in neoconstructs, which is the opposite of fibrosis).

Relevance for Healthy Ageing

Trauma, disease, and even aging can leave critical defects that the body cannot heal by itself. The resultant loss of function can be debilitating or life threatening. Using a combination of cells, bioactive molecules, biomaterials, and even mechanical conditioning, regenerative medicine seeks to achieve functional restoration of tissues and organs. Regenerative medicine will help to produce extended healthy longevity, as we will be able to repair some of the damage caused by aging, organ by organ. Ageing can be viewed as a set of precursors of the diseases and disabilities of old age: a set of side-effects of normal metabolism that accumulate throughout life and eventually impair and overwhelm our biology. Regenerative medicine is the medicine of the 21st century: with (stem) cells, biomaterials and other techniques, we will be able to repair diseased and disabled bodies with increasing effectiveness. In improving patient care, especially in relation with tissue loss or dysfunction, the use of proper biomaterials plays a key role. The shift from tissue removal to tissue replacement and at present, tissue regeneration is driven by the evolution of biomaterials from bioinert to bioactive and bioresorbable associated with advances in molecular biology, and by the increasingly complex biomedical problems of an aging and more active population. Especially fibrosis is prominent in many chronic diseases and aging processes, and represents an enormous health burden; it is estimated that > 25% of deaths can be attributed to fibrosing disorders.

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PLATFORM PROGRAMME: CENTER FOR MEDICAL IMAGING

Programme leaders: prof. dr. RAJO Dierkcx, prof. dr. M. Oudkerk

The CMI-Groningen research programme is embedded in and supports all institutes.

Mission

CMI^{NEN} is one of the eight Centers of Research Excellence (CoRE) of the Innovative Medical Devices Initiative programme (IMDI), acknowledged by the Netherlands Organisation for Scientific Research (NWO) and the Netherlands Organisation for Health Research and Development (ZonMW). CMI^{NEN} is a public-private initiative, founded by the universities of Groningen and Twente, UMCG, and Siemens Netherlands. The CMI-Groningen research programme is part of the CMI^{NEN}.

The CMI-Groninge research programme aims at research and development of minimal to non-invasive medical imaging techniques and will improve existing technologies and optimize their integrated use. The CMI-Groningen research programme will use medical technology assessment (MTA) of new and existing imaging techniques to contribute to a higher quality and more affordable healthcare. Oncology (including inflammation), cardiovascular diseases, and neural and neuromuscular diseases are the major themes of the CMI-Groningen research programme. Only through innovation we can improve the quality and contain the costs of future health care. Medical imaging will play a major role in this exercise. Next generation imaging technologies will enable the early diagnosis of, for example, cancer and Alzheimer's disease. This will lead to early interventions which delay or prevent the onset or spread of disease and mitigate its effects. New and more effective imaging tools and methods will also facilitate the transition from invasive to minimally-invasive to non-invasive diagnosis and therapy. Medical imaging addresses the main factors for the quality and costs of medical interventions: diagnostic accuracy, the need for (revision) surgery, side effects and recovery times.

Description of the Programme

The research will focus on problem definitions originating from three clinical fields: oncology (particularly breast, lung and prostate cancer, including inflammation), cardiovascular diseases and neuro(muscular) diseases. To solve these problems, the research will concentrate on (combinations of) existing and new imaging technologies developed on those platforms: ultrasound, optics, magnetic resonance, X-rays and molecular imaging. Finally, four 'enablers' bring a third dimension to the strategic agenda to ensure accuracy, controllability, efficiency and effectiveness of research & development in medical imaging and its applications in diagnosis and treatment. The enablers, i.e., targeted contrast agents, navigation technology, medical imaging informatics, and MTA, cover all imaging technology and disease areas.

The CMI-Groningen research programme will focus on breast, lung and prostate cancer. Two major strategies are likely to reduce cancer morbidity and mortality: 1) Early detection, making curative treatment easier to apply, and 2) personalized (patient-tailored) tumor treatment. Anatomical imaging techniques such as CT, MRI and mammography already play a, far from perfect, role in cancer treatment. It is to be expected that the combination with molecular imaging techniques such as fluorescent imaging can support early detection with SPECT and PET scanning and can facilitate the design of optimal radiotherapy and systemic treatment. Cardiovascular complications were the second most significant cause of death in the Netherlands in 2007 (> 30% of all deaths). As with cancer, important strategies to reduce these numbers are early detection and prevention and tailored-made treatment strategies. Developments in medical imaging will lead to improved identification of high-risk groups,

enabling focused monitoring and early intervention which will help reduce mortality and morbidity rates. Non-invasive imaging techniques, such as MRI and CT, can be used in early detection strategies.
Currently, most research on neuro(muscular) diseases focuses on the fundamental understanding of the brain. This field of research will continue to advance rapidly as a result of improving capabilities of neuroimaging methods and techniques. The extensive data provided by improved medical imaging expands the knowledge of the function and organization of the human brain.

Multidisciplinary research projects
The CMI-Groningen research groups will be formed for each imaging technology by expanding existing cooperative research groups and, where appropriate, by establishing new research associations. Unique among research initiatives in medical imaging, CMI-Groningen research groups will, by definition, consist of both technological and medical researchers (complemented by biologists, pharmacists, MTA specialists etc. if required), meaning that technical and medical knowledge and competences are integrated.

Relevance for Healthy Ageing
The CMI-Groningen research programme will help to realize the vision that, by 2020, individuals with an elevated risk of developing cancer, cardiovascular and neurological diseases can be identified at an early state. Patients are likely to be cured with less pain, lesser hospitalization duration and a shorter recovery period, which will allow for a quicker restart at work. The CMI-Groningen research programme will achieve this by:
- First, developing systematic pathways for the appropriate application of new and existing medical imaging technology, including new and existing biomarkers, in optimal diagnostic algorithms (sets of rules and procedures to solve diagnostic problems);
- Second, focusing on techniques with high predictive power to exclude rather than demonstrate diseases. Low cost, high sensitivity tests to exclude diseases are expected to become very important in reassuring patients, reducing medicalization and containing healthcare cost;
- Third, developing a model of the diagnostic and minimally invasive treatment center of the future. Such a center will contain all procedures for primary diagnosis, starting from a clinical question and resulting in a final diagnosis – preferably within one day. A limited number of high-end university diagnostic centers can serve the entire population, while follow-up diagnostic care remains an intramural procedure;It is important to note that, although the CMI-Groningen research programme's primary focus is on imaging-enabled diagnosis, its impact will extend far into therapy. Better imaging and more accurate navigation lead to smaller interventions posing a lesser burden on patients. They also produce better results, leading to fewer relapses.

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