

# Research Themes 2016

## For MSc Students

**Research Master Health Sciences  
& Research Master Clinical Research**

# Research Themes for MSc-students

## Edition 2016

### Research Master Health Sciences & Research Master Clinical Research

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## Foreword

Thanks to the work of researchers round the world, knowledge and skills are developing rapidly in the medical sciences. At the center of each new development is a doctor who has successfully formulated the right questions about patient-related problems and written them up as a research protocol – for laboratory research, for applied clinical research, or for a combination of the two. In short, the medical sciences depend on doctors with a facility for combining patient care with research in an academic setting.

The Research Master programmes in Clinical Research and in Health Sciences is open to motivated second-year medical students. As well as providing a comprehensive background to clinical research methods, it gives a working knowledge of a clinical specialist area. In addition, students are taught to write a research protocol and to conduct research.

An important part of this program is dedicated to a research project in which students work under the guidance and supervision of a personal tutor, to whom they are assigned at the start of the academic year. These activities lead to the writing of a thesis and may lead to the submission of an article to an international scientific journal.

This guide summarizes the research activities and research lines of the departments and research groups participating in the Clinical Research and Health Sciences programmes. It could represent your first step towards a varied and exciting professional career. We sincerely hope it will inspire you to join this challenging program!



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# 1. Endocrinology and Neuro-Endocrine Immunology

## Theme 1: Endocrinology and Ageing

All subthemes of 'Endocrinology and Ageing' try to implement their basic research data from the bench in the patient and the population, while at the same time answering the questions from studies in the population by working at the bench.

Keeping a constant eye on the clinical relevance of basic research for the patient and population at large and vice versa, has positioned these themes at a recognized high level in the scientific community, as can be demonstrated by e.g. the scientific output and obtained grants, both from national and international sources. In the following pages, each of the themes is described in more detail.

### Subtheme 1: Neuro-endocrinology

Dr. L.J. Hofland, Dr. F.J.W. Koper, Dept. of Internal Medicine; Section of Endocrinology, Prof. dr. Dr. E.P. Krenning, Dept. of Nuclear Medicine; Dr E.F.C. van Rossum, Prof. dr. Dr. S.W.J. Lamberts and Prof. dr. Dr. A.J. van der Lely, Dept. of Internal Medicine; Section of Endocrinology

This subtheme studies disorders in neuro-endocrinology, neuro-immunology and endocrine oncology. It develops new modalities for molecular imaging and treatment using peptide receptors as primary targets and aims to unravel the endocrine and immunological basis of important diseases in the community.

In particular, the research includes the following main topics:

- Pituitary adenomas (Dr. L.J. Hofland)  
Pituitary adenomas cause severe clinical syndromes due to hormonal overproduction by the adenoma cells. Striking examples are acromegaly due to a GH secreting pituitary adenoma and Cushing's disease due to excessive ACTH secretion by a pituitary adenoma. The search for novel medical therapies for these diseases is one of our main aims.
- Neuroendocrine tumors (NET) (Dr. L.J. Hofland)  
Most NET cells express peptide hormone receptors. Such receptors can be used as molecular targets for diagnosis and therapy. The most striking example is the localization and treatment of neuroendocrine tumors using radionuclide coupled peptide somatostatin analogs. Apart from somatostatin receptors, also other peptide hormone receptors are expressed on tumors, such as bombesin receptors on prostate- and breast cancer. The expression of peptide hormone receptors on tumors and the role of radiolabeled peptides in the in vivo localization and treatment of tumors is studied.
- Ghrelin (Prof. dr. Dr. A.J. van der Lely)  
We have discovered that ghrelin can influence insulin sensitivity and that its unacylated form can significantly improve insulin sensitivity by antagonizing the acylated form of ghrelin, which makes the combination a candidate for treatment of the many disorders which can be characterized by an increased insulin resistance. Studies on the metabolic activities of ghrelin and the role of ghrelin receptors herein form a main arm of the current research activities.
- Glucocorticoid receptors (Dr F.J.W. Koper, Dr E.F.C. van Rossum)  
We identified a number of polymorphisms in the glucocorticoid receptor (GR)-gene that are associated with changes in the glucocorticoid sensitivity. A main research goal is the identification of the effects of these variations on numerous aspects of health and ageing.
- Cortisol in relation to cardiometabolic diseases and psychiatric diseases (Dr E.F.C. van Rossum, Dr F.J.W. Koper)  
We are one of the few laboratories in the world who developed an innovative method to determine long-term cortisol levels using scalp hair. Studying relations between the stress hormone cortisol and the metabolic syndrome, cardiovascular disease, mental illnesses and numerous other disease was previously limited by the only available highly variable point measurements in e.g. blood and saliva. In contrast, our novel cortisol analysis in hair resulted in numerous promising insights in these stress-related diseases and yielded many possibilities to study other diseases or conditions, which are related to cortisol. Most of the findings are directly relevant for clinical practice.
- Insulin-like growth factor I (IGF-I)  
We recently studied genetic polymorphisms in the regulatory region of the IGF-I gene and found that both the risk

of type 2 diabetes and myocardial infarction were significantly increased in non-carriers of a 192-bp allele when compared with carriers of this polymorphism. This suggests that a genetically determined exposure to low IGF-I levels plays a role in the pathogenesis of both type 2 diabetes as well as myocardial infarction. Considering the high complexity of the IGF-I system, which includes many binding proteins, we have now developed an IGF-I bioassay to determine more in detail the role of genetic variations in the IGF-I gene in relation to circulating IGF-I bioactivity.

#### - Peptides and their receptors in immune disease

We have found that peptide receptors for somatostatin are expressed on normal immune cells, as well as on activated lymphocytes and monocytes in affected tissues of patients with rheumatoid arthritis and patients with granulomatous disease. An important line of research is to investigate the potential role of somatostatin analogs (unlabeled, radiolabeled-, or labeled with photosensitizers) in the treatment of various types of immune disease.

### Subtheme 2: Role of the thyroid gland in disease

Prof. dr. T.J. Visser, PhD, Department of Internal Medicine, Section of Endocrinology

Dr. R.P. Peeters, Department of Internal Medicine, Section of Endocrinology, Rotterdam Thyroid Center

Thyroid hormone (TH) is crucial for normal development and tissue function. Its actions are mediated via binding to nuclear TH receptors (TRs), encoded by the *THRA* and *THRB* genes. It is known for decades that inactivating mutations in *THRB* result in a well-documented clinical syndrome of TH resistance. Ever since the characterization of the *THRA* gene in 1987, investigators have searched for patients with mutations in TR $\alpha$ . This was without success until we and others recently identified the first patients with a defective TR $\alpha$ 1, suffering from marked growth retardation, mild cognitive defects, and biochemical alterations resembling those in patients with combined pituitary hormone deficiency (van Mullem et al, NEJM 2013).

Our group currently studies this newly discovered clinical phenotype in detail. The overall approach includes: 1) identification and characterization of new patients with mutations in *THRA*, 2) elucidation of the molecular mechanisms causing the phenotype of patients with a mutation in TR $\alpha$ 1. By combining clinical data from patients with mutations in *THRA* with animal data and *in vitro* data from transfected cells, we will obtain important new insights into the mechanisms underlying this new clinical syndrome. Identification of additional patients with mutations in *THRA* is of crucial importance because current evidence predicts that these patients will benefit from treatment with TH, which is easily available and costs only €30 per year.

Additional studies of our group focus on genetic defects in other TH pathway genes, such as TH transporters. Since the action of T3 is large exerted by binding to nuclear receptors, transport of T4 and T3 across the plasma membrane by specific transporters is required.

Recent studies in our lab have identified two members of the monocarboxylate transporter family, MCT8 and MCT10, as active and specific thyroid hormone transporters. The pivotal importance of MCT8 has been demonstrated by our identification of mutations therein in patients with severe psychomotor retardation and abnormal thyroid hormone levels. Thyroid hormone is crucial for normal brain development, and mutations in MCT8 are believed to impair T3 uptake in central neurons, leading to the defect in neurological development. Similar abnormalities in brain thyroid hormone homeostasis may result from mutations in other TH pathway genes, such as those coding for MCT10, or the enzymes involved in intracellular metabolism of TH (deiodinases).

We have started a large study aimed at identification and characterization of mutations in thyroid hormone-related genes in patients with psychomotor retardation and abnormal thyroid parameters. Aspects of this study range from clinical to very basic. If you wish to read more about deiodinases and transporters and our recent work in patients with psychomotor retardation, see our recent review (Visser et al. Mol Endocrinol 2011; 20: 1-14).

### Subtheme 3: Calcium and Bone related research

Prof. dr. J.P.T.M. van Leeuwen, Prof. dr. H.A.P. Pols, Prof. dr. A.G. Uitterlinden, Department of Internal Medicine, Section of Endocrinology

Calcium and bone metabolism research focuses on the regulation of skeletal and calcium homeostasis and the development and progression of diseases in particular during ageing. The eventual goal is by integration of molecular and cell biological, experimental animal models, epidemiological and genetic epidemiological and clinical research to achieve improved diagnostics and treatment of skeletal diseases and disturbances in calcium metabolism. The current therapies for osteoporosis are predominantly directed to inhibit bone resorption and thereby progression. There is, however, a great need for anabolic therapies that stimulate bone formation because bone loss has already occurred at the moment that the consequences of osteoporosis become overt. In line with this, the improvement of early diagnosis is of great importance.

Four major interrelated research lines directed to aetiology, diagnostics and treatment of calcium and bone related diseases can be identified.

1. Molecular mechanisms of bone cell differentiation and regulation of bone formation and resorption.

The aim is:

- to identify novel therapeutic targets and therapies for osteoporosis and to obtain new insights into mesenchymal stem cell differentiation important for tissue engineering, and
- to assess new leads for the identification and characterization of risk determinants (see Research line 2) by genomic and proteomic approaches.
- Identification and characterization of risk determinants for osteoporosis.

The aim is:

- to analyse genes/proteins identified in Research line 1 as risk determinants, and
- to identify new markers by serum protein profiling of individuals with specific osteoporotic characteristics (e.g. fractures).

This research can be perfectly coupled to the genome wide association studies that are planned to be performed within the Rotterdam Study.

2. Relationship of osteoporosis and osteoarthritis and the significance for development of osteoarthritis.

In the clinic severe forms of osteoporosis and osteoarthritis seem to exclude each other, however, there also seem to be overlapping aetiological mechanisms. The aim is to include in the research lines 1 and 2 also the osteoporosis – osteoarthritis relationship and to assess differences but also to analyse common mechanisms.

3. Calcium homeostasis in relation to bone metabolism and osteoporosis.

The aim is to investigate changes in calcium homeostasis and bone metabolism during aging by human population and experimental animal studies. The combination of human population and experimental animal studies provide the opportunity to analyse the epidemiological observations at a more mechanistic level. These studies will provide new insights into the calcium and skeletal homeostasis and potential novel therapeutic and diagnostic targets which are coupled to research lines 1 and 2.

#### **Subtheme 4: Metabolism and Reproduction**

Dr.ir. J.A. Visser, Prof. dr. A.J. van der Lelij, Dept. of Internal Medicine; Section of Endocrinology

The research of the Metabolism and Reproduction group is directed at gonadal and metabolic dysfunction. Through a combination of physiological, genetic and signal transduction studies our group aims to understand the role of steroid hormones, peptide hormones, and growth factors in the interaction between gonadal function and metabolism (such as reproductive aging, PCOS) and metabolism (including metabolic aging). The hormones studied include estrogens, androgens and glucocorticoids, ghrelin and unacylated ghrelin, and TGF $\beta$  family members such as anti-Müllerian hormone and bone-morphogenetic proteins. An important focus of our studies is on white and brown adipose tissue functioning, insulin sensitivity and lipids. Additionally, we aim to understand the sex differences in metabolic dysfunction. The ultimate goal is to unravel the mechanisms by which hormones and growth factors contribute to metabolic disorders, such as obesity, diabetes, and cardiovascular disease in order to identify novel risk markers and novel therapeutic targets.

Within our group we have three interrelated research lines. All lines use a combination of molecular, cellular and animal research and studies in humans.

*The sex-specific regulation of the activity of fat metabolism (Dr. Aldo Grefhorst & Dr. ir. Jenny A. Visser).*

There are clear differences between men and women in fat distribution and the development of obesity and associated metabolic diseases. This suggests that sex-specific approaches may be needed to combat obesity and associated diseases. By detailed investigation of the differences between male and female metabolism and the role of sex steroids herein, we aim to understand sex differences in metabolism, especially in the white adipose tissue (WAT), brown adipose tissue (BAT) and the liver. We and others have shown in animal experiments that females have more active BAT than males. Furthermore we recently showed that the TGF $\beta$  family member BMP8b might be involved in this sex-difference in BAT activity, because BAT of female mice had a higher BMP8b expression than BAT of male mice.

Since the brain plays an important role in the regulation of metabolism, we also study how sex steroids act in the brain to control the function of peripheral metabolic tissues.

*The development of un-acylated ghrelin (UAG) as a drug to combat obesity and its accompanying physiological aberrations (Dr. Patric Delhanty & Prof. dr. Aart Jan van der Lely).*

The acylated form of ghrelin (AG) is known as the hunger hormone that induces obesity and insulin resistance. Un-acylated ghrelin (UAG) is the naturally occurring non-acylated form of ghrelin and an increasing number of studies suggest that UAG is a functional inhibitor of AG. An analogue of UAG is currently in phase I clinical trials to discover if it can reverse the effects of obesity and/or diabetes. However, despite evidence for biological activity of UAG on various cell types and in animals and humans, and that inhibition of a range of signaling pathways block its activity, we still do not know its precise mechanism of action, since a receptor for UAG has not yet been discovered. One of our main ongoing research themes is to investigate the mechanism of action of UAG and its analogues in animal models of obesity and insulin resistance, as well as mice that have had the ghrelin gene deleted. The goal is to identify discrete physiological effects which could impact on these pathologies, such as effects on energy metabolism, as well as sites of action, for example the pancreas, adipose tissue and brain. The goal here is to more precisely define the biological function of UAG and give clues to its mechanism of action. An important related research aim is to discover the UAG receptor using cell-lines known to respond to UAG. Approaches we are using include investigation of signal transduction pathways, receptor-ligand interactions and proteomic techniques.

*The interaction between female fertility and metabolism (Dr. ir. Jenny A. Visser)*

This research line focuses on the regulation of ovarian function and the interaction with metabolism as in reproductive aging and polycystic ovary syndrome (PCOS). Ovarian folliculogenesis is a dynamic process that declines with increasing age ultimately resulting in menopause. Menopause not only leads to a loss of estrogens but also of ovarian growth factors. In contrast, in PCOS ovarian production of androgens and growth factors is increased. Both conditions, menopause and PCOS, are associated with an increase in metabolic risk factors. Using mouse models with altered gonadal function (AMH knockout mice, DHT-induced PCOS mouse model), we have recently shown that gonadal growth factors regulate the function of white and brown adipose tissue and lead to sex-specific differences in glucose tolerance. The aim of our studies is to understand the underlying mechanisms by which gonadal growth factors contribute to the (sex-specific) regulation of metabolism and to identify the gonadal factors involved.

MSc. students who are interested to participate in one of the research lines of the subthemes of 'Endocrinology and Ageing' are encouraged to contact one of the working group leaders.

## Theme 2: Neuro-Endocrine Immunology

Autoimmune diseases of the neuro-endocrine system are leading causes of morbidity, psychosocial burden and economic loss in our western society. Neuro-endocrine autoimmune diseases in which the Dept. of Immunology is in particular interested are type I diabetes (T1D), autoimmune thyroid diseases (AIT), multiple sclerosis (MS), Guillain-Barré syndrome (GBS) and systemic sclerosis). Other autoimmune diseases of interest are rheumatoid arthritis (RA), Sjögren syndrome and psoriasis. The Dept. also studies diseases, which are related or associated to these autoimmune diseases, such as bipolar disorder (BD), other mood disorders (major depressive disorder, MDD; post partum psychosis, PPP), and schizophrenia (SCZ). The premise is that an activated inflammatory response system (IRS) drives all these pathologic processes, yet differences occur between these complex diseases due to a difference in eliciting or protecting co-factors of genetic and environmental character, such as e.g. the polymorphisms in the HLA system, iodine consumption, smoking, gut infections, pregnancy and stress. The neuro-endocrine system is an important regulator of the IRS, both via the HPA-axis and the vagus nerve.

In the research the Dept. of Immunology predominantly focusses:

- On aberrant pro- and anti-inflammatory set points of monocytes/macrophages/dendritic cells and of Th1, Th17 and T regulatory cells as important causes of the activation of the IRS. Aberrations of these cells are studied in T1D, AIT, BD, MDD, PPP, SCZ, MS and atherosclerosis. At present a large scale EU program (19 partners from 10 EU countries.) is coordinated by Prof Drexhage, which has as short title MOODINFLAME and this program views mood disorders as 'low-grade special inflammations of the brain'.
- On molecular mimicry between auto-antigens and environmental antigens as another important cause of autoimmune diseases, such as GBS.
- On abnormal interactions between inflammatory cells/antibodies and the fibroblast, leading to abnormal fibrotic processes, such as in systemic sclerosis and Graves' ophthalmopathy.

Further focuses are the amelioration of MS, AIT and RA during pregnancy, the exacerbation of these diseases and of mood disorders in the post-partum period and the immune regulation exerted by pregnancy-related and lactation related hormones and peptides.

Our research covers a broad area ranging from patient cohort studies via functional in vitro and genetic analyses of patient material to several animal disease models in rodents and non-human primates.

Via our research we hope to develop better diagnostic procedures and treatment modalities.

We perform our research in close collaboration with clinical researchers who are well trained in immunology, endocrinology and neuroscience. This allows the joint construction of scientifically relevant research questions and well-characterized patient cohorts.

### **Subtheme 1: The immunology of endocrine autoimmune diseases, major psychiatric diseases and atherosclerosis**

Dr. M. Versnel and dr P. Leenen (Autoimmune Unit, Dept. of Immunology, Erasmus MC)

In our research over the past 5-10 years we have identified various functional abnormalities of monocytes/macrophages/dendritic cells and T cells in T1D, AIT and Sjögren syndrome. This research was performed on patient materials (serum and leukocyte preparations) and – in parallel – in animal models of these autoimmune diseases, in particular the NOD mouse and the BB-DP rat. We have also assessed the role of these monocyte/macrophage/dendritic cell and T cell abnormalities in defective tolerance induction.

In our research we also found a heightened risk for T1D and AIT in bipolar disorder patients and their family members (twins and children) and vice-versa, e.g. more mood disorders in patients with AIT and T1D. It is also known that endocrine autoimmune diseases and mood disorders are associated with a higher risk for atherosclerosis. Our studies and observations thus pointed in the direction of a shared vulnerability factor for endocrine autoimmune diseases, mood disturbances and atherosclerosis. We presently study the combination of a pro-inflammatory activated monocyte/macrophage/dendritic cell system, an activated T helper cell system and a defective regulator cell system as the shared abnormal vulnerability factor between mood disorders, autoimmunity and atherosclerosis. In the latter inflammatory disorder we also focus on special descendants of the monocytes, i.e. the endothelial precursor cells.

To approach the problem on a molecular level we have identified genes aberrantly expressed in monocytes of T1D, AIT, SCZ, MDD, PPP and BD patients. These gene products are linked to the previously found functional monocyte abnormalities and around 50 key aberrant genes have now been selected. We have designed custom made (RQ-PCR) arrays for these genes and test the ability of these arrays to distinguish in the lab various subtypes of T1D, to identify pre-diabetic individuals and individuals at risk for the development of MDD and SCZ. We also target these key molecules with novel drugs (anti-cytokines, 2nd generation COX-2 inhibitors, KMO-inhibitors) in an attempt to correct the pro-inflammatory set point of the immune system to lower the risk for the development of the aforementioned diseases.

### **Subtheme 2: Pathogenesis of the Guillain-Barré syndrome**

Dr. B.C. Jacobs (Depts. of Neurology and Immunology, Erasmus MC) and Prof. dr. J.D. Laman (Unit Immune regulation, Dept. of Immunology, Erasmus MC)

The Guillain-Barré syndrome (GBS) is the most common form of acute neuromuscular paresis. Patients with GBS have a rapidly progressive immune-mediated neuropathy resulting in severe paresis of limb and respiratory muscles, from which patients may die. Research in our group showed that GBS is a molecular mimicry mediated disease in which preceding infections trigger the production of toxic cross-reactive antibodies to neural structures. In about 40% of patients these antibodies are directed to neural glycolipids or gangliosides. *Campylobacter jejuni* is the predominant cause of infection in GBS and lipo-oligosaccharides from these bacteria indeed exactly mimic gangliosides. Infusion with immunoglobulins is an effective treatment in GBS, although the mechanism of action of this treatment is unknown.

Four important issues remain unsolved in GBS:

1. What are the immuno-targets in patients without anti-ganglioside antibodies? Pilot studies have identified new targets, but these need to be tested in the available large cohorts of patients, in relation to neurological deficits and prognosis.
2. What is the cellular mechanism driving the production of these cross-reactive antibodies? Our recent studies indicate that *C. jejuni* directly activates dendritic cells and B-cells. This in vitro model for GBS will therefore enable us to determine the responsible cellular pathways.

3. Can genetic host factors explain why only 1 in 1000 persons with a *Campylobacter* infection develops GBS? We are studying single nucleotide polymorphisms in immune response genes, which may determine this abnormal response to infection.
4. Which mechanism of action is responsible for the therapeutic effect of immunoglobulins? Several serological and cellular models have been developed to identify the effective fractions of these immunoglobulins and clarify the mechanisms of action.

At the Erasmus MC there is a unique collaboration between the departments of Neurology, Immunology, Medical Microbiology & Infectious Diseases regarding GBS research. Central to this collaboration is the patient-related laboratory research, which gives us excellent opportunity to address these four study objectives and in which students are gladly invited to participate.

### **Subtheme 3: Central Nervous system inflammation and MS**

Dr. R.Q. Hintzen (Dept. of Neurology, Erasmus MC) and Prof. dr. J.D. Laman (Unit Immune regulation, Dept. of Immunology, Erasmus MC)

Inflammation plays a role in most neuro-degenerative diseases:

The sub-unit Central Nervous System (CNS) Inflammation of the Erasmus MC originates from the clinical and scientific focus on multiple sclerosis (MS). MS is the most common cause of neurological disability in young people in the European community. Many inflammatory CNS disorders can mimic MS, such as viral infections (meningoencephalitis), systemic autoimmune diseases (SLE, Sjögren syndrome), sarcoidosis and neurobehçet.

Despite distinct pathologies in the clinical array of these CNS disorders, several common pathways appear to exist. In MS it is probably a myelin directed T- and B-cell mediated autoimmune process that stands at the base of the pathology. MS is caused by a fatal interaction of yet poorly identified genes (e.g. HLA) with environmental factors (viral infections, specifically EBV, vitamin D and perhaps smoking).

Aim of this program is to enhance insight in the different routes that lead to white matter inflammation as well as neuronal and axonal damage, mainly using MS as a model.

The unit has a strong focus on biology and translational medicine, with a general theme around 'Biological determinants of the disease course'. Intense collaborations exist within the following areas: Clinical Neurology, Immunology, Genetics, Epidemiology, Virology, MRI and Proteomics. Clinical material consists of data and samples from various cohorts as well as DNA of Dutch multiplex MS families and a unique family with 26 persons suffering from MS, which is the largest MS pedigree in the world. In addition, post mortem tissue of brain and lymph node of MS patients is readily available.

### **Subtheme 4: Systemic sclerosis, endocrine opthalmopathy, inflammation and fibrosis**

Dr. P.L.A. van Daele, dr. W. Dik, dr. M. Versnel, Prof. dr. H. Hooijkaas, (Department of Internal Medicine, Section of Clinical Immunology and Department of Immunology)

Inflammatory reactions are normally resolved in a phase of scar formation involving the activation of fibroblasts. Fibroblasts are anyway involved in the inflammatory process by providing a scaffold for the inflammation. In addition there is an intensive molecular cross talk between tissue fibroblasts and resident and infiltrating immune cells during the inflammatory process. In certain immune pathological conditions these interactions are aberrant and result in abnormal inflammation and fibrosis, e.g. during systemic sclerosis and endocrine opthalmopathy. Excessive fibroblast activation may also play a role in liver cirrhosis and in fibrosis following rejection after kidney transplantation.

The first two conditions (systemic sclerosis and endocrine opthalmopathy) are our current models for further study, focusing on receptor antibodies and other immune stimulators for fibroblasts and the resulting stimulation of kinase pathways in fibroblasts.

Attempts are made to intervene in such pathways (both clinically and in the laboratory) with kinase inhibitors such as Imatinib mesylate, AMN107 and Dasanitib.

## 2. Cardiovascular research

### Cardiovascular research

Cardiovascular diseases remain the main cause of death in the Netherlands, as well as in most other countries. About 1 in 3 subjects die as a result of a cardiovascular disorder, while the disease afflicts about 50% of all subjects during the course of their lives. Atherosclerosis is the main causative characteristic of the various clinical syndromes. Insight into the factors that determine the causes and consequences of atherosclerotic disease has increased tremendously in the last 30 years. As a result, mortality from cardiovascular disease has been halved in that time period, and it is likely that this trend will continue. However, this success has come with a prize: increased survival from a cardiovascular event leads to increased risk of heart failure in later life.

At Erasmus MC, the Cardiovascular Research School COEUR coordinates the cardiovascular research and training. The mission of the research school is to conduct world-class cardiovascular research, to train new leaders, and to improve the perspectives of subjects with diseases of blood vessels and the heart or at high risk for such disease. Within COEUR, 10 different medical Departments participate. The research school comprises about 300 scientists, and publishes over 500 international scientific reports per year. The cardiovascular research program includes a wide spectrum of disciplines, all focused on different elements of cardiovascular disease, e.g. from vascular molecular biology to biomedical engineering, and from prevention and early detection to end-stage heart disease including heart-transplantation.

### COEUR welcomes Research Master students.

COEUR very much welcomes Research Master students. They will have a wealth of opportunities to initiate and conduct basic, preclinical, clinical or translational cardiovascular research under the supervision of top-level scientists. An up-to-date overview of research projects can be found on the COEUR website <http://www.erasmusmc.nl/coeur>. You may contact Prof. Boersma, Director ([h.boersma@erasmusmc.nl](mailto:h.boersma@erasmusmc.nl)) or Dr. Verhoeven, Secretary ([a.verhoeven@erasmusmc.nl](mailto:a.verhoeven@erasmusmc.nl)) for additional information on research possibilities within COEUR.

### Research Organisation and Projects

Research within COEUR is organized in 3 main themes: *Vascular Medicine*, *Acute Cardiovascular Syndromes* and *Chronic Cardiac Diseases*. Altogether, these research themes contain 37 projects, which cover the disciplines *Aetiology & Pathogenesis*, *Imaging & Diagnostics*, and *Therapy & Prevention*. Most projects cover more than one theme, and more than one discipline. Organization of projects in such a matrix structure facilitates mutual interaction and ensures multidisciplinary approach towards different research questions

Discipline	Aetiology & Pathogenesis	Imaging & Diagnostics	Therapy & Prevention
Theme			
<b><i>Vascular Medicine:</i></b> Atherosclerosis Disorders of the microcirculation Cardiovascular Genetics Aneurysm disease			
<b><i>Acute CV syndromes:</i></b> Hemostasis and Thrombosis Acute Coronary Syndromes Stroke & Migraine Critical Illness & Sepsis			
<b><i>Chronic Cardiac Disease:</i></b> Cardiac Remodeling and failure Arrhythmias Congenital Heart Disease			

In the following projects, research master students are welcome.

## Theme 1 Cardiac (mal) adaptation to stress and damage

Principal Investigators: [Prof. DJGM Duncker](mailto:d.duncker@erasmusmc.nl) (d.duncker@erasmusmc.nl), Dr. D Merkus

Ischemic heart disease, in particular myocardial infarction, and hypertension are major causes of heart failure in western countries. Following myocardial infarction or chronic exposure to pressure-overload, the heart undergoes extensive alterations in muscle mass and geometry. This cardiac remodeling is associated with an increased likelihood of progression towards overt heart failure, particularly in the setting of an ageing population.

Research within Project Group 1 is aimed at improving our understanding of the mechanisms underlying the progression from ischemic heart disease towards heart failure in order to identify novel targets for therapy. For this purpose, our research focuses on the pathogenesis and therapy of (i) myocardial infarction as a result of ischemia-reperfusion damage, (ii) the cardiac remodeling that follows in the days-weeks after myocardial infarction, including infarct expansion and cardiac hypertrophy and dysfunction, (iii) myocardial perfusion abnormalities in post-infarct remodeled and pressure-overload hypertrophied myocardium, (iiii) pulmonary hypertension secondary to the left ventricular dysfunction produced by myocardial infarction or systemic pressure overload. Furthermore, we study (v) the effects of aging and exercise training on cardiac remodeling and dysfunction following myocardial infarction and chronic pressure overload and (vi) the influence of age on the cardiac responses to hemodynamic overload.

## Theme 2 Experimental interventional cardiology, vascular injury and repair

Principal Investigators: Dr. HMM van Beusekom, [Prof. DJGM Duncker](mailto:d.duncker@erasmusmc.nl) (d.duncker@erasmusmc.nl), Dr. ES Regar

In this project our focus is to study vascular wound healing with a focus on:

1. the vascular response to coronary (PCI) and peripheral vascular interventions and
2. treatment strategies and sequellae following experimental "ischemia and reperfusion".

PCI studies are performed in different species as well as in disease models. We have found that these play an important role as they significantly affect the response to vascular injury and repair in both coronary and peripheral arteries. We employ simple models such as direct stenting and balloon angioplasty (injury) prior to PCI in healthy young animals, but also more complex models such as diet and Diabetes Mellitus induced or accelerated atherosclerosis. Different imaging modalities (invasive by e.g. OCT, NIRS, IVUS, and non-invasive by CT or MRI) allow us to characterize the baseline environment and to study the vascular response to drug eluting stents and scaffolds in a longitudinal setting. In these models we study the pharmacodynamics and polymer degradation behavior using drug eluting stents and biodegradable scaffolds in different vascular environments in health and disease.

Ischemia-reperfusion studies, both acute and chronic, are geared towards novel vascular (adjunctive) therapies for acute myocardial infarction. By means of invasive and non-invasive imaging and histology, we routinely characterize LV-function, and the composition and geometry of the infarct and no-reflow zones. We can successfully achieve therapy by means of local drug delivery and post-conditioning strategies. For the longitudinal studies we have set-up an early and sensitive assay for the determination of baseline infarct size and no reflow upon reperfusion. In addition and in collaboration with the clinical catheterization laboratory we are building a biobank of coronary thrombus aspirates (CorTAsk) to aid in understanding no-reflow in the clinical setting.

## Theme 3 Circulation, ventilation and ethics during multiple organ failure

Principal Investigators: Prof. J Bakker, Dr. J van Bommel, [Dr. DAMPJ Gommers](mailto:d.gommers@erasmusmc.nl) (d.gommers@erasmusmc.nl), Prof ABJ Groeneveld, Prof. C Ince, Dr. EJO Kompanje.

Critical illness often results in multiple organ failure. Sepsis is a common source and the syndrome affects the circulation and ventilation among other vital organ functions. The research around this typical intense care syndrome is thus programmed around these topics, as can be deduced from the individual projects enumerated below. Research on the circulation in the syndrome focuses on peripheral perfusion, among others. New techniques, like side stream dark field (SDF), laser speckle imaging and near-infrared spectroscopy (NIRS) have been studied for assessing microvascular perfusion in septic patients. In order to minimize inflammatory response in mechanically ventilated septic patients, a new lung monitoring device (Electrical Impedance Tomography) is used to optimize ventilator settings. Ultimately, the syndrome can be intractable, raising ethical issues on end-of life decisions.

## Theme 4 Shear-stress related plaque formation: from bench to bedside to population studies

Principal Investigator: [Dr. JJ Wentzel](mailto:j.wentzel@erasmusmc.nl) (j.wentzel@erasmusmc.nl)

Shear stress plays an important role in the pathobiology of the endothelium. Among others, it primes the endothelium for atherosclerotic plaque formation, which can be found at the low and oscillatory shear stress regions in the vasculature. However, evidence is accumulating for a role of high shear stress in plaque destabilization. This project



focuses on the different (molecular) aspects of the role of low or high shear stress in the generation and destabilization of vulnerable plaques. For that reason studies are performed in an established animal model of vulnerable plaque formation as well as in patients that are treated for pathological lumen obstruction. For those studies a combination of computational fluid dynamics and advanced catheter based or non-invasive imaging techniques for the assessment of plaque composition is applied. Using the information from the before described studies, we investigate whether shear stress can contribute to prediction models of atherosclerotic plaque growth and events in a population based study.

## **Theme 5      Biomechanics of the vascular wall**

Principal Investigators: [Dr. FJH Gijssen](mailto:f.gijssen@erasmusmc.nl) (f.gijssen@erasmusmc.nl), Dr. JJ Wentzel

Plaque rupture is in the majority of the cases the underlying cause of cardiovascular events. Plaque rupture occurs at the locations where the stress exceeds the local plaque strength. Plaques are very heterogeneous in composition and local tissue strength. However, not much is known on the biomechanical properties of the different plaque components. In this project we investigate at which pressure and at what location the plaque would rupture by studying the local stress distribution and deformation of the different plaque components under increasing loading. Therefore, in an in vitro setup atherosclerotic plaques from patients or animal models of atherosclerosis are subjected to different pressure loadings and the local deformations are imaged using advanced imaging techniques. This information will be used to validate computations on stress distributions in these plaques. Advances will be made in imaging of plaque deformation and (multiscale) modelling of the different plaque components.

## **Theme 6      Hypertension, the kidney and vascular ageing: focus on the renin-angiotensin-aldosterone system**

Principal Investigators: [Prof. AHJ Danser](mailto:a.danser@erasmusmc.nl) (a.danser@erasmusmc.nl), Dr. J Essers, Dr. EJ Hoorn, Dr. AH van den Meiracker, Dr. AJM Roks, Prof. R Zietse

This project focuses on hypertension, capitalizing on four pathways to discover novel intervention pathways, namely:

- the role of aldosterone in difficult-to-treat hypertensive subjects,
- hypertension induced by angiogenesis inhibition in patients with cancer,
- the impact of genomic instability on hypertension, and vascular and renal function, and
- the regulation of volume and osmoregulation in kidneys by WNKs and exosomes

An important unifying aspect in all the above topics, apart from the common relationship with hypertension, is the involvement of the renin-angiotensin-aldosterone system (RAAS), resulting in projects that investigate angiotensin/aldosterone interaction in the kidney, the role prorenin in diabetes, the function of the (pro)renin receptor in intercalated cells, the vasodilator effects of endothelial angiotensin II type 2 receptors, the angiotensin-(1-7) / Mas receptor axis, the non-genomic effects of aldosterone in the vessel wall, and the role of RAAS and related interventions on genomic instability-related vascular and renal dysfunction. The studies concerning genomic instability involves transgenic mice with decreased DNA repair function, and are performed in close collaboration with the Dept. of Genetics and of Vascular Surgery.

## **Theme 9      Pharmacology of migraine**

Principal Investigator: [Dr. A Maassen van den Brink](mailto:a.vanharen-maassenvandenbrink@erasmusmc.nl) (a.vanharen-maassenvandenbrink@erasmusmc.nl)

Migraine is a paroxysmal neurovascular disorder, which is 2-3 time more prevalent in women than in men. Currently available drugs for the acute treatment of migraine all constrict cranial blood vessels, which most likely mediates their therapeutic action. However, since these drugs may also constrict peripheral blood vessels, including the coronary artery, there is a concern about cardiac side effects and these drugs are thus contraindicated in patients with cardiovascular disease. We are investigating the neurovascular properties of prospective antimigraine drugs that may act via a primary neuronal mechanism. This could result in a reduced coronary side-effect potential of these prospective drugs. Further, since migraine occurs more often in women and depends on hormonal fluctuations such as occurring around the menstruation, we investigate the effects of (changing levels of) female sex hormones on mechanisms implied in the pathophysiology of migraine.

## Theme 10 Acute Coronary syndromes and (intensive) coronary care

Principal Investigators: [Dr. KM Akkerhuis](mailto:k.m.akkerhuis@erasmusmc.nl) (k.m.akkerhuis@erasmusmc.nl), Prof. H Boersma, Dr. K. Nieman,

Current research addresses the detection and management of heart failure and cardiogenic shock in patients with Acute Coronary Syndromes (myocardial infarction). In particular it is investigated whether impaired microcirculation in patients with acute heart failure or shock can be improved by specific interventions, and whether such interventions improve prognosis of these patients. Furthermore the implications are investigated of cardiomyopathies, in particular non-compaction cardiomyopathy.

## Theme 11 Cardiovascular Aging

Principal Investigator: Dr. FUS Mattace Raso (f.mattaceraso@Erasmus MC)

The study of the structural and functional age-related vascular changes represents a good model to unravel the complex process of senescence. We investigate mainly three items:

- The environmental and genetic determinants of vascular aging
- The consequences of vascular aging on short and long term blood pressure regulation
- The consequence of vascular aging on morbidity and mortality and its possible role in cardiovascular risk stratification

These investigations are performed within several settings, in the general population but also in specific categories of patients including persons with end stage renal disease and with a history of syncope and patients' first signs and symptoms of dementia.

## Theme 12 Cardiovascular genetics and metabolic diseases

Principal Investigators: [Prof. EJG Sijbrands](mailto:e.sijbrands@erasmusmc.nl) (e.sijbrands@erasmusmc.nl), Prof. F Zijlstra

At the Erasmus outpatient clinic for cardiovascular genetics, family based approaches are employed to study inherited cardiovascular diseases: cardiomyopathies, congenital heart malformations, arrhythmias, dyslipidemias, diabetes mellitus, hypertension and severe premature coronary artery disease. Technical innovation is a hall mark of this research: for example, novel imaging modalities are used to identify new phenotypes and high-throughput molecular analyses are performed to identify modifier genes in addition to major locus effects.

We have identified a large number of novel genes that are associated with cardiovascular disease and related traits. We perform molecular and biochemical studies to get a better understanding of the mechanisms underlying the diseases and the complications.

Our clinical research is performed in patients with very rare diseases, like  $\beta$ -myosin heavy chain defects in noncompaction cardiomyopathy, but also more common disorders of synthesis and processing of insulin in families with type 2 diabetes.

## Theme 13 Stroke: risk factors and etiology, prognosis and treatment

Principal Investigators: Prof. DWJ Dippel, [Prof. PJ Koudstaal](mailto:p.j.koudstaal@erasmusmc.nl) (p.j.koudstaal@erasmusmc.nl)

Stroke is a heterogeneous disease, it comprises ischemic stroke, intracerebral hemorrhage and subarachnoid hemorrhage. Stroke is a high ranking cause of death and the most common cause of acquired disability in The Netherlands and Western Europe. Causes of disability include motor function and disturbances of language, memory and cognition.

Etiologic studies include genetics (MetaboChip), hemostasis (von Willebrand factor, fibrinogen), glucose metabolism, cardioembolic disorders (SURTAVI), and carotid plaque morphology (PARISK).

Intervention studies include a series of multicenter RCT's of the effect of prevention of high body temperature and fever (PAIS). Also, we conduct a large national multicenter study of the effect of intra-arterial treatment for acute ischemic stroke (MR CLEAN). Moreover, we evaluate early cognitive linguistic treatment of aphasia in a series of multicenter RCT's (RATS).

Prognostic studies include prediction of outcome after stroke, recurrent vascular events and vascular cognitive impairment, and functional imaging (FIAT) and outcome (SPEAK) of aphasia caused by stroke in large patient-cohorts.

Data for genetic, prognostic and etiologic studies are derived from the Erasmus Stroke Study, an ongoing hospital based registry, and from the Rotterdam study, a large population based cohort study.

## **Theme 14 Management of hemorrhagic and thrombotic disorders**

Principal Investigators: [Prof. FWG Leebeek](mailto:f.leebeek@erasmusmc.nl) (f.leebeek@erasmusmc.nl), Dr. MJHA Kruijff

Clinical studies on bleeding disorders, including von Willebrand disease are currently performed within this theme. The Willebrand in the Netherlands (WiN) study is a nation-wide study coordinated by the Erasmus MC on the clinical aspects of von Willebrand disease. In this study in whom over 800 patients with moderate and severe VWD are included, we study the impact of the disease on quality of life and obtain more insight in diagnosis and disease burden. In addition we focus on optimal treatment of this bleeding disorder. The etiology, diagnosis and treatment of various clinical entities of venous thrombosis are also focus of our research. One of our interests is the site specificity of venous thrombosis, for instance hepatic and portal vein thrombosis. In collaboration with other partners we have initiated studies on prevention and treatment of arterial and venous thrombosis using new oral anticoagulant drugs, including factor IIa and Xa inhibitors.

## **Theme 15 Role of hemostasis in arterial thrombosis**

Principal Investigators: Prof. FWG Leebeek, [Dr. MPM de Maat](mailto:m.demaat@erasmusmc.nl) (m.demaat@erasmusmc.nl), Dr. DC Rijken

The studies performed in this theme are focusing on the role of coagulation factors and platelets in the development of arterial thrombosis. Several case-control studies have been initiated to investigate whether hemostatic or inflammatory factors determine the risk of first and recurrent arterial thrombotic events, including stroke and ACS. Our special interest is on von Willebrand factor and fibrinolysis. Several genetic approaches are used, including GWA, SNP and haplotype analysis. We have obtained more insight in the mechanism of fibrin formation and fibrinolysis by identifying new proteins binding to fibrin using plasma proteomics techniques. The effect of fibrin structure on the risk of thrombosis and the relationship with atherosclerosis and angiogenesis, is studied using recombinant and plasma-purified fibrinogen forms.

## **Theme 16 Ultrasound contrast agents**

Principal Investigator: [Prof. N de Jong](mailto:n.dejong@erasmusmc.nl) (n.dejong@erasmusmc.nl)

Ultrasound contrast agents (UCA) consist of gas microbubbles (1-10  $\mu\text{m}$ ) that are coated by a protein, lipid or polymer. In addition to their diagnostic value, microbubbles have great potential as local drug delivery systems. In project 16 we investigate the clinical and the more fundamental/ future use of UCA.

The clinical use includes the left ventricle opacification and myocardial perfusion during normal and stress echocardiography. Further, a clinical study (Parisk) is running to detect the presence and properties of atherosclerotic plaques in the carotid artery after administration of UCA.

Future use of UCA lies in molecular ultrasonic imaging uses tiny microbubbles that bind to cellular disease processes. These microbubbles can be functionalized using specific ligands and injected into the human body. Upon excitation by an appropriate ultrasonic field the microbubbles start to vibrate thereby acting as an ultrasound source. This source shows a very specific signature which differs to a great extent from the scattering by normal/pathological tissue. For therapy the bubble can be either loaded with the drug of choice where the drug can be locally released upon ultrasound and/or the vibrating bubble is used to enhance the uptake of the drug. Essential in this whole process is the knowledge of the vibrating bubble, the ultrasound field and the imaging capabilities of the ultrasound system.

## **Theme 17 Echocardiography: Transducers and image processing**

Principal Investigators: [Dr. JG Bosch](mailto:j.bosch@erasmusmc.nl) (j.bosch@erasmusmc.nl), Prof. N de Jong, Prof. AFW van der Steen

Research focuses on novel ultrasound transducers and image processing for ultrasound, with a strong accent on novel 3D cardiovascular imaging. This includes matrix transducers, electronics and new beamforming for 2D and 3D imaging of the heart, the carotid artery, the bladder etc. Moreover, image processing approaches for 3D image generation, 2D and 3D image analysis and quantification by segmentation, tracking and classification are pursued. Advanced geometric and statistical modelling is employed. Current applications include improved realtime 3D TEE imaging, 3D echocardiography analysis, stress echo, analysis of plaque vulnerability in carotid arteries, and monitoring of electrophysiological interventions with 3D ultrasound.

## Theme 18 Intravascular ultrasound techniques

Principal Investigator: Prof. AFW van der Steen (a.vandersteen@erasmusmc.nl)

Intravascular imaging is momentarily highly focusing on characterizing the composition of the atherosclerotic plaque. Characterizing lipid content, plaque vascularization and thickness of thin caps are of particular interest. These characteristics discriminate a stable plaque from a rupture prone or vulnerable plaque. The latter one can cause myocardial infarctions or stroke. Plaque vascularization is measured by intravascular ultrasound in combination with ultrasound contrast agents. Several strategies are developed to characterize lipid content. These are based on optical coherence tomography or combination catheters where light and sounds are combined.

## Theme 19 Intravascular imaging and interventional cardiology

Principal Investigator: PW Serruys (p.w.j.c.serruys@erasmusmc.nl)

The decision making process for patients with obstructive coronary artery disease requiring revascularization is evolving. Historically, patients with the most complex coronary artery disease were preferentially treated by surgical revascularization: however technological advances in percutaneous therapy have ensured that many of these patients can now receive equally effective treatment with percutaneous coronary intervention (PCI). Intertwined with these developments are a lower threshold to investigate patients with symptoms suggestive of coronary artery disease, an increasingly elderly population in need of revascularization, the changing dynamics of the doctor-patient relationship, and a greater emphasis on guideline driven patient care. Consequently decisions regarding revascularization are now more complex than ever before.

The advent of drug eluting stents (DES), which consist of a drug (immunosuppressive or antiproliferative drug), a polymer and a metallic platform, has revolutionized the practice of interventional cardiology by significantly reducing the rates of restenosis and repeat revascularization as compared to bare metal stents. Within this project, this subject is studied in detail while taking into account involvement in stent development, as well as secular trends in acute and chronic benefits of percutaneous coronary interventions.

## Theme 20 Cardiac Imaging(MRI and CT)

Principal Investigators: Dr. RJM van Geuns, Dr. K Nieman (k.nieman@erasmusmc.nl)

The cardiac CT group is a joint initiative by the departments of cardiology and radiology and collaborates with several (pre-)clinical departments within the Erasmus MC. In 2010 research activities included assessment of several technological innovations and new clinical applications, i.e. various scan protocols to reduce radiation exposure, dual-energy imaging for improved contrast resolution and stress myocardial perfusion imaging to assess the hemodynamic significance of obstructive coronary disease. Ongoing investigation into the implementation of cardiac CT in clinical practice includes the use of cardiac CT in patients with stable angina (fast-track chest pain clinic), to exclude coronary disease in patients with congestive heart failure, and as a tool for triage of acute chest pain in the emergency ward. Also the potential role of cardiac CT in high-risk populations, including patients with familial hypercholesterolemia and diabetes, is being explored. The incremental value of CT imaging prior to valvular and coronary interventions is being investigated.

## Theme 21 Cardiac imaging (ultrasound)

Principal Investigator: Dr. ML Geleijnse (m.geleijnse@erasmusmc.nl)

Echocardiography is the most important diagnostic tool in cardiology. Recent advances in ultrasound hardware and software have made 3-dimensional echocardiography and speckle tracking echocardiography possible. These techniques are used for estimation of left ventricular pump function according to the classically defined volumes and ejections fraction but also deformation and rotation. Newer developments are

- 1) 3D trans-oesophageal echo,
- 2) Imaging of the vasa vasorum and
- 3) Plane-wave imaging.

## Theme 22 Neurovascular imaging (MRI and CT)

Principal Investigator: Prof. A van der Lugt (a.vanderlugt@erasmusmc.nl)

Ischemic cerebral infarcts are related to the presence of atherosclerotic disease in the carotid artery. Severity of the stenosis is a predictor of clinical symptoms and is used as parameter in the therapeutic decision as to which patients will benefit from carotid intervention. Next to stenosis severity, plaque morphology is thought to be a major determinant of cerebrovascular events.

Within this project, imaging of the atherosclerotic plaque in the carotid bifurcation with multidetector CT and MRI is evaluated. We focus on 1) the validation of imaging parameters by comparison of images with histology, 2) development of new structural and haemodynamic parameters atherosclerotic disease, 3) development and validation of automated measurements, 4) prospective studies in patients and healthy volunteers to prove the additional value of plaque parameters in risk prediction, 5) Serial imaging studies to evaluate the natural course of the atherosclerotic disease, 6) Studies into the relationship between atherosclerotic plaque parameters and brain infarcts and white matter lesions on CT and MRI.

### **Theme 23      Biomedical Image Analysis**

Principal Investigator: Prof. WJ Niessen ([w.niessen@erasmusmc.nl](mailto:w.niessen@erasmusmc.nl))

In the management of disease, advances in imaging devices have drastically increased our capabilities to (non-invasively) study both anatomy and function. With these advances, the sheer size, complexity, and heterogeneity of imaging data available for biomedical research and clinical practice have increased enormously. To fully utilize the wealth of information available in imaging data, techniques for automated analysis and interpretation are required. In this subtheme, quantitative image analysis techniques are developed and applied to improve diagnosis, therapy planning and therapy monitoring. Application areas include cardiovascular disease, neurodegenerative diseases and oncology. In the cardiovascular domain, we e.g. quantify atherosclerotic disease from non-invasive imaging techniques, for improved diagnosis and prognosis. In the neurodegenerative domain, we perform large scale analysis of neuro imaging data, both from population imaging studies and clinical studies, to improve early detection, differential diagnosis, and prognosis of neurodegenerative disease. In oncology, we aim to improve treatment planning and predict and monitor treatment success.

### **Theme 24      Molecular biology of aneurysm formation**

Principal Investigator: [Dr. J Essers](mailto:j.essers@erasmusmc.nl) ([j.essers@erasmusmc.nl](mailto:j.essers@erasmusmc.nl))

In the basic research line 'Molecular biology of aneurysm formation' of the Laboratory for Experimental Vascular Surgery (LEVAS), the molecular processes that underlie aneurysm formation are investigated through close collaboration between the department of Genetics & Cell Biology and the department of Vascular Surgery. The goal of this translational research line is to decrease aneurysm related mortality and reduce the need for surgical intervention. Consequently, we focus on two research areas: 1) early detection of degenerative changes in the aortic wall, and 2) pharmacological intervention to treat aortic wall degeneration. To this end we make use of the scientific expertise and state-of-the-art infrastructure of our research institute as well as the practical implications, anonymous patient data and bio-bank of the clinical research group. This intensive collaboration ensures innovative basic research based on clear clinical relevance. This research line is embedded in the Erasmus MC research schools Medical Genetics Centre South-West Netherlands (MGC) and COEUR in collaboration with among others the departments of pharmacology, cardiology, clinical genetics, bioinformatics and biochemistry.

### **Theme 25      Endovascular management of aortic aneurysms**

Principal Investigator: [Prof. HJM Verhagen](mailto:h.verhagen@erasmusmc.nl) ([h.verhagen@erasmusmc.nl](mailto:h.verhagen@erasmusmc.nl))

Aortic pathology like aneurysms, dissections and traumatic ruptures were traditionally treated by open repair. In the last decade, endovascular technology became available as a minimally invasive alternative. Like with all other new and innovative treatment modalities, results, especially long-term, are unknown and it remains unclear whether this minimal invasive treatment is beneficial for all patients or only for the ones declared "unfit for surgery". Furthermore, many uncertainties remain on the best indications for stentgraft placement: is it only advisable for aneurysmal disease or should it be used for all aortic pathology known to eventually lead to life-threatening dilatation of the aorta. If so, in what stage of the disease should it be used: as treatment or as prevention? Can it be seen as definitive treatment or will it turn out to be just a "bridge to surgery"? Within this project, many sides of this new treatment are being investigated.

### **Theme 26      Lung surgery and lung transplantation**

Principal Investigator: [Prof. AJJC Bogers](mailto:a.j.j.c.bogers@erasmusmc.nl) ([a.j.j.c.bogers@erasmusmc.nl](mailto:a.j.j.c.bogers@erasmusmc.nl))

Technological developments in lung/thoracic surgery in the direction of video-assisted surgery as well as improvements in peri-operative care are actual issues, resulting in concentration in larger centres. Larger series and better quality of care are the result and form a sound basis for further clinical research and cooperation at international level. A multidisciplinary approach is the key to this goal. This also holds for lung transplantation for which also preclinical studies on organ preservation are undertaken. This project aims at outcome research with emphasis on clinical decision making.

## Theme 27 Percutaneous interventions in structural heart disease

Principal Investigators: [Prof. PPT de Jaegere](mailto:p.dejaegere@erasmusmc.nl) (p.dejaegere@erasmusmc.nl), Prof. PW Serruys

Catheter-based treatment of structural heart disease is a recent but rapidly evolving treatment modality. At present it is primarily reserved for patients with aortic stenosis who are considered poor candidate for surgical valve replacement. As a result of ongoing research and innovations in catheter technology, bioprosthetic materials (scaffolding frame and tissue), imaging (3-4D, co-registration) in addition to operator experience, it is expected that catheter-based treatment will also be available for other forms of structural heart disease such as mitral – and aortic regurgitation, left ventricular systolic dysfunction in addition to the application of these techniques in patients who are candidate for surgical treatment.

Research in this domain will encompass 1] clinical cohort research examining the safety and efficacy, the evaluation of responder and non-responder by the definition of determinants of (clinical and technical) outcome by means of single- and multicenter collaborative efforts, 2] pathophysiological assessment of the effects of treatment on the morphology, function and haemodynamics of various cardiac components (myocardium, valves, ascending aorta) in collaboration with the department of radiology and experimental cardiology, 3] randomised clinical comparison between catheter-based and surgical treatment of structural heart disease, 4] advanced imaging allowing 3 and eventually 4 D co-registration of the anatomy during treatment (collaboration with experimental cardiology, radiology and industry).

## Theme 28 Translational electrophysiology

Principal Investigator: [Dr. N.M.S. de Groot](mailto:n.m.s.degroot@erasmusmc.nl) (n.m.s.degroot@erasmusmc.nl)

The research projects of the unit translational electrophysiology are aimed at developing innovative diagnostic tools and therapies by implementing experimental electrophysiology in daily clinical practice.

Atrial fibrillation (AF) is associated with significant morbidity and mortality. The prevalence of AF will continue to rise and AF will persist to pose a major burden on public health costs. Anti-arrhythmic drugs are often not effective in eliminating AF episodes and ablative therapy is also not so successful as first assumed. The expected epidemic of AF necessitates research in order to develop preventive strategies, to improve existing treatment modalities and design novel therapies. After the discovery that paroxysms of AF can be triggered by pulmonary vein foci, isolation of the pulmonary veins was introduced as a potential curative treatment modality. It is in general assumed that in patients with persistent AF, AF has progressed from a trigger-driven to a substrate mediated arrhythmia. In these patients, persistence of AF no longer depends on the presence of a trigger ('true fibrillation') but is maintained by an arrhythmogenic substrate. Although animal studies have provided extensive insights into the various mechanisms that can explain perpetuation of AF, it is unknown which specific electropathological changes are relevant for the development of a substrate of persistent AF in humans. Also, it is unknown whether different cardiac diseases result in different electro-pathological alterations. Particularly in patients with congenital heart disease, there are no mapping data available. Clinical mapping data of AF are scarce and the available studies are often limited to parts of the atria or a small number of beats. Theoretically, multi-site high density mapping can be used to localize sources generating AF in patients with trigger-driven AF and to identify areas perpetuating AF in patients with substrate mediated-AF. Based on the premise that AF can be eliminated by ablation of either the trigger or the substrate perpetuating AF it is expected that multi-site high density mapping is a suitable tool to diagnose AF thereby allowing individualization of AF treatment. The mechanism of early post-operative dysrhythmias is studied by correlating continuous rhythm registrations with hemodynamic alterations.

## Theme 29 Surgical aspects of acute and chronic cardiovascular disease and heart failure

Principal Investigator: [Prof. AJJC Bogers](mailto:a.j.j.c.bogers@erasmusmc.nl) (a.j.j.c.bogers@erasmusmc.nl)

Technological developments in surgery (and interventional cardiology as well) and peri-operative/peri-procedural care continue to evolve at a rapid pace. In particular, the field evidence with regard to the treatment of coronary artery disease and cardiac valvular disease is rapidly expanding. The search for hybrid approaches applying minimal invasive techniques continues. This is also relevant for the further development of robotic techniques. It was shown that a multidisciplinary approach delivers the best results, and collaboration between engineers, cardiologists, cardiothoracic and vascular surgeons and radiologists is the preferred and chosen route. This project aims at outcome research with emphasis on clinical decision making.

### **Theme 30 Determinants of outcome of pediatric (congenital) heart disease**

Principal Investigators: [Prof. WA Helbing](mailto:w.a.helbing@erasmusmc.nl) (w.a.helbing@erasmusmc.nl),

Treatment of congenital heart disease in early childhood has resulted in excellent survival in the pediatric age range. However, residual cardiac loading abnormalities and the effects of pre-treatment hypoxaemia may impair long term survival and quality of life. The project aims to identify early (bio)markers of suboptimal outcome following treatment in childhood and to develop new treatment modalities to improve outcome. Novel imaging methods and animal experiments are used for these purposes.

### **Theme 31 Surgery for congenital heart disease**

Principal Investigator: [Prof. AJJC Bogers](mailto:a.j.j.c.bogers@erasmusmc.nl) (a.j.j.c.bogers@erasmusmc.nl)

Surgical management of congenital heart disease has improved significantly in the last decades, which has resulted in improved survival into adulthood. Thus the number of adult patients is growing. While the number of patients to be operated at young age is more or less constant, the number of patients needing an operation at adult age is increasing, both the number of primary operations as well as the number of reoperations due to residual cardiac abnormalities. In particular, abnormal loads are commonly imposed on the right ventricle or on single ventricular hearts. Residual abnormalities may cause heart failure, rhythm disturbances and may affect quality of life. Evidence-based treatment is often lacking. Guidelines for timing of catheter intervention and surgical therapy also lack sufficient evidence. This project aims at outcome research with emphasis on assessment cardiac function in the right ventricle and in structurally abnormal hearts with conventional imaging techniques. An important part of this theme concerns these imaging techniques on one hand and improvement of clinical decision-making and therapy on the other.

### **Theme 32 Perioperative cardiac care in noncardiac surgery**

Principal Investigators: [Prof. RJ Stolker](mailto:r.stolker@erasmusmc.nl) (r.stolker@erasmusmc.nl), Prof. H Verhagen

Cardiovascular disease is the major cause of postoperative morbidity and mortality. In Europe, 40.000.000 surgical procedures are performed every year, with a cardiovascular mortality rate of 0.3% (133.000 patients). To improve postoperative outcome, preoperative identification of patients at risk is performed using clinical risk scores, biomarkers for coronary artery disease and heart failure, and cardiac imaging. The preoperative risk assessment is linked to the intraoperative identification of acute coronary syndromes using electrocardiography and cardiac imaging as well as newly identified biomarkers. The follow-up of these patients is performed regularly, for early identification of cardiac events. The identification of a genetic predisposition in relation with biomarkers and subsequent treatment is the research line of this group.

### **Theme 33 Clinical decision making in cardio-thoracic surgery**

Principal Investigators: Prof. AJJC Bogers, Prof. JJM Takkenberg ([j.j.m.takkenberg@erasmusmc.nl](mailto:j.j.m.takkenberg@erasmusmc.nl))

This project concerns risk modelling, decision making, innovative statistical analysis and health technology assessment of appropriate diagnostic and therapeutic measures in the area of cardio-thoracic interventions.

One of the challenges for contemporary medicine is to apply evidence-based medicine and to rationally implement the available therapies in clinical practice, in the appropriate patients at the appropriate time.

Current research includes the application of longitudinal statistical models on serial data such as cardiac biomarkers and echocardiographic measurements over time for the purpose of outcome prediction, the optimization of individualized prognosis prediction through the development of novel risk models, shared decision making studies in prosthetic heart valve selection and NSCLC treatment selection, and cost-effectiveness studies of novel cardio-thoracic interventions. The results are applied in outcome research and should support clinical decision making.

### **Theme 34 Clinical epidemiology of cardiovascular diseases**

Principal Investigator: [Prof. H Boersma](mailto:h.boersma@erasmusmc.nl) (h.boersma@erasmusmc.nl)

In the past decades, significant improvement has been achieved in the management and outcome of patients with cardiovascular disease (CVD). Despite these developments, CVD still is a major cause of the loss of healthy years in The Netherlands: the annual number of fatal events is as high as 40,000. The burden of CVD is expected to increase in the decades ahead, and it is crucial to develop and improve CVD risk prediction instruments, and implement appropriate preventive and therapeutic measures. Traditionally, the assessment of CVD risk is based on global risk models. However, these models fall short, as they do not utilize contemporary knowledge on the pathophysiology of CVD. Project 36 Clinical epidemiology of cardiovascular diseases is designed to improve CVD risk assessment and risk reduction. Several concepts are currently studied: (multiple) CVD biomarkers, repeated biomarker assessment, cardiac imaging, dynamic risk modelling and simulation risk modelling.

## **Theme 35     Adult congenital heart disease**

Principal Investigator: Prof. JW Roos-Hesselink (j.roos@erasmusmc.nl)

In the Netherlands, 8 out of 1000 children are born with a congenital heart defect. Due to improved diagnostics, the introduction of the heart long machine and open heart surgery, more than 85% of these patients reach adulthood and nowadays there are 30.000 adults living in the Netherlands. Many of them have late complications, such as valvular dysfunction, arrhythmias or heart failure. In addition often surgical or catheter reintervention is necessary. Research in project 37 focuses on long-term outcome in these patients, both after surgical correction, interventional treatment or natural history. Special emphasis on psychological outcome, pregnancy and sports participation is important in this specific group of young adults. Also genetic research, imaging of the complex cardiac anatomy and biomarker studies are being conducted.



### 3. Haemato-Oncology

Research within this main theme deals with the search into the key molecular processes regulating the proliferation and differentiation of myeloid and lymphoid cells (particularly stem cell biology, erythropoiesis, granulopoiesis, lymphocyte development), and aberrations determining malignant transformation (e.g. in murine models and pathogenetic clinical studies). The basic aspects of the program are complemented by research components related to the function and dysfunction and deficiency of the differentiated "end" cells both in physiological conditions and in disease. Specific programs have an extension towards clinical application and involve investigations related to developmental diagnostics and therapeutics (e.g. molecular diagnostics, pharmacogenomics, therapeutic targeting in leukemia as well as stem cell transplantation, gene therapy). Thus the program covers a spectrum from basic towards clinically applied investigations. Traditionally these programs have had their main basis in the Dept. of Hematology of the Erasmus University Medical Center. More recently the pediatric division of hematology-oncology has joined this main theme. The research program is solidly embedded in and interacting with investigators, scientific groups and networks in a broad international context (e.g. cooperative clinical trial groups, European consortia, scientific groups). This holds both for the laboratory parts and the clinical activities.

#### Theme 1: Regulation of proliferation and differentiation of hematopoietic stem cells

Prof. dr. Delwel, dr. M. Raaijmakers, Prof. dr. I.P. Touw, dr. J.M.J.M. Zijlmans

Research within this subtheme deals with the control of hematopoietic stem cell and progenitor cell fate. One section deals with the role of extrinsic regulators such as hematopoietic growth factors (G-CSF, EPO, SCF) and chemokines (SDF-1, Cb2 ligands, somatostatin) and their spatial organization within specific cellular components of the hematopoietic stem cell niche. Other sections deal with stem cell plasticity, homing and aging. The overall aim of these studies is to elucidate the molecular and cellular mechanisms underlying the principle features of hematopoietic stem cells and precursors: self-renewal, lineage commitment and differentiation, proliferation and survival, migration and aging. They provide insights in the control of normal blood cell development that are crucial to our understanding of how these mechanisms may play a role in the pathogenesis of hematopoietic disorders, such as leukopenia, myelodysplasia and leukemia. Furthermore, investigations are anticipated to generate insights into cues, both environmentally and cell-intrinsic, that maintain and expand hematopoietic stem cell numbers and can be exploited for regenerative purposes. Experimental approaches within this theme include e.g., the generation of animal models employing transgenesis and knockout/knocking strategies, advanced cell culture assays for primary hematopoietic stem cell and progenitor cell subsets, retroviral gene transfer technology, isolation and functional/biochemical analysis of protein complexes analysis and advanced live cell (quantitative) imaging technology (e.g., fluorescence resonance energy transfer and fluorescence recovery after photo bleaching).

#### Theme 2: Transplantation and genetic modification of hematopoietic stem cells

Dr. E. Braakman, dr. J.J. Cornelissen, dr. T. Cupedo, dr. J. W. Gratama, Prof. dr. G. Wagemaker

Within this theme there is a longstanding research effort in murine models for human diseases and nonhuman primate models for stem cell biology and transplantation, which is concerned with the manipulation of immune modulation and the development of gene transfer for therapeutic purposes. Hematopoietic stem cell transplantation (SCT) is currently an important therapeutic modality for many malignant hematological disorders, its use for the treatment of metastatic solid tumors is under investigation as well as its development for gene transfer as a therapeutic modality. Alternative stem cell sources (cord blood) and alternative donors (matched unrelated donors) are increasingly used for hematopoietic stem cell transplantation.

Transplant-related morbidity and mortality of allogeneic SCT is still significant due to acute and chronic graft-versus-host disease (GVHD) and opportunistic infections (mainly reactivations of endogenous herpes viruses). A major cause of opportunistic infections is an impaired immune recovery due to deficient thymopoiesis.

Our research focuses on:

- The identification and treatment of patients with an impaired immune recovery after transplantation at high risk for specific progressive viral infections.
- The development of interventions, including cytokine intervention therapy and thymic regenerative cellular therapy to improve thymopoiesis and immune recovery after transplantation.
- The development of alternative approaches to facilitate engraftment and mitigate GVHD including selective peripheral expansion of regulatory

- T cells.
- The development of gene therapeutic approaches for inherited diseases ([www.inherinet.org](http://www.inherinet.org)), spin-off acquired diseases, further preclinical development of hematopoietic and mesenchymal stem cell transplantation using gene marked cells.
- The development of hematopoietic stem cell transplantation using alternative donors and/or alternative stem cell sources.

### Theme 3: Malignant transformation of hematopoietic stem cells

Prof. dr. R. Delwel, Prof. dr. I.P. Touw, dr. P. Valk, dr. M. Raaijmakers

The research program aims to elucidate key regulatory abnormalities of leukemogenesis. Emphasis of the program is currently on growth factor receptor and signal transduction derangements and perturbations of transcription and epigenetic control determining functional abnormalities of survival, proliferative, cell cycle, and maturation fates of hematopoietic stem cells. Another section addresses the role of the interaction between hematopoietic cells and their microenvironment in leukemogenesis. Specific focus is on leukemic progression of leukemia predisposition states, including severe congenital neutropenia (and the role of G-CSF receptor defects (nonsense mutations) in this process) and myelodysplasia.

Genes responsible for leukemic transformation are frequently located near non-random chromosomal translocations. However, in approximately 50% of the clinically diagnosed myeloid leukemias no cytogenetic abnormalities have been detected. Furthermore, in a number of cases that do carry a cytogenetic abnormality the genes located near the breakpoints are still unknown. Moreover, since leukemia is believed to be a multi-step process, aberrant expression of different disease genes affecting multiple pathways are required to obtain full leukemic transformation. An alternative procedure to identify leukemia disease genes is the cloning of common virus integration sites (cVIS). This approach has proven to be a sensitive tool to identify novel proto-oncogenes as well as tumor-suppressor genes. In fact, several genes located near chromosomal breakpoints or otherwise aberrantly expressed in human hematopoietic malignancies have been identified through retroviral insertional mutagenesis in murine leukemias or lymphomas as well, e.g. Evi, Evi2 (NF), Evi6 (Hoxa9), Bcl1 (Cyclin D1), N-Myc, and Erg. The two main lines of investigation that follow from the identification of novel transforming genes in myeloid leukemia are aimed at:

- the mechanisms of myeloid transformation using in vitro and in vivo models
- the role of these mechanisms in human disease.

By means of high throughput sequencing, gene array analysis and real-time PCR we study in a large cohort of AML ( $\pm$  300 cases) the involvement of novel "leukaemia disease" genes identified by retroviral insertional mutagenesis. Novel disease genes based on the mouse and primary AML screen and, which predict unique pathways and mechanisms of transformation, have been and will be selected for further study. Inducible in vitro and in vivo models will be applied to unravel the exact mechanism of transformation by the distinct transforming genes that have been or will be identified. A program has been designed to assess the clinical significance (prognostic) of findings from high throughput expression profiling and mutational analyses and implement these in clinical molecular diagnostics, and identify targets for treatment intervention.

### Theme 4: Diagnosis, classification and treatment evaluation of leukemias and malignant lymphomas

Prof. dr. J.J.M. van Dongen, dr. A.W. Langerak, dr. F.J.T. Staal, dr. V.H.J. van der Velden

This research program focuses on the diagnosis and classification of leukemias and malignant lymphomas as well as on the evaluation of treatment effectiveness during follow-up via detection of low frequencies of malignant cells, i.e. detection of "minimal residual disease" (MRD). The research program combines molecular and cellular studies on normal and malignant hematopoiesis, particularly focusing on immature lymphoid differentiation. The various types of lymphoid malignancies (leukemias and lymphomas) resemble their normal counterparts. Despite this comparability, the malignant cells exhibit aberrant cellular and genetic characteristics, which can be used for diagnosis, classification, and MRD studies. Thorough insight into normal lymphoid differentiation appears to be highly relevant for translation of new immunobiological information into improved diagnostics. The research program consists of three main projects:

## **Normal and aberrant V(D)J recombination in leukemias and malignant lymphomas: basic aspects and diagnostic applications**

V(D)J recombination of immunoglobulin (Ig) and T-cell receptor (TCR) genes is a key process during early lymphoid differentiation, which is required to establish a broad repertoire of antigen-recognizing receptors. Although the V(D)J recombination process is tightly regulated, aberrant V(D)J recombination occurs, resulting in the coupling of Ig/TCR loci to oncogenes. As a consequence, the involved oncogene is transcriptionally deregulated, eventually resulting in a block in lymphoid differentiation. This differentiation arrest is postulated to lead to a pre-leukemic cell population. Multiple additional genetic hits will result in overt (acute) leukemias or lymphomas.

Insight into normal and oncogenic recombination events will shed light on the pathogenic mechanisms underlying acute leukemia formation. This fundamental knowledge can be translated into better prognostic classification and improved treatment stratification of lymphoid malignancies. As a direct spin-off, these studies might contribute to the identification of novel therapeutic targets.

## **Immunobiology of acute leukemia and treatment evaluation**

Acute leukemia is the most common form of cancer in childhood. Current treatment protocols, consisting of chemotherapy with or without stem cell transplantation can cure the vast majority of patients. However, in 20 to 40% of children the leukemia sooner or later reappears. Apparently, low numbers of leukemic cells, that is, "minimal residual disease" (MRD), remain present despite the therapy and finally result in a relapse. How can we detect these low levels of leukemic cells and how can we use MRD information for improving clinical outcome? Over the last couple of years we have developed PCR methods that can detect one leukemic cell amongst up to one million normal cells. Our studies in children with acute lymphoblastic leukemia (ALL) show that such detection of MRD is a very powerful and independent prognostic factor that allows the recognition of patients at high or low risk of relapse. Our current studies are focused on the development of other sensitive methods for MRD detection, particularly flow cytometric immunophenotyping, and on the evaluation of the clinical significance of MRD in children with acute myeloid leukemia, infants with ALL, and in specific genetic subgroups of childhood ALL. The aims of these studies are to improve MRD monitoring and to establish its clinical significance, thereby allowing patient-tailored therapy of children with leukemia. Such patient-tailored therapy will hopefully result in an improved clinical outcome in children at high risk for relapse and in less intense therapy, and thereby less side effects, in children with a very low risk of relapse.

## **Gene expression profiles in immature lymphoid cells and acute lymphoblastic leukemias:**

Gene expression profiles determine the differentiation lineage, developmental stage, and activation stage of the involved cells. Just like in any other cell type, regulation of gene expression in lymphocytes is largely controlled at the level of transcription initiation by transcription factors and transcriptional repressors. The study focuses on transcription factors and signaling routes that are controlling the most immature steps of lymphoid differentiation. In parallel, the abnormal regulation of gene expression in acute lymphoblastic leukemias is studied and compared to corresponding normal immature T and B cell subpopulations. Results of these comparative studies are being exploited for developing new diagnostic tools.

## **Theme 5: Implementation of molecular diagnostics and novel therapeutic strategies into clinical practice**

Prof. dr. J.J. Cornelissen, Prof. dr. R. Delwel, Prof. dr. B. Löwenberg, dr. P. Lugtenburg, Prof. dr. P. Sonneveld, dr. P. Valk, dr. J.M. Zijlmans

Within this theme we link the identification of the molecular mechanisms in the development of hematopoietic neoplasm (in retroviral models and high throughput analysis of clinical samples) to developmental diagnostics and therapeutics and we evaluate and implement clinical investigational procedures. Key-issues of this theme are:

- Clinical trials and correlative lab studies
- Prognostic factors and clinical decisions
- Impact of genetic studies on diagnosis and treatment
- Molecular therapeutics (e.g., ATRA treatment of APL, use of imatinib in CML)
- Ethical issues in clinical trials

## **Early implementation of potential active oncolytic agents (small molecules) in a controlled clinical trial setting of Phase I/II trials, designed for designated targets in hemato-oncology diseases:**

A Clinical Trial Unit (CTU) for this specific goal is operative. Through this unit we have been able to get access to promising "pipe-line" products from international development programs of several pharmaceutical companies to test

in our programs for these diseases. The department has established a leading role in initiating and conducting pivotal clinical studies with new agents in local phase I/II trials and national phase II/III clinical trials with targeted therapies, including Imatinib in Chronic Myeloid Leukemia, Bortezomib in Multiple Myeloma, Gantuzumab and farnesyl Transferase Inhibitors in Acute Myeloid Leukemia and Histone Deacetylase Inhibitors in various leukemias.

#### **Development of allogeneic stem cell transplantation into a widely applicable modality of immunotherapy of leukemia, lymphoma and related diseases:**

This program has been built on a 20-year experience of allogeneic and autologous stem cell transplantation. It has transformed from an experimental treatment modality into a well-structured program that focuses on „graft vs leukemia,” as a means to control and eradicate Minimal Residual Disease (MRD). The program has developed special interest and background in

- 1) immune reconstitution after stem cell transplantation;
- 2) broad application of „Reduced Intensity Conditioning” as a non-toxic approach to immunotherapy;
- 3) Cellular immunotherapy of MRD by Reduced Intensity Conditioning (RIC). This program has been extended into a broad approach to the value of RIC in prospective trials in leukemia and myeloma. A part of the program dealing with viral activation and immune reconstitution is conducted in collaboration with the department of Virology (Prof. A. Osterhaus).

National and international conducted phase III trials on critical questions in hemato-oncology diseases:

The department of Hematology has an initiating and leading position in (inter-)national trials groups such as the national trial group HOVON and the European Organization for Research and Treatment of Cancer (EORTC). The number of patients included in these trials exceeds 10.000. Many trials have been conducted together with parallel biological studies on tumor samples. In addition, members of the scientific staff are coordinators of clinical trials that are conducted in the EORTC. The activities in this field reflect the focus on translational medicine, which has been defined as the most important challenge for clinical research in the department. An extensive data and tissue bank has been generated. This source is now being used for large-scale genomic analysis for disease-related risk analysis, based on high-throughput techniques.

## **4. Medical Oncology**

Prof. dr. E.P.M.J.J. Berns (coordinator), dr. R. Debets, Prof. dr. J.A. Foekens, dr. J.W. Martens, Dr. E. Wiemer, Prof. dr. K. van der Rijt, dr. C. Seynaeve, Prof. R. Matthijssen, Prof. dr. S. Sleijfer, and Dr. E. Wiemer

‘Cancer develops through an accumulation of (epi) genetic alterations. The selection of cells with crucial defects allows survival and growth advantage. Ultimately this results in invasive and metastatic cancer cells that can survive and grow outside their normal niche. It is the metastasis, originating from the primary tumour, which is the ultimate threat to the patient, as is therapy failure.’

Our successful discovery of profiles for resistance continuous, as this will lead to the discovery of novel targets for treatment.

Research within the main theme ‘Medical Oncology’ concerns mostly solid cancers. The main goal of this theme is to understand human solid cancers at the molecular mechanistic level and to apply this knowledge in the clinic, thus translational research. We improve methods for screening, diagnosis, prognosis and treatment, through all kinds of ‘-omics’ (genomics, transcriptomics, proteomics, pharmacogenomics), (gene)-therapy and functional therapeutic targeting approaches. In all studied diseases the research strategy is primarily based on investigation of patient cohorts and tumor samples, circulating tumor cells and body fluids (so called liquid biopsies) of the included patients. The direct study of the patient material is supported by study of in vitro and in vivo models systems: cell lines, xenografts and genetically modified mice.

Sporadic and hereditary breast tumors, for example, have been examined using a wide variety of molecular approaches, for example gene-expression-, miRNA-, DNA-methylation-, and or SNP-arrays. Besides, advanced mass-spectrometry and kinase-chip assays are used. These data are linked to pathological and clinical outcomes, with the ultimate goal to better classify cancer which will lead to personalized cancer therapy. As a consequence the program covers a range of programs from basic to clinically applied research.

Research programs:

- Personalized Medicine Translational Pharmacology and Tumor Immunology, ( E. Wiemer, , R. Mathijssen, R Debets, j),
- Cancer Genomics and Proteomics and (P.M.J.J. Berns, J.A. Foekens, J. Martens, S. Sleijfer)
- Palliative and Supportive care (K. v der Rijt)

The Department of Medical Oncology (see website for actual research and teaching programs and respective coordinators) has an initiating and leading position both for the laboratory as well as the clinical activities. Papers are numerous and published in highly ranked journals. The research program is solidly embedded and interactive with investigators in scientific groups and networks in a broad (inter)national context. These include cooperative clinical trial groups, European consortia and outstanding scientific groups.

## 5. Gynaecology and Gynaecologic Oncology

Prof. dr. C.W. Burger, Gynecologic Oncologist

Are hormonal and reproductive factors associated with the risk of ovarian- and other hormone-related cancers in later life of the women? Are preconceptional and prenatal hormonal exposures associated with adverse reproductive performance and health in offspring?

Currently, more than 1.5 % of all births are the result of a successful IVF treatment. Since hormonal and reproductive factors are known to be involved in the etiology of cancers of the female reproductive system, a stimulating effect of fertility drugs on the risk of these cancers is possible. In addition, evidence is increasing that prenatal exposures affect health and disease risk in later life. Low statistical power, lack of control for important confounders, and short follow up time (mostly average of five years) of women and offspring have limited previous studies of fertility treatment.

The Dutch study OMEGA is a large-scale nation-wide historical study consisting of OMEGA cohort I (from 1980-1995) and OMEGA cohort II (from 1980-2001) including 25.353 and 17.771 women, respectively: in total 43.124 women. All participants were identified in all twelve IVF hospitals that have legal permission to provide IVF-treatment in the Netherlands. The total exposed group consists of 32.265 women who were treated with at least one IVF cycle, and 10.859 women who were subfertile but not treated with IVF.

This study examines whether women who received one or more IVF treatment cycle(s) with ovarian stimulation are at increased risk of ovarian cancer and other hormone-related cancers. Data on reproductive variables and other risk factors for hormone-related cancers were obtained from the participating women, whereas detailed information on subfertility treatment was abstracted from the medical files. Unique is that data from the offspring of a subgroup of these women has been collected as well; 68% of all women completed a questionnaire.

Research activities: Students who are participating in our research themes will participate in all phases of the studies; the designing of the study, the recruitment and clinical data sampling, the performing of measurements and the data analysis. The final aim is the writing of a full paper. Because of the complexity of the data base statistical knowledge and experience with complex data warehouse is mandatory.

In the OMEGA study the following research themes can be investigated:

### Research theme 1. 'Hormonal stimulation treatment and women, and health in later life

1. Ovarian cancer and other hormone-related cancers. In 2011 this group has published for the first time a significant relation between IVF treatment and Borderline Tumor of the Ovary (BTO). Furthermore, a significant relation with the occurrence of ovarian cancer was noted after 15 years of IVF. We now can perform the second analyses including OMEGA II study expanding the number of women consequently increasing statistical power. At this moment analyses are ongoing.
2. Age of starting tobacco smoking and the risk of breast cancer. The nationwide OMEGA cohort study comprises 40.000 women who were treated for subfertility in one of the 12 Dutch IVF-clinics between 1980-2000. All women were asked to fill in a questionnaire, including questions on start and period of smoking, amount of cigarettes per day, menarche, menopause, parity and family history of cancer. Approximately 25.000 women returned a completed questionnaire. Breast cancer incidence in the period 1989-2013 was ascertained through linkage with the population-based Netherlands Cancer Registry (NCR).
3. Because in The Netherlands many girls start smoking at an early age, this large cohort is suitable to investigate the association between smoking at an early age and the risk of breast cancer. It is important to adjust for (possible) confounding, such as age at menarche and menopause, number of children and family history of cancer. Person-years analyses and Cox regression analyses will be performed using Stata statistical software.
4. Menopause. Five papers were published between the relation of early menopause and poor IVF outcome. Due to lack of further funding this item was expired.

## 6. Pediatric Research

Theme 1: Childhood asthma - a multifaceted disease.

The Generation R Study and the KinderHaven asthma clinic

Dr. L. Duijts and Prof. dr. J.C. de Jongste and dr. L. Duijts (Erasmus MC-Sophia)

The Generation R Study is a population-based prospective cohort study from early fetal life in of originally 9,778 children and their parents. The study is designed to identify early environmental and genetic causes and causal pathways leading to normal and abnormal growth, development and health during fetal life, childhood and adulthood in a multi-ethnic urban population. One of the main research areas is focused on Asthma, Allergy and Eczema. Main exposures of interest include environmental, endocrine, genetic and epigenetic, lifestyle related, nutritional and socio-demographic determinants. General follow-up rates until the age of 6 years exceed 80 %. Data collection in mothers, fathers and children include questionnaires, detailed physical and ultrasound examinations, behavioural observations, and biological samples. A genome and epigenome wide association screen is available in the participating children. From the age of 6 years, regular detailed hands-on assessments are performed in a dedicated research center including airway resistance (Rint) and exhaled nitric oxide, a noninvasive marker of asthmatic airway inflammation. Currently, children are aged 9 years and specific examinations include lung function using spirometry, lung structure evaluation using unique and advanced MR imaging, and allergic sensitization using skin prick tests. Eventually, results contribute to the development of novel strategies for optimizing health for children.

Main research projects that are presently being addressed are:

- What are early life environmental factors that lead to adapted lung structure and lung function, and subsequent respiratory disease such as asthma?
- What are genetic and epigenetic factors that lead to adapted lung structure and lung function, and subsequent respiratory disease such as asthma?
- What are early life environmental factors leading to eczema and allergy?
- What are genetic and epigenetic factors leading to eczema and allergy?

MSc students actively participate in one of the projects with the aim to write a paper suitable publication.

At our KinderHaven asthma and allergy clinic, highly protocolized care is provided to a large group of asthmatic and allergic children. Asthma treatment follows a step-up step down-approach depending on the level of asthma control and according to guidelines. All clinical data including assessments of asthma symptoms, lung function and airway inflammation, and all treatment decisions are accessible in the electronic patient record system of Erasmus MC and can be analyzed for scientific purposes.

Specific research questions related to asthma care at KinderHaven include:

- How do the treatment steps as defined in guideline algorithms for childhood asthma relate to clinical asthma control?
- Are there prognostic factors which predict a differential response in step 3 treatment (add on of long-acting beta agonists versus doubling doses of inhaled corticosteroids) in children with uncontrolled asthma on step 2 treatment?
- Does including lung function measurements in clinical asthma care improve asthma outcomes like asthma control?
- Can specific asthma phenotypes be validated in the 'KinderHaven' cohort?
- Are there risk factors for accelerated lung function decline in children with asthma?

For a NIHES fellowship, the KinderHaven clinical databases, containing data from longitudinal follow-up in a clinical routine setting, will be used to answer selected questions.

## Theme 2: Genetics and epigenetics of childhood diseases – the Generation R Study

Dr. J.F. Felix, Prof. dr. V.W.V. Jaddoe

The research on genetics and epigenetics of childhood diseases in Generation R focuses on the role of genetic and epigenetic factors in common childhood diseases and phenotypes, such as birth weight, obesity, insulin resistance and growth. For this, we use data from our genome-wide and epigenome-wide profiles, which are a unique source of information. The work in this group is often part of large-scale international collaborations. In the epigenetic studies, a particular focus is on the associations between maternal risk factors during pregnancy and epigenetic markers in children, as well as on epigenetic characteristics and their role in common childhood diseases.

Examples of projects in this theme are:

- Maternal smoking and epigenetic markers in cord blood
- Maternal folate levels and epigenetic markers in cord blood
- Cord blood epigenetic markers and childhood obesity
- Cord blood epigenetic markers and childhood growth

MSc students actively participate in one of the projects with the aim to write a paper that can be submitted for publication.

## Theme 3: Pediatric emergency care

### Triage and decision making in febrile children in an international study

Prof. dr. HA Moll, dr. R Oostenbrink

Evidence based medicine is the standard for current clinical practice. Several clinical decision rules including triage tools for acute pediatric problems are developed, but only a few are validated. Decision rules aim to distinguish patients with severe (infectious) illnesses from patients with mild self-limiting illnesses.

The pediatric emergency department in the ErasmusMC-Sophia Children Hospital is visited by an urban, multi-ethnic population of nearly 9000 children per year: 75% is younger than 4 years of age and 50% presents with infectious diseases. Triage in the emergency department is used to prioritize patients by urgency of care. Triage aims to determine a patient's acuity level in order to facilitate timely and effective care before their condition worsens. Currently available triage methods are predominantly based on the adult population. The Manchester Triage System is widely used in European hospitals. . . We started an international study on the validity of the MTS in six different European settings with different healthcare systems. Effective triage aims to have low undertriage (incorrectly classified as low urgent), while limiting overtriage (incorrectly classified as high urgent). Undertriaged patients wait longer and the delay in diagnosis and treatment increases morbidity and mortality. Overtriage obstructs patient flow of the true urgent patients with consequent delays in treatment and quality of care. Therefore triage is an important tool, to manage patient flow safely at the ED.

Fever is one of the most common acute illnesses in children visiting the emergency department and constitutes a diagnostic and therapeutic dilemma for paediatricians. The causes of the fever vary from meningitis, sepsis, pneumonia and other serious bacterial infections to mild viral diseases. The challenge is to identify children with possible serious infections based on clinical symptoms and laboratory tests.

In our research we focus on the validation and modification of decision rules in the pediatric population. In this study, data on triage, initial patient evaluation, diagnostics, treatment and follow-up are collected at 6 European emergency care departments. Data collection in these settings is part of the research as participating in patient evaluation at the pediatric emergency care of the Sophia's children's Hospital – Erasmus MC.

Aim: The project aims to modify and validate triage for the pediatric population in order to determine the best initial management for the acutely ill child. The following research questions will be assessed:

- What is the efficacy of the Manchester Triage System for pediatric patients in different European settings?
- How can we modify the system for pediatric patients at the emergency department based on the international results?



- The project subsequently focuses on the validation of prediction rules in children with fever in pediatric emergency care.

We address the following questions:

- What is the diagnostic value of new diagnostic tests in the evaluation of children with fever in addition to present prediction rules?
- How to update prediction rules for children suspected of bacterial meningitis, pneumonia or other serious bacterial infections?
- What is the actual impact of the implementation of clinical decision rules with the use information technology (clinical decision support system) in the emergency department?

#### Theme 4: Biological determinants of outcome and development of targeted therapies in childhood cancer

Prof. dr. Rob Pieters, Prof. dr. Monique L. den Boer, dr. Jules Meijerink(UHD), dr. M.Fornerod (UHD), dr. Max van Noesel, dr. Ronald Stam, dr. Michel Zwaan(UHD), dr. Marry M. van den Heuvel-Eibrink(UHD)

The pediatric oncology translational research program has the following aims: 1) Developing clinically and biologically relevant classification of leukemia. Identification of molecules associated with chemotherapy resistance, and identification of new therapeutic targets as well as development of new treatment strategies for children with cancer. 2) Clinical phase I and II studies in children. (The Department of Pediatric Oncology of the Erasmus MC-Sophia Children's Hospital is part of the European network of centers to perform these studies. The research laboratory of Pediatric Oncology is selected by the European ITCC (Innovative Therapies for Children with Cancer) network to perform the preclinical studies in especially leukemia for Europe). 3) translational research on pediatric solid tumours. 4) Early and late side effects of treatment, and palliative care. The umbrella of the research program is to develop targeted therapies for children with cancer. This should lead to more effective and less toxic treatment strategies.

For the Research Master Health Sciences & Research Master Clinical Research for Medical Students the following projects are available for NIHES students:

##### **Subtheme 4.1. Molecular markers and drugable targets in pediatric acute leukemia**

(working group leader Prof. dr. Monique L. den Boer)

For childhood ALL the cure rates are about 80%. Further optimization of therapy requires insights in the biology of leukemia cells and its microenvironment. This will lead to more specific therapies with more efficacy and less side effects. Our work focusses on the following topics: 1)improving classification of leukemia by identifying novel genetic ALL-types that are clinically relevant, 2)elucidating causes of cellular drug resistance, 3)Studying the contribution of the mesenchymal niche in maintenance of leukemic cells, 4)identifying genes functionally important to viability of leukemic cells that may be targeted by specific drugs, 5)preclinical testing of the efficacy and specificity of targeted drugs (ALL xenograft mouse models).

**Student project 1.**In the last years we have shown that new genetic types of ALL can be identified by gene expression signatures (mRNA level) and genomics (DNA level). In ongoing studies we determine the clinical application of these genomic abnormalities, e.g. the genomic EBF1-PDGFRB fusion was found in a highly unfavorable prognostic group of BCR-ABL1-like ALL that we recently discovered by gene expression studies. In the student's project we will characterize the genetic and molecular defects of this novel subtype aiming to point to drugable targets.

**Student project 2.**Besides biological variation between patients' leukemic cells, we hypothesize that also the microenvironment in which leukemic cells reside contributes to the fate of the leukemic cell (and hence response of a patient to chemotherapy). At present, information about the bone marrow niche is lacking and therefore not used for therapeutic purposes. In the student's project we investigate the characteristics of the mesenchymal stromal cells which are taken from patients and determine which genes may be suitable to target the nurturing stromal cells and whether treatment directed towards the stromal cells works synergistically or antagonistically with current combination chemotherapy

#### **Subtheme 4.2 Molecular unraveling of pediatric myeloid malignancies.**

(Workgroup leaders: MM van den Heuvel-Eibrink, M.Fornerod, CM Zwaan)

Although acute myeloid leukemia (AML) accounts for only 15-20% of pediatric leukemias, primary refractory and relapsed pediatric AML lead to a significant number of childhood cancer deaths. Despite the current chemotherapeutic regimens, survival rates have plateaued at 60-70% and further treatment intensification is not feasible. Thus, there is a need to develop new drugs for pediatric AML. In adult AML and myelodysplastic syndromes, epigenetic regulation, and in particular hypermethylation of relevant tumor suppressor genes have been shown to be involved in leukemogenesis. Based on this demethylating agents have been successfully applied in clinical settings. Preliminary data showed that also in children with MDS hypermethylation occurs, but studies on the frequency of epigenetic regulator gene mutations are scarce and numbers are small. This project is aimed at identifying differences in methylation patterns in pediatric AML especially focused on, MPL-RARA and AML1-ETO subgroups based on genome-wide DNA methylation profiling analysis. This, to provide the rational for treatment of pediatric AML patients with demethylating-agents and to identify novel deregulated genes in pediatric AML.

**Student project 3(MDS) and 4(AML).** In the current project, selected epigenetic regulator genes will be studied in a national and international collected cohort of children with MDS(n=110) as well as in the selected above mentioned selected subgroup of pediatric AMLcohort (n=500). Approval of this study and ethical committee consent has been obtained. The results may provide further evidence that epigenetic regulation is important, and that demethylating agents may be of value for children with MDS and AML. In both projects, apart from studying epigenetic mutation status, available methylation array findings on loci of interest. In PML-RARA and/or AML1-ETO patients and other AML subgroups will be validated by means of MS-PCR and bisulfite sequencing. Correlation of methylation status and expression levels of genes of interest in the different AML and MDS subgroups will be performed by comparing methylation array data to gene expression array data and qPCR. In addition expression of the genes of interest that are regulated through methylation will be further functionally validated by means of in vitro assays using demethylating-agents.

#### **Subtheme 4.3 Preclinical validation of drug targets for phase I and II studies in pediatric cancer**

(PI CM Zwaan)

**Student project 5.** Most novel anti-cancer drugs introduced in pediatric oncology have first been developed in adult oncology. In order to understand their potential value for use in pediatric oncology pre-clinical studies are needed including target identification and validation in pediatric cancers. Various types of drugs are studied in our lab for this purpose, including nuclear transport inhibitors, DOT1L-inhibitors, ibrutinib, PD-1L inhibitors and various others. The results will be used to generate early clinical trials in pediatric oncology

#### **Subtheme 4.4. Research on pediatric solid abdominal tumours.**

(Pis MM van Noesel and MM van den Heuvel-Eibrink)

No projects this year

#### **Subtheme 4.5 Early and late side effects of treatment**

(Pis MM van den Heuvel-Eibrink, pediatric oncologist, S Pluijm, epidemiologist, S.Neggers, Internal Medicine)

As childhood cancer survival rates are improving, the number of survivors is increasing. Therefore direct long term side effects are of great interest for identifying determinants that may lead to identification of risk groups, that may benefit from early intervention

#### **Student project 6. Designing a prediction model for osteogenic side effects in children with acute lymphoblastic leukemia(ALL)**

(Pis MM van den Heuvel-Eibrink/S.Pluijm).

In a well-documented national cohort of children with ALL, bone mineral density has been studied over time(n>700 patients). Results show that osteopenia occurs in over 40% of all cases and osteoporosis in 16% of the cases. Variables that determine the risk of bone loss have now been identified, however risk models, including genetic variation as well as clinical predictors of bone loss are lacking. The current study aims to design such a model in order to identify subjects at risk and to apply intervention studies that may prevent such serious sequelae.

**Student project 7. Identification of socio-economic sequelae of childhood cancer survival**(PIs MM van den Huevel-Eibrink/ S.Pluijm/S.Neggers). In a well-documented cohort of 700 long term adult childhood cancer survivors(CCS), treated in the Erasmus MC-Sophia Children's Hospital, by questionnaires, data were collected on health status, educational level and socio-economic status, employment, problems with insurances and health perception. These data will be analysed in the current descriptive project with regard to disease type, age at diagnosis, gender, treatment, era of treatment and be linked to emotional distress status data. The results will give insight in the socio-economic sequelae long after discontinuating treatment of childhood cancer.

## Theme 5: Epidemiology of pediatric Inflammatory Bowel Disease (IBD)

Dr. J.C. Escher

Crohn's disease may present before the age of 20 years in 25-30% of the patients. Epidemiology of IBD has been studied widely in adults, showing incidence and prevalence rates that vary considerably. Part of the variation might be due to differences in disease definition, recognition, and coding, but there is little doubt that disease incidence varies with geographic area. In the USA as well as in Europe, IBD seems to be more common in northern than in southern areas.

In the paediatric age group, several epidemiological studies have been published with evidence suggesting that the incidence of IBD has increased over the last 10 years. Both retrospective and prospective studies were performed in Sweden, Denmark, Scotland, Wales, and the United Kingdom. These studies show incidence rates of 0.2 to 5.9 per 100.000 per year in children for Crohn's disease, and 0.5 to 3.2 for ulcerative colitis. Prevalence of Crohn's disease is reported as 6 to 16 per 100.000 per population studied, and 3.4 to 9.2 for ulcerative colitis. A definite increase in the incidence of Crohn's disease in children as well as in adults has been observed for the last decade.

Certain features are unique to paediatric IBD as compared to adult onset disease. One feature is growth failure, which is present at diagnosis in

10-40% of affected children. Less obvious, but nevertheless clinically important are the differences in clinical presentation: abdominal pain is the most frequent symptom in children with IBD, whereas adults tend to present most often with rectal bleeding (in ulcerative colitis) or diarrhea (in Crohn's disease).

Future collection of epidemiological information on disease expression at presentation, characteristics during the course of disease, potential predisposing factors, extra intestinal manifestations, treatment course, surgery and outcome may generate additional knowledge about the differences between early-onset and adult-onset inflammatory bowel disease.

A database that is used to characterize disease on a prospective basis is an absolute necessity for investigators studying genetics, drug therapy, health outcomes, and the socioeconomic impact of these diseases. Moreover, a large and well-organized database greatly facilitates the collection of sufficient amounts of human material (specimens), enabling research on the etiology and pathophysiology of early onset IBD. The format of this IBD core database has been developed by consensus of the ESPGHAN IBD working group. A successful European paediatric IBD database is active since May 2004, and is being coordinated by Dr Escher. Aim of the MSc. project is to prospectively include new cases of paediatric IBD in Sophia Children's Hospital as well as organise a platform for prospective regional and national data collection the Netherlands.

## 7. Periconception and Prenatal Medicine, Obstetrics and Reproduction

Prof. dr. R.P.M. Steegers-Theunissen ([r.steegers@erasmusmc.nl](mailto:r.steegers@erasmusmc.nl)), Prof. dr. J.S.E. Laven, Prof. dr. E.A.P. Steegers

Can you identify genetic and environmental causes for fertility problems, congenital malformations, miscarriages, pre-eclampsia and fetal growth restriction?

The genes of the child and placenta are derived from the gametes of both parents. Therefore, the genetic background together with the parental environmental exposures, such as nutrition, lifestyle, occupational exposure, medication and health, determine the quality of the gametes, fertilisation and pregnancy. The environment of the conceptus (embryo and fetus) is formed by the mother. The genes of the conceptus and maternal environmental exposures are both involved in embryogenesis and placentation in early pregnancy, as well as in fetal programming, growth and development in the second and third trimester of pregnancy.

Focus: Our research is directed on the periconception period and early pregnancy. The phenotypes of interest are periconception and embryonic health, subfertility, congenital malformations, miscarriages, pre-eclampsia, premature birth, fetal growth restriction and low birth weight.

Studies: To investigate this topic, we started in November 2010 the Rotterdam periconception cohort study, in which pregnancies are monitored from the preconceptional period until 1 year after delivery. Unique are the serial 3D ultrasound measurements of the embryonic structures and placenta in the first 12 weeks of pregnancy which are investigated in the I-space with V-scope software in association with exposures and long term outcome parameters. Furthermore, we conduct clinical and case-control studies, and a datawarehouse is available for research on data from patients visiting the Erasmus MC Sophia, and Mother and Child Centre.

Determinants: General characteristics, serial 3D ultrasound measurements of the embryo, brain, placenta, yolk sac, and embryonic and fetal organs, nutrition, lifestyle, occupational exposures, biomarkers of nutrients and hormones in blood, - cord blood, - chorionic villous samples, - amniotic fluid, - placental tissue, - semen, and follicular fluids (obtained via in vitro fertilisation and pre-implantation genetic screening techniques). All materials and isolated DNA are available for sophisticated (nutri)genomics, epigenetics, metabolomic and proteomic techniques.

Relevance: The importance of this collaborative research at the department of Obstetrics and Gynaecology is the identification of modifiable risk factors and underlying epigenetic mechanisms. This may be used in future preconception counselling.

Research activities: Students who are participating in our research themes will participate in all phases of the studies; the design of the study, the recruitment and clinical data sampling, the performing of 3D ultrasound measurements at the outpatient clinic and I-space, and the data analysis. The final aim is the writing of a full paper.

Main research themes: 1. Periconception and embryonic health 2. Subfertility 3. Congenital malformations 4. Maternal and perinatal complications, including embryonic- placental and fetal growth restriction

### Theme 1: Periconception and embryonic health

Periconception health of the couple and the health of the embryo are new themes for research with the aim to further improve preconception and obstetrical care and treatment. The focus is on poor modifiable behaviors such as nutrition and lifestyle of the couple for which 2 randomised controlled intervention studies with the mHealth tool [www.SlimmerZwanger.nl](http://www.SlimmerZwanger.nl) on the smart phone are being conducted. Outcomes are the improvement of nutrition and lifestyle and clinical endpoints are the chance of pregnancy and embryo quality, growth and development in the subfertile IVF population. In the general population additional outcomes are the reduction of congenital malformations, premature birth and fetal growth restriction.

Research questions:

1. What are the effects of preconception lifestyle intervention of the m-health tool [www.SlimmerZwanger.nl](http://www.SlimmerZwanger.nl) in the woman and her partner on:
  - nutrition and lifestyle
  - pregnancy chance
  - embryo quality, growth and development
  - the occurrence of congenital malformations, premature birth and fetal growth restriction.
2. What is the influence of periconception health on embryonic health?

## Theme 2: Subfertility

Subfertility is an increasing problem and affects around 15% of the reproductive population. Nutrition and lifestyle factors play a role in the fertilization process. In the Predict Study subfertile couples undergoing fertility treatment are included, where lifestyle and environmental determinants are assessed by questionnaires and biomarkers measured in blood, follicle fluid and seminal plasma. Outcomes are: semen parameters, number of oocytes, embryo quality, (ongoing) pregnancy, and DNA methylation patterns in several tissues. Interventions on lifestyle factors of the couple (nutrition, smoking, alcohol, weight reduction) using sophisticated tools are performed as well. The effects of these interventions on fertility outcome and epigenetic patterns are evaluated. General aim: To unravel gene-environment interactions and underlying epigenetic mechanisms in the pathogenesis and prevention of subfertility in human.

Research questions:

1. What are the effects of preconception lifestyles (interventions; M-health tool [www.SlimmerZwanger.nl](http://www.SlimmerZwanger.nl)), environmental exposures and genes on:
  - the causes of subfertility
  - the fertility parameters: semen, oocyte and embryo quality
2. What is the influence of grandparent health on fertility of their children?
3. Prediction of fertility outcome parameters with the Rotterdam Reproductive Risk Score (R3-score).

## Theme 3: Congenital Malformations

Every year 17 million children are born with a congenital malformation worldwide, of which congenital heart defects, cleft lip and/or palate, neural tube defects (spina bifida, anencephaly), and Down syndrome form the largest groups. Genetic factors and environmental exposures in the periconception period play a significant role in the pathogenesis and prevention of such malformations. Recently it has been observed that the birth prevalence rate of congenital malformations is extremely high in several parts of Rotterdam. Therefore, we conducted large scale case-control family studies on the previously mentioned congenital malformations (SPINA BIFIDA Study, EUROCRAN, HAVEN Study). Furthermore, the Predict Study also includes pregnant women carrying a fetus with one of these malformations. Lifestyle and environmental determinants are collected by questionnaires and biomarkers (focus on periconception period) measured in blood, coelomic and amniotic fluids. Outcomes: pregnancies with one of the 4 above mentioned congenital malformations, DNA methylation patterns in several tissues.

General aim: To explore gene-environment interactions and underlying epigenetic mechanisms in the pathogenesis and prevention of 4 major congenital malformations in humans.

Research questions:

1. What are the effects of periconception lifestyle (intervention; M-health tool [www.SlimmerZwanger.nl](http://www.SlimmerZwanger.nl)), environmental exposures and genes on:
  - the occurrence of congenital malformations determined by ultrasound examination?
  - the DNA methylation patterns in offspring and in several tissues?
2. What is the influence of the grandparent health on the risk of congenital malformations in their children?
3. Prediction of the risk of the 4 congenital malformations with the Rotterdam Reproductive Risk Score (R3-score).

## Theme 4: Maternal and perinatal complications

Last decade the perinatal mortality and morbidity is significantly increased in the largest urban cities in the Netherlands, in particular in Rotterdam. Evidence is increasing that nutrition and lifestyle factors, in the preconception period of both parents-to-be and in early pregnancy, herewith play a significant role. Therefore, we are conducting the Predict Study among normal and high risk couples in which lifestyle and environmental exposures are collected by questionnaires and biomarkers are measured in stored blood. Outcome parameters are: miscarriage, embryonic and fetal growth (in first second and third trimester of pregnancy), placental related pregnancy complications and birth weight. Interventions on lifestyle factors of the couple (nutrition, smoking, alcohol, weight reduction) using sophisticated tools will be initiated as well. The effects of preconceptional interventions on pregnancy course and outcome will be evaluated.

General aim: To identify periconception lifestyle factors and epigenetic mechanisms on maternal and perinatal complications.

Research questions:

1. What are the effects of periconception lifestyle (interventions; M-health tool [www.SlimmerZwanger.nl](http://www.SlimmerZwanger.nl)), environmental exposures and genes on:
  - first trimester growth (embryo, fetus, yolk sac, placenta) determined by repeated ultrasound measurements?
  - pregnancy complications (miscarriage, placental related vascular diseases, IUGR, low birth weight etc)?
  - the DNA methylation patterns in offspring and in placental tissue?
2. What is the influence of the grandparent health on the risk of maternal and perinatal complications in their (grand)children?
3. Prediction of maternal and perinatal complications with the Rotterdam Reproductive Risk Score (R3-score).

## 8. Urology

Urologic research flows...

The department of Urology of Erasmus MC focuses on translational research in various subspecialties in Urology (oncology, functional urology, andrology, pediatric urology, stone disease). Each of these subspecialties has its preclinical research laboratory, and findings are validated in the clinic. In order to facilitate (pre-)clinical research, a Trial and Research Coordination organizes the initiation of clinical trials, patient monitoring, and statistical analysis of data. Large data and biomaterial sets have been build up carefully over the last twenty years, especially for prostate and bladder cancer. The department is top-ranked within Erasmus MC with regard to its scientific output.

A number of research projects have been formulated below. Principle investigators can be contacted for further information directly by email, copying the chairman of Urology, Prof Chris H. Bangma, and the Coordinator of Education Mrs Merit Domscheit.

### Theme 1: my assay smells cancer prognosis...

Prof. dr. Chris Bangma

Biomarkers indicating aggressive prostate cancer

Prostate cancer shows a large variation in biologic and clinical growth. Current markers like Gleason score (histologic grading) and PSA (prostate specific antigen in serum) are inadequate to predict the biologic behaviour of a cancer at the time of diagnosis. Therefore, the choice for a tailored therapy, whether by surgery, by radiotherapy, or by active surveillance avoiding invasive therapy, is complex.

Preclinical research has identified candidate prognostic biomarkers in serum and laboratory models (Dr Guido Jenster, Dr Theo Luidier, the results of a research project from the European P-mark consortium led by Erasmus Urology). These markers need to be validated in the large biobanks of patient sera. We have made a priority listing of candidate markers according to their biologic relevance and other criteria. For these markers we need to construct simple antibody based assays (ELISA) that can test a large set of patient sera simultaneously.

What are you going to do?

The student will observe the diagnostic and therapeutic procedures of a number of prostate cancer patients in outpatient clinic, the clinic, in operation theatre or while being irradiated. Next, the database with long term follow-up of over 500 patients that underwent radical prostatectomy will be analysed for survival and treatment effects in the trial and research unit (Dr Mark Wildhagen). The outcomes will be compared with the literature, and form the base of a manuscript. The biomaterials of these patients will serve for the analysis of new biomarkers. The student will construct a new ELISA assay in the laboratory (Dr Guido Jenster), and perform the testing. The biomarker results will be correlated with the biological outcome of the patients from the database.

### Theme 2: Botox for Bladders

Dr. Bertil Blok

Research programs in Functional Urology

During the last decade, our understanding of the control of the urinary bladder and its sphincter has been increased exponentially. Concomitantly, major improvements have been achieved in diagnostic and therapeutic possibilities and in patient management and outcome. Basic animal experiments and functional imaging techniques in humans have shown which areas of the brain are involved in the control of the bladder, and which areas are dysfunctional in incontinence. Clinically, the introduction of botulinum toxin A (Botox) injections in the bladder has prevented renal insufficiency in many patients with spinal cord injury and decreased the need for major abdominal surgery in case of urinary deviation. Furthermore, stress and urge incontinence can be treated sufficiently with minimal invasive surgery and extended release oral medication, respectively.

The focus of this research theme is on translational research. This means ideally that the main answers acquired from basic research questions are used directly for clinical application. The student will participate and interact with research groups of other investigators of urology and other clinical departments, like radiology. This research theme comprises both experimental and clinical aspects.

Research programs:

- Study of the effects of botulinum toxin A on the lower urinary tract of rats.
- Bone marrow stem cell myogenic differentiation for implantation in the lower urinary tract of rats.
- Functional imaging of the effects of anti-cholinergics used in urge incontinence.
- Functional imaging of the effects of anti-androgens used in prostate cancer.
- Treatment evaluation of new anti-incontinence devices.

### Theme 3: Nuts and male (sub)fertility

Dr. Gert Dohle, Prof. dr. Regine P.M. Steegers-Theunissen

The relationship between dietary factors and sperm parameters

Male subfertility is present in 30-50% of subfertile couples and is unexplained in 75% of cases. Usually, the patient presents with poor sperm quality (oligo-asteno-teratozoospermia OAT syndrome) without obvious health problems or medical history that can explain the impaired sperm parameters. Potential explanations for idiopathic OAT are testicular dysgenesis caused by gene-environment interactions in early pregnancy, genetic defects such as an abnormal karyotype or Y-chromosome deletion, obesity and life-style factors like the use of anabolic steroids, and nutritional factors. Based on the literature it is postulated that certain nutritional factors and dietary patterns may be associated with abnormal spermatogenesis.

What are you going to do?

An analysis is performed of a database containing medical history, food frequency questionnaires, physical examination, scrotal ultrasound and the results of semen analysis, including DNA-fragmentation of spermatozoa. The goal is to detect dietary factors/patterns that are associated with male subfertility and increased DNA damage. This may result in randomised placebo controlled intervention studies to determine the influence on sperm quality and pregnancy rates.

### Theme 4: Sperm morphology and DNA-damage. Can we predict male fertility?

Dr Gert Dohle

Male infertility is present in 30-50% of infertile couples and is unexplained in 75% of cases. Usually, the patient presents with poor sperm quality (oligo-asteno-teratozoospermia) for which there is no evidence based treatment. The couples are offered artificial reproductive techniques (ART) such as in vitro fertilisation and intracytoplasmic sperm injection. Sperm count and motility score are limited predictors of spontaneous pregnancy and the results of ART. Sperm morphology and sperm DNA damage may be better predictors of fertilisation rate and pregnancy.

What are you going to do?

First we start with an analysis of the predictive value of sperm morphology according to the kruger Strict criteria and the WHO-criteria. Data are extracted from semen analysis performed since 2004 and the outcome of ART in our IVF lab. Secondly, we will perform sperm chromatine structure analysis (SCSA) on specimens containing different levels of normal morphology before and after sperm preparation for IVF/ICSI. Also morphology is repeated after sperm preparation and compared to the pre-preparation specimen and the SCSA data. Finally we hope to answer the question if sperm DNA damage (SCSA) is a better predictor for spontaneous pregnancy and the results of ART.

### Theme 5: PSA based prostate cancer screening, pitfalls and possible improvements

Dr Monique Roobol

The European Randomized study of Screening for Prostate Cancer (ERSPC) is designed to study the effects of prostate-specific antigen (PSA) driven prostate cancer (PC) screening on PC-mortality. By November 2006 a total of 276,949 men have been randomized between a screening and control arm in 8 European countries. Next to the main endpoint, the study of prostate cancer mortality, prostate cancer morbidity, the value of the screening procedures, and quality of life in the screening and control arms are subject to investigation.



The ERSPC screening study applied a PSA based screening algorithm i.e. the trigger for further evaluation (prostate biopsy) was solely based on the outcome of the PSA test. This has resulted in a considerable percentage of unnecessary tests and is considered one of the drawbacks of population based prostate cancer screening. Currently there is no population based screening program, in fact offering screening for prostate cancer is not illegal. However PSA testing on request is quite common. A better risk stratification enabling better guidance for both physician and patient is therefore warranted.

What are you going to do?

The student will assess the outcomes of the screening process and will focus in particular on repeat screening rounds. With the available data an attempt will be made to develop a more efficient screening algorithm especially suitable for men with repeated negative test results in the past. To achieve this goal the student will work with large databases and perform advanced statistical analyses developing multivariable models to predict biopsy outcome. Next to this the student will have the opportunity to actively participate within the ongoing studies and the screening program of ERSPC. This will entail blood drawing, DRE and TRUS examinations and prostate biopsies of men randomised to the screening arm of the ERSPC.

## 9. Transplantation Medicine

Prof. dr. W.Weimar, dr. C.C. Baan

After organ transplantation the immune system becomes activated after interaction with donor cells. Induction of specific cytokine- and chemokine expression profiles and cross-talk between various immune competent cells result in effector, regulatory and memory immune mechanisms. Ultimately this will lead to destruction of the grafted organ. Therefore, manipulation of the immune system is necessary for successful organ transplantation. This may be achieved by prescribing immunosuppressive medication, allowing the engraftment. In the clinical organ transplant setting this has resulted in successful short time, but not long term results. Patients still need continual immunosuppression and therefore suffer from enhanced risks of infections, malignancies and cardiovascular mortality, while at the same time chronic allograft loss is not prevented.

The field of clinical transplant immunology focuses on strategies to induce clinical operational tolerance, i.e. drug-free graft survival. For this purpose it is essential to explore in detail the donor-specific effector, regulatory and memory immune responses in relation to graft acceptance and failure. The identification of suppressor cells with donor specific properties has opened an important new area of cellular immunotherapy and individual immunosuppression.

The main theme includes two subthemes:

1. Donor specific effector mechanisms and immune tolerance
2. Cytokines and chemokines in transplantation

The subthemes covers projects aiming to:

- To investigate donor specific effector T-cells (i.e. cytotoxic T-cells, helper T-cells) in an attempt to understand the immunological pathways leading to success or failure.
- To determine the in vivo induction of tolerogenic regulatory (i.e. CD25+brightFoxp3+) T-cells in organ transplant patients weaned from immunosuppressive medication.
- To study the role of cytokines in anti-donor responses and immune regulation. These molecules affect proliferation, differentiation, death, and the function of cells involved in rejection and operational tolerance.
- To study the role of immunological and non-immunological factors like cold ischemia and reperfusion in the development of chronic allograft dysfunction.

Scientific achievements during the last 5 years:

- Renal and cardiac allograft recipients are hyporesponsive towards donor antigens > 2 years after transplantation.
- Immune reactivity after HLA identical living related kidney transplantation can be analyzed by measuring the number of IFN- $\gamma$  Elispots.
- Immune regulation is the consequence of an immune response. High FOXP3 mRNA levels are measured during allogeneic responses in vivo and in vitro and suggest that regulatory activities of CD25 bright+ T-cells or the generation of these cells is an intrinsic part of activation.
- Immunosuppressive agents to prevent rejection interfere with the induction of FOXP3 mRNA and may actually hinder the development of tolerance.
- Identification of specific chemokine receptors expression profiles in cardiac allograft recipients. Accelerated trafficking of T-cells to the lymphoid tissues via chemokine receptors may increase the risk for rejection.
- The immunosuppressive agents cyclosporine and anti-CD25 monoclonal antibodies hinder the mechanisms by which the immune system eliminates alloreactive cells. They affect apoptotic pathways.
- The frequency of Dendritic Cells (DC) is low and remains low in immunosuppressed allograft recipients.
- Genetic profiles enabled us to identify patients at risk for complications after heart and kidney transplantation.

- Expression levels of HIF-1 $\alpha$ , the transcription factor that is induced in the adaptive response to hypoxia and critical for initiating the transcriptional activation of growth factors, correlated with cold ischemia time after kidney transplantation. High mRNA expression levels of cytoprotective genes i.e. heme oxygenase-1 and vascular endothelial growth factor at the moment of transplantation are correlated with graft function early after clinical kidney transplantation.

Future plans: special goals and approach

Tapering the immunosuppressive load is an important issue for transplant patients. In these studies we will focus on suppressor T-cells that regulate basic immune processes and are designed to maintain tolerance. Antigen specific CD4<sup>+</sup>CD25<sup>+</sup>brightFoxp3<sup>+</sup> regulatory T-cells have emerged as the regulator of immunity to foreign antigens and might therefore be the target for therapeutic intervention and therapy. The objective is to induce operational tolerance in stable allograft recipients by weaning them from the immunosuppressive medication. These autologous Tregs will also be expanded and functionally characterized as a first step to Treg based immunotherapy.

Studies to unravel the mechanism by which the immune system via cytokine pathways trigger graft acceptance. Furthermore, trials with new immunosuppressive agents will be monitored to gain insight in drug related side effects and how the immune system mediates anti-donor responses.

## 10. Gastroenterology & Hepatology

The Erasmus Medical Center has a main research program with focus on Digestive Diseases and Sciences. This program is performed at the collaborating departments of Gastrointestinal Surgery, Pediatrics, Pediatric Surgery, and Gastroenterology and Hepatology, in close collaboration with the departments of Clinical Genetics, Medical Microbiology, Pharmaco-Epidemiology, Pathology, Radiology and Virology. The mission of the research program is to unravel the mechanisms underlying normal function and disorders of the gastrointestinal tract including the liver and pancreas by means of integrated pre-clinical and clinical research. This research aims at the development of strategies for prevention, diagnosis, and treatment of gastrointestinal diseases. Within the Department of Gastroenterology & Hepatology, the research includes three major lines of research.

### Theme 1: Chronic inflammation and carcinogenesis of the digestive tract.

Prof. dr. M.P. Peppelenbosch, Prof. dr. M.J. Bruno

The gastrointestinal tract can be affected by a large variety of disorders, many of which are characterized by chronic active inflammation, ultimately leading to morphological and functional changes. A considerable proportion of these chronic inflammatory disorders promote the development of dysplasia and neoplasia of the affected organ. Together, the gastrointestinal tract is more frequently affected by chronic inflammation and malignancy than any other organ system in the human body. This induces a great need for further insight into the mechanisms underlying infections, inflammation and malignancy of the digestive tract, as well as methods for prevention, early diagnosis and treatment.

The research within this theme focuses on the causes and the mechanisms underlying chronic inflammation and the processes, which lead to morphological and functional disturbances, and neoplasia development of the affected organ. Diagnosis, treatment, screening and surveillance are key items within this focus. Clinical topics within this theme include Barrett's esophagitis and esophageal carcinoma, chronic *Helicobacter pylori* gastritis and gastric cancer, chronic inflammation biliary tract including pre- and post-transplantation disorders, chronic pancreatitis and pancreatic cancer, and inflammatory bowel disease and colonic neoplasia. Research projects within this theme are diverse and include laboratory research, as well as clinical and epidemiological studies. One of the ongoing projects is a large colon cancer prevention study in the Rijnmond area.

### Theme 2: Liver disorders and liver transplantation

Dr. R.A. de Man, Prof. dr. H. Metselaar, dr. J. Kwekkeboom

Effective treatment of chronic viral hepatitis was largely lacking until fifteen years ago. In our day however, the medical world has gained significantly more knowledge about the pathogenesis of liver inflammation and viral hepatitis, leading to appropriate medication and treatment in many cases. Thus, hepatitis B can now be treated effectively in over 30% of patients and can be kept under control permanently in 70 to 80% of these patients. With regard to chronic hepatitis C, 50-80% of patients may recover by now.

Our research focuses on two major issues, a/ mapping the cells that 'pick up' the hepatitis B and C viruses and present these to the immune system, and b/ exploration of the influence of regulatory T-cells on viruses causing hepatitis. The scientific knowledge obtained from these studies direct translates into patient care. Concerning research in the field of liver transplantation (medical) biologists and clinicians closely co-operate in two fields: one is prevention and treatment of recurrent hepatitis C virus (HCV) in liver transplants, the other is optimisation of immune suppression with the aim of attaining transplant tolerance.

### Theme 3: Inflammatory bowel diseases

Dr. C.J. van der Woude, dr. P. Dewint

Chronic inflammatory bowel diseases are very common and their incidence is still further rising. The etiology of these diseases is multifactorial, with interactions between gut flora, multigenetic host factors, and environmental factors all contributing. Patients with inflammatory bowel diseases are preferentially treated with combination drug therapy, mostly including immunosuppressive drugs. Surgery and endoscopic treatment is however often needed. The past decades have generated a wealth of knowledge about the causes of two types of IBD, Crohn's disease and ulcerative colitis. These appear to have much in common. In both types the intestinal immune system reacts vigorously to harmless stimuli, such as the normal intestinal flora. Our research focuses on epidemiology and genetics of IBD, as well as on the effects of immunosuppressives on the mucosal level. The combination of outpatient clinic and laboratory makes a unique exchange of expertise. The joint efforts will gradually give more insight into the diseases from young to old.

## Theme 4: Can you solve the problem of viral hepatitis?

Dr. A.M. Woltman, Dr. A. Boonstra, Dr. L.J. W. van der Laan, dr. R.A. de Man, Dr. R.J. de Knegt

Viral hepatitis is a major global health problem with more than 500 million patients chronically infected. Both chronic hepatitis B and C lead to liver cirrhosis, liver failure and hepatocellular carcinoma, accounting for approximately 1 million deaths annually. The importance of developing adequate therapy for these diseases is obvious and the Rotterdam Liver Unit is one of the foremost groups in the world to develop such treatments. Taking full advantage of recent knowledge acquired in clinical and immunological medicine, our studies combine epidemiological and fundamental research in a cross-disciplinary approach while collaborating with the most experienced centers in the field of viral hepatitis.

Twenty years ago we were not able to treat any patient with chronic viral hepatitis, whereas nowadays some 50% of the patients can be kept in long-term remission. Our challenge is to find an adequate treatment to achieve a full cure of disease in all patients. In the clinic, we investigate new antiviral drugs as well as immune modulating agents to increase the response rate. In this field our group has published many landmark studies during the last decade. In the laboratory, our research is mainly devoted to understanding the apparently inadequate immune response of chronic viral hepatitis. Gaining better understanding of these mechanisms, will eventually contribute to innovations in treatment regimens. Research is focused on the role of dendritic cells (DC), (regulatory) T cells and NK cells. Patients with chronic viral hepatitis exhibit an impaired DC function and increased percentages of regulatory T cells as compared to healthy volunteers. This may contribute to the insufficient T cell response in these chronic infections. NK cells also play a pivotal role in anti-viral responses, but their role in anti-HBV responses is as yet largely unknown.

Our facility, being the largest clinic and laboratory for chronic viral hepatitis in The Netherlands, offers a unique environment to combine fundamental and clinical research. There is intensive collaboration with important liver groups around the globe and with our translational approach we will be able to elucidate key pathways to eradicate viral hepatitis. Let's hope that you can help us to further invigorate and energize the unexplored scientific field of the battle against viral hepatitis!

Research themes include:

- effect of antiviral therapy on the immune response to HBV
- mechanism of immunological tolerance to HBV

## Theme 5: TP53 mutation in cell free DNA as a marker for tumor response to neoadjuvant chemoradiotherapy for esophageal cancer.

B.P.L. Wijnhoven, W.N.M. Dinjens

Department of Surgery and Pathology, Erasmus MC Rotterdam.

Neoadjuvant chemoradiotherapy (nCRT) followed by surgery is the standard of care for patients with potentially curable esophageal cancer. In about 30% of the patients, a pathologically complete response (pCR) is seen in the resection specimen, i.e. no viable tumor cells can be detected. In these patients, it is questionable whether an esophagectomy is indicated, which exposes the patient at risk for complications without impacting on survival. To assess whether a patient still bears viable tumor, the detection of tumor-specific TP53 mutations in cell free DNA (cfDNA) from patients' serum could be useful. It can be anticipated that in patients with a pCR, the tumor-derived cfDNA is initially increased in the serum due to tumor cell lysis. cfDNA derived from tumor can be recognized by specific TP53 mutations, which are present in mostly all esophageal carcinomas. In an available series of esophageal carcinomas the TP53 mutation status will be determined in diagnostic pretreatment biopsies by Ion Torrent Next Generation Sequencing (NGS). The identified TP53 mutations will be investigated quantitatively by digital PCR in longitudinally collected sera before, during and after nCRT. The results will be compared with nCRT response as determined in the resection specimen. Potentially, the results of this study can lead to the early identification of complete responders and non-responders, which both will have important impact on patient treatment.

This project will both involve practicing laboratorial activities; DNA isolation, PCR, sequencing, data analysis, as well as database managing and performing statistical analysis.

## 11. Surgical Research

### Theme 1: 'Wound closure after abdominal and inguinal surgery'

Prof. dr. J.F. Lange, REPAIR-research group, Department of Surgery

After abdominal surgery or inguinal surgery the skin is closed with sutures or staples. Subcutaneous, transcutaneous, intracutaneous sutures and staples are being used to relieve tension on the edges of the wound and to evert the wound edges. Although wound closure with sutures is safe and effective, it requires specialized instruments, is time consuming, operator dependent and requires a subsequent visit for suture removal. Other disadvantages of cutaneous sutures are the potential for inflammation, bacterial migration into the wound bed and discomfort during the removal of the sutures. Complications as wound infection are associated with pain, prolonged hospital stay and poor cosmetic results. A product consisting of an incision foil and a flip over closing system strips has been developed. The incision foil keeps the wound edges sterile and protected during the operation. The flip-over strip system provides a fast, accurate and simple closure of the skin. The system is comfortable during wearing and removal is pain free. A cohort study with this innovative new wound closure system showed promising results in cosmetic results and patient comfort.

Under supervision of one of the professors of the REPAIR-research group (REsearch Projects for Abdominal surgery Innovation Rotterdam) the Research Master-student Clinical Research will have ample opportunities to conduct his or her own international randomized clinical trial. The REPAIR-research group has extensive (published) expertise with regard to (multicentre) randomized clinical trials on abdominal wall surgery (and colorectal surgery) and cultivates excellent international research contacts with centers in Belgium, Germany, Sweden and the United States of America. For this trial a research collaboration between the department general surgery, plastic surgery and dermatology has been established. The clinical trial will compare this new wound closure system with conventional methods of skin closure after abdominal or inguinal surgery. The Research Master-student will be involved in improving the study protocol and acquiring medical ethical committee approval. During the trial he or she will coordinate the trial nationally and internationally, participate and assist in surgeries and perform the follow-up and data collection and interpretation. The Research Master-student will take part in patient care, improve surgical skills, learn to write a study protocol and is part of innovations in medicine. At the end of the research project a scientific article will be written by the student as first author and submitted to a peer-reviewed medical journal.

### Theme 2: 'Nicotine Gum Chewing Pilot Trial'

Prof. dr. J.F. Lange, REPAIR-research group, Department of Surgery

Postoperative ileus (POI) is a common complication after abdominal surgeries. It is a transit cessation of bowel mobility after surgery and presents as an inability to tolerate enteral nutrition, nausea, abdominal distension, and lack of flatus and defecation, all leading to patient discomfort and prolonged hospital stay. The activation of the Cholinergic Anti-Inflammatory Pathway mediated by the vagus nerve could significantly increase the postoperative bowel motility as well as control the inflammatory cell recruitment and thus prevent the pathological changes of POI. Chewing gum, which mimics the cephalic phase of digestion, stimulates the electrical, motor, and secretory activities of the gastrointestinal tract through neurohormonal and vagal pathways. Nicotine, a selective cholinergic agonist, has been proven to improve survival rates in animal models of sepsis. The analgesic effect of nicotine significantly reduced postoperative opioid consumption, while reducing the opioids was also an important strategy of shortening POI. Nicotine gum chewing combines the cephalic vagal reflex induced by gum chewing, cholinergic anti-inflammatory effect and analgesic modulation induced by nicotine administration, it might be potentially beneficial in the prevention of POI.

The aim of the current pilot study is to estimate the effect of chewing nicotine gum on patients who underwent open gastrointestinal surgeries regarding the prevention of POI and reduction of opioid use, and assessing its systemic adverse effects as well. The Research Master-student will be involved in the whole pilot trial, coordinating the trial, including patients, performing the follow-up in the outpatient clinic and data collection and interpretation. If successful, a randomized clinical trial will commence. This includes writing a METC protocol based on the pilot study and setting up the trial. During the above, experimental research can be done to understand postoperative ileus better.

The student will extensively participate in all aspects of clinical trial; learn to write a study protocol and academic paper; learn to modify or innovate new medicine/method for clinical use. After the trial, at least one article will be written by the student and submitted to a peer-reviewed medical journal and presented at medical conferences.

## Theme 3: Kidney Transplantation

Prof. dr. Jan N.M. IJzermans

### **Aim of the project:**

- to determine the efficacy of ureteral stenting in kidney transplantation

### **Background:**

Kidney transplantation has been demonstrated to be the best treatment option for patients with renal failure. The recipient operation has been optimized from a surgical point of view and is correlated with minimal morbidity and mortality. Especially due to the development of the living donation program there is a significant increase in the number of kidney transplantations in the last decade.

One of the complications after kidney transplantation is leakage and/ or obstruction of the ureteral anastomosis. This complication leads to a long-term morbidity, the use of antibiotics, radiological as well as surgical interventions, and in a minority of cases loss of the renal graft.

As to date no well-designed study has been published evaluating the use of a ureteral stent to prevent this complication. The database of the Erasmus MC, one of the largest transplant centers in the Netherlands, contains adequate numbers of transplant recipients to elucidate this topic.

In this research program the candidate will analyse the data available in the Erasmus MC and he/she will determine the cost-effectiveness of ureteral stenting by a matched control study. In addition, the candidate will develop a prospective randomized study directed to determine the clinical value of ureteral stenting in relation to the quality of life of renal transplant patients.

The candidate will be supported to present this study on national and international meetings and to write a manuscript to be published in a peer-reviewed journal. The project may be extended to more publications in the next years and the candidate, if proven qualified, may be selected to coordinate these studies.

## Theme 4: Cost-effectiveness analysis of treatment of traumatic injuries

Prof. dr. P. Patka, dr. E.M.M. van Lieshout (Department of Surgery-Traumatology)

### **Introduction:**

Most traumatic injuries such as fractures, luxations, and tendon ruptures can be managed by different treatment methods. The department of Surgery-Traumatology is involved in (international) prospective randomized clinical trials (RCTs) studying outcome in patients who sustained, e.g., a hip fracture, humeral fracture, elbow luxation, or Achilles tendon rupture. In each RCT two interventions are being compared. Outcome measures include functional outcome, consolidation time, treatment failure rates, complication rates, patient satisfaction, and health-related quality of life. Health care consumption will be monitored in order to perform health-economic analyses.

### **Aim:**

- The aim of this study is to analyse cost-effectiveness of management approaches in patients sustaining a traumatic injury.

The Master student will be responsible for cost-effectiveness analysis of one of the RCTs.

### **Methods:**

As part of current RCTs healthcare consumption data are being collected for both treatment arms. The incremental cost-effectiveness ratio for each intervention will be expressed in a cost-utility ratio, i.e., cost per QALY. The economic evaluation will be performed from a societal perspective. Both health care costs and costs of production losses (e.g., of the care giver) will be included. Health care costs will include costs of general practice care, medical specialist care, physical therapy, hospitalization, medication and other costs directly associated with diagnosis, treatment and rehabilitation. Patients will be asked to administer questionnaires to register other health care needs (including physical therapy, visits to GP's and specialists, nursing care and medication). The costs of health care will be assessed using standard prices.

## Theme 5: Atherosclerosis as a predictor for outcome after PTA / Stenting: A retrospective analysis of abdominal CT-scans.

Prof. dr. H.J.M. Verhagen

### **Background:**

In patients with occlusive or stenotic arterial disease, treatment is necessary when Fontaine stage III/IV, i.e. critical ischemia, is reached. Initially the treatment of choice is PTA, or percutaneous transluminal angioplasty, with or without stenting.

Occlusive or stenotic arterial disease often occurs in the iliac trajectory and is caused by atherosclerosis. It is a slowly progressive, systemic, disease that causes massive arterial damage before it becomes clinically manifest. This is illustrated by the large quantity and volume of the calcifications in the atherosclerotic plaques.

The major complication of PTA with or without stenting is recurrence, which requires another PTA with stenting. When this is insufficient a bypass operation is necessary. The period between the initial complaints of the patient and the bypass is substantial since one or more PTA procedures with or without stenting are performed.

The influence of the atherosclerotic load on recurrence after PTA/stenting is unknown. However, the thought of higher recurrence rates in patients with higher atherosclerotic loads is conceivable and perhaps these patients should receive a bypass directly instead of multiple PTA's.

To date, the atherosclerotic load can be determined by means of calcium scoring on CT-scan. The radio-opaque atherosclerotic lesions can be quantified with specific calcium scoring software, which expresses the atherosclerotic calcifications in Agatston-score, calcium mass and –volume. Multiple studies show the Agatston-score to be a predictor for congestive heart failure.

The aim of this research project is to study the potential of the calcium score in the iliac trajectory as a predictor for the long term outcome of PTA and stenting and to determine whether it is possible to distinguish patients that will be better off with a bypass.

## Theme 6: 'Molecular imaging of aneurysms'

Prof. dr. H.J.M. Verhagen

Molecular imaging is an important new technology in translational medicine. For this project, we aim at molecular imaging of protease activity of MMPs/cathepsins upregulated during aneurysm formation, using protease-activatable near-infrared fluorescence (NIRF) probes, so-called smart optical probes. These protease-activatable sensors directly report the in vivo/ex-vivo activity of the key biomarkers in aneurysm, providing information complementary to immunolocalization in tissue sections. We will test smart-optical NIRF probes specific for MMPs in tissue sections from patients and aneurysm mouse models.

To obtain a more holistic view on the proteome changes occurring during aneurysm formation, we plan to follow a proteomic approach. We will start with candidate-based proteomics on tissue sections from patients and analyze several candidate proteins. Furthermore, we will compare protease activity of a variety of proteases (such as MMP8 and Cathepsins) by immunohistochemical and biochemical analysis among patient material, and established models for thoraceous and abdominal aortic aneurysm. A full un-biased proteomic screen will be performed using 2D gel based DIGE. 2D-DIGE uses differential labeling of protein samples by Cy-dyes enabling detection and quantitation of two different protein samples in a single 2D-gel. Changes in the protein expression of the samples of the aneurysm mice will then be identified using state-of-the-art mass spectrometric techniques (such as MALDI-TOF/TOF and LC-MS/MS). An important goal of the proteome analysis of Fibulin-4 mouse models is to obtain a lead for development of optical probes for molecular imaging of aneurysms and medical therapy. This project will yield smart optical probes that detect aneurysms in human tissue material, which will be invaluable for future medicine and image-guided surgery.



## Theme 7: Project: Inflammation response during surgery and postoperative outcome in vascular patients.

Drs. O. Schouten

Background: Postoperative cardiac events are the major cause of morbidity and mortality in vascular surgery patients. Cardiac events are related to the presence and extend of coronary artery disease. Coronary inflammation, leading to coronary plaque rupture and thrombosis plays an important role. Coronary plaque rupture can lead to myocardial infarction and cardiac arrhythmias.

### Aim:

- To assess the relation between inflammation responses during surgery, assessed in blood and tissue and postoperative cardiac outcome.

Methods: 50 consecutive vascular surgery patients will be enrolled over 9 months. In all patients, cardiac risk factors, quality of life assessment, inflammations markers and ECG will be assessed prior to surgery. During surgery repeated inflammation markers in blood and tissue are collected. After surgery patients are screened for late cardiac events. Inflammation markers determined in blood and tissue are interleukin-6 and high-sensitive c-reactive protein.

Expected results: Inflammation response during surgery can predict postoperative cardiac outcome, irrespective of inflammation complications.

Task of student: to be involved in perioperative care, including outpatient clinic, surgery, postoperative care at the ward. The results will be presented as an abstract for a scientific session and manuscript.

## Theme 8: Prognostic/Predictive Factors and Treatment Outcome in TNF-based Isolated Limb Perfusion (ILP) for Irresectable tumors of the Extremities

Dr. Cornelis Verhoef, Prof. dr. Alexander M.M. Eggermont

The Department of Surgical Oncology of the Erasmus MC-Daniel den Hoed Cancer Center has the largest experience world-wide in an ILP-based limb salvage program for irresectable extremity tumors. Rotterdam-co-ordinated multicenter trials utilizing Tumor Necrosis Factor-alpha lead to the approval of ILP with TNF in combination with melphalan by the EMEA as the limb salvage treatment modality for irresectable extremity tumors. Hereafter 40 European Cancer Centers were trained at the ErasmusMC-Daniel den Hoed to conduct TNF-based ILP and were activated and accredited all over Europe. The prospective Rotterdam Data Base defines over 40 patient, tumor and perfusion characteristics and is the cornerstone to define prognostic and predictive factors for treatment outcome.

With > 400 ILPs for irresectable soft tissue sarcomas and > 200 ILPs for patients with multiple in transit metastases, as well as ILPs for a variety of rare tumors or rare limb-threatening conditions, it is unique in size and quality.

This size allows to refine questions with respect to different histologies in soft tissue sarcomas (outcome by grade 1-2-3, outcome by the about 20 different histologic types, borderline malignancies, aggressive fibromatosis, desmoid tumors etc.) and outcome, tumor site characteristics and outcome (for instance proximal vs distal tumors; upper vs lower extremity tumors).

The 'Rotterdam-Prospective Database' provides a rare opportunity to study, define and hence tailor treatment options to patients with limb-threatening extremity tumors.

## Theme 9: Prognostic Factors in Sentinel Node Positive Melanoma Patients: The Rotterdam Criteria for Tumor Load

Drs. Alexander C.J. van Akkooi, Prof. dr. Alexander M.M. Eggermont

In Rotterdam we have gathered the largest SN-tumor load reclassified database of Sentinel Node (SN) positive melanoma patients in the world (n=1000). This data base will be expanded over the next year to about 1500 cases. This project has been conducted within the framework of the European Organization for Research and Treatment of Cancer (EORTC). It includes large centers from the U.K., France, Germany, Poland, Italy and the Netherlands.

Previous studies from our group have demonstrated that patients with minimal SN tumor burden have a significantly better prognosis, equal to SN negative patients and might not require a lymph node dissection. The regional relapse rate in these patients is virtually none, identical to SN negative patients. However, the exact value of these small dormant metastases is not yet certain. When taking SN tumor burden into consideration as a false positive result of SN staging, there does not seem to be a survival benefit for performing this staging procedure when compared to lymph node dissection in case of palpable nodal relapses.

Further research is needed, with an increased study power to further analyze the prognostic value and possible treatment implications of minimal SN tumor burden. For this purpose slides will need to be reviewed from all participating centers. A case-controlled study with SN negative patients will also be conducted.

The student will be trained to analyze SN tumor burden on pathological material, will update and analyze the database with help of a statistician, will have the possibility to visit EORTC centers. Combinations with other study projects and clinical internships are also possible. Several publications are foreseen which guarantees co-authorships. Minimally 1 publication as first author will be guaranteed.

## Theme 10: Prevalence, severity and impact of gastrointestinal symptoms after oesophagectomy for cancer

Dr. B.P.L. Wijnhoven

The incidence of oesophageal cancer is rising in the Netherlands. Resection of the oesophagus (oesophagectomy) is the corner stone in the treatment of this highly aggressive disease and offers the best chance for long term survival. However, 50-60% of patients after oesophagectomy will develop a loco-regional recurrence and/or distant metastases and ultimately succumb.

Oesophagectomy is a highly invasive surgical procedure. Via a thoracic or abdominal route the oesophagus is resected and continuity of the gastrointestinal tract restored with the stomach: a so called gastric tube. Hence, intake, transportation and digestion of food will change and is restricted in most patients. Moreover, approximately 50% of patients after oesophagectomy develop a stricture of the anastomosis between the remnant oesophagus in the neck and the gastric conduit resulting in troublesome dysphagia. The occurrence of bile and acid reflux, nausea and diarrhoea are also well known debilitating symptoms after oesophagectomy. Surprisingly, not many studies are known that have looked at these gastrointestinal symptoms after oesophagectomy and its impact on the patients quality of life. Also the permanent fear of recurrence of the disease together with a decreased physical fitness, has an enormous impact on patients' quality of life already.

The aim of this research project is to determine the prevalence, severity and impact of gastrointestinal symptoms in a large cohort of patients before and after oesophagectomy for cancer. How many patients report symptoms after oesophagectomy? Does it have an impact on their daily living? Is there any effective treatment? Published and new designed symptom- and quality of life questionnaires will be used to answer these questions.

The department of surgery at the Erasmus MC has a national and international reputation on the treatment of oesophageal cancer patients. About 80 patients undergo oesophagectomy for cancer on an annual basis. Close collaboration with the departments of gastroenterology and medical oncology will be sought. It is expected that the results will be presented at a scientific meeting and that a manuscript constructed for publication in an international journal.

## Theme 11: Radiation induced soft tissue sarcoma (RISTS)

Dr. A.N. van Geel

Four out of 100 patients with a soft tissue sarcoma have a history of previous radiation therapy in the same area. Most initial cancers were breast cancer and lymphomas. RISTS are frequently high grade sarcomas and the treatment options are restricted because subsequent radiotherapy after resection is not feasible anymore. The prognosis is poor.

Data in the literature are very limited and the series are small. The purpose of this study is to define the risk of RISTS in cancer patients and to identify clinical and pathological risk factors for prognosis. The study is intended to be a nationwide study in all centers with a radiation department in collaboration with the department of pathology and radiotherapy. A similar study was started a few years ago, but failed. Retrieving the data showed to be very time consuming. It is expected this study will be the largest study in RISTS.

## Theme 12: Efficacy of RFA in the treatment of liver tumors

Prof. dr. J.N.M. IJzermans (Hepatobiliair surgery)

Introduction: Benign as well as malignant liver tumors may be treated by surgical resection. The Department of Surgery of the Erasmus MC has one of the largest hepatobiliary programs in the Netherlands and up to 100 patients are being treated by a liver resection each year. Although the surgical techniques and the peri-operative care have improved significantly in the last decade a liver resection still has a large impact on the quality of life of a patient. Alternative treatment modalities are being developed and one of these is radiofrequent ablation. By using this technique a 17 gauge needle is being introduced into the tumor and via this route a current is released in the centre of the lesion leading to a temperature increase and ablation of the surrounding tissue. The treatment can be conducted with a low morbidity and with a short hospital stay.

However, it remains to be determined whether this treatment may compete with the golden standard of liver surgery. The candidate will design a cost-effectiveness study and with the availability of data from the Erasmus MC liver tumor database he/she will determine the criteria for the use of RFA. The candidate will work together with the liver surgeons and intervention radiologists to collect more data on the RFA treatment and the surgical resections. He/she will write a manuscript and present the work to expert meetings.

## Theme 13: Hepatocellular adenoma

Prof. dr. J.N.M. IJzermans, surgeon, dr. T. Terkivatan, surgeon

Study Design: Hepatocellular adenoma is a benign liver tumor that most often occurs in young female patients and is associated with the use of oral contraceptives.

The most optimal treatment in case of an asymptomatic hepatocellular adenoma still remains to be determined. Due to the low incidence of this tumor no large series have been reported and management depends heavily on small retrospective studies or case-reports.

Despite the fact that we are dealing with a benign tumor, the small risk of bleeding and the very rare cases of malignant degeneration tend to be the most important reasons to perform a surgical resection, even in case of small tumors. Such an approach is inevitably associated with morbidity and mortality rates.

In our centre we already treated many of these patients by surgery and some of them with a percutaneous thermal ablation technique, the radiofrequency ablation (RFA). Furthermore, some patients are followed by radiological means, showing that regression of the tumor occurs in a significant number of patients after they have stopped the use of oral contraceptives. It is interesting to collect all data from these patients to be informed about the natural course when a conservative approach is being followed and the outcomes of different kinds of interventional or surgical therapies. This will lead to a more evidence-based approach in the management of this benign lesion and may be a first step towards the organisation of a multinational database leading eventually to the most optimal management strategy of hepatocellular adenomas.

The student will perform an update of a data file with all patients having a hepatocellular adenoma who were seen in our clinic between 1975 and 2007, and he or she will be enabled to write a manuscript on this research. Besides a prospective data-base will be organised for institutional and (inter)national use.

## Theme 14: Research theme: Hand Surgery and Hand Rehabilitation

Ruud Selles MSc, PhD; Steven Hovius MD, PhD

Shaking hands, writing, typing, eating, driving a car, inserting a key .....these are normal daily life activities. We perform them without thinking. Unfortunately every year thousands of babies, children and adults are confronted with a variety of disorders preventing normal use of their hands and wrists. Diseases can be present at birth or acquired either by trauma or a degenerative disease. Suddenly patients are not independent anymore as they cannot rely on the normal use of their hands. For this reason, Hand, Wrist and Nerve surgery is such an important part of the specialty of Plastic and Reconstructive and Hand Surgery.

Within the research theme Hand Surgery and Hand Rehabilitation, our research is combined with the department of Rehabilitation Medicine and focused around three main themes:

1. Development and evaluation of innovative clinical interventions, either in randomized or cohort studies (for instance an RCT with a novel technique vs the gold standard in Dupuytren's disease or a study on the long term evaluation in congenital hand deformities)
2. Development and application of new assessment tools, such as new imaging techniques and measurement tools to be used for both diagnosis and outcome assessment (for instance the use of ultra sound in neuroma formation and tendon or nerve replacement)
3. Development and evaluation of innovative experimental interventions with a close relation to the clinic (for instance experimental nerve regeneration studies)

These themes are applied within a range of patients groups, such as hand trauma, congenital hand deformities, pain disorders, and chronic disorders such as CMC1 osteoarthritis and Dupuytren's disease.

Within this theme, we offer a range of projects, such as designing or participating in a randomized controlled clinical trial or working on the development and validation of a new assessment tool. Often, our projects are translational, combining research tools and clinical expertise from a number of different departments and specialties.

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## Theme 15: Research theme: Craniofacial anomalies and their treatment

I.M.J. Mathijssen, MD PhD

In the craniofacial center of the Erasmus MC we treat most patients born in the Netherlands with a craniofacial disorders, such as craniosynostosis and rare facial clefts. The problems that these patients encounter range from functional problems such as elevated intracranial pressure, brain anomalies such as hydrocephalus, Chiari I malformation, and white matter disorders, breathing disorders, and hearing and vision loss. On the other hand, living with a different face and being judged on that daily by the outside world is an enormous challenge.

Our research line on craniofacial anomalies ranges from discovering new genetic mutations that cause these congenital disorders, understanding the embryogenesis of the face, studying the various brain anomalies and their treatment, detecting the risk factors for elevated intracranial pressure, psychosocial functioning, to studying the outcomes of various surgical techniques.

All the departments that are represented in the craniofacial team participate in this research line: Plastic and Reconstructive Surgery, Neurosurgery, Maxillofacial Surgery, Orthodontics, Clinical Genetics, ENT, Ophthalmology, Radiology, Pediatrics, and Psychology. In addition, the department of Bioinformatics is involved.

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## 12. Musculoskeletal Science

Prof. dr. Bart Koes, Dr Sita Bierma-Zeinstra, Dr Arianne Verhagen

Musculoskeletal disorders are a major public health problem. More than 40% of the people aged 25 years or more reports at least one musculoskeletal disorder. Commonly reported musculoskeletal diseases are tendinitis or capsulitis, (osteo)arthritis and complaints as a result of a trauma. Evidence based information is needed to understand, treat and prevent musculoskeletal disorders.

MUSC (Musculoskeletal Science Center) is the multidisciplinary musculoskeletal research institute of the Erasmus MC. Within MUSC, the Erasmus MC departments of Rehabilitation Medicine, Orthopaedics, Rheumatology, Plastic and Reconstructive Surgery, Public Health, General Practice, Traumatology, and Biomedical Physics participate. Over 100 researchers carry out fundamental (basic) as well as patient oriented (applied) research. Structural research co-operation exists with, among others, the Department of Neuroscience and the Netherlands Expert Centre for Work related Musculoskeletal disorders. Musculoskeletal research questions are related to (consequences of) diseases, accidents, chronic overuse, and congenital defects. This includes chronic or chronic recurrent diseases, impairment and disabilities of the elderly, primary and secondary prevention, as well as work and health.

The three main clinical topics of MUSC are:

1. Back and pelvic pain
2. Hip- and knee disorders
3. Upper extremity disorders

MUSC offers the participating departments a multidisciplinary environment to fruitfully address musculoskeletal research questions from fundamental to patient-related clinical research and public health issues.

### Objectives

The objective of the fundamental research is to identify underlying mechanism of injuries to the lower back and pelvis, hip- and knee disorders and disorders of the upper extremity. The research projects focus on questions as: which biological structures are vulnerable to overuse of high-energy impact, and which postures and movements are responsible for patient's complaints? Patient-related research questions include the effect of a broad range of health care interventions including rehabilitation, determinants and pathogenic mechanisms of systemic bone and joint disorders such as (osteo)arthritis and osteoporosis, ambulatory recording of daily life activities, posture and movement at work, activities of pain patients and elderly, and data acquisition of true natural activities instead of laboratory measurements. Measurement instruments are developed and tested for validity and reproducibility. An important goal of the public health research is to identify the determinants of the occurrence of incident and recurrent musculoskeletal disorders and to investigate the association between work and musculoskeletal disorders.

Two examples of MUSC projects:

- In the MUSC randomised double-blinded trial 'glucosamines and osteoarthritis', 220 patients with hip osteoarthritis take glucosamines or placebo for a period of two years. Pain and function scores are obtained at regular intervals. X-rays, DXA scans are made at the start and the end of the study to determine joint space narrowing and bone density changes. In the clinical part of the study the effect of glucosamines on these outcomes are studied.
- In the fundamental part of the study, cartilage and subchondral bone is cultured from patients who develop severe osteoarthritis during the course of the study and undergo a total joint replacement. The effects of glucosamines on cartilage cell metabolism as well as gene expression analysis are determined in these cultures. This fundamental part of the project can elucidate the working mechanism of glucosamines and may lead to improved intervention methods and new targets to treat osteoarthritis.

In the research project 'Magnetic Resonance Imaging (MRI) of hand, hip and knee' different MUSC participating departments work together to

1. enhance reliable measurements with MRI of tissue changes over time in (early) osteoarthritic joints, by validation of quantitative scores that will be developed;
2. quantify pathological characteristics of tendon in the hand;

3. find pathological characteristics that can be used to identify the status of osteoarthritis;
4. describe disease development of osteoarthritis at the structural (tissue) level and find the most essential characteristics that can predict disease progression.

MUSC participants are internationally well recognized with respect to osteoarthritis research and this research project aims to strengthen research on osteoarthritis and tendons within MUSC and it with novel MRI techniques to evaluate e.g. cartilage degeneration in osteoarthritis of hand, hip and knee and in tendon disorders of the hand. The MUSC research on osteoarthritis is connected to the ERGO cohort (Dept. of Epidemiology) that concerns a large open population cohort study among over 8000 subjects.

For a NIHES fellowship, there are suitable methodological questions available within the musculoskeletal databases at the department of General Practice. For example we combine data from different cohort studies to evaluate prognostic factors and create a prediction model. Furthermore this combined dataset will be used to evaluate the association between pain, function and recovery and to evaluate the influence and timing of dichotomising variables for selecting in a prediction model.

## 13. Medical Informatics

Through innovative fundamental and applied research Medical Informatics aims at developing and validating advanced techniques for the processing and analysis of large, complex, and heterogeneous medical and biological data sets.

### Theme 1: Biomedical Image Processing

Prof. dr. Wiro Niessen

#### Subtheme 1: Cardiovascular Image Analysis

Prof. dr. Wiro Niessen

State-of-the art imaging techniques have the potential to provide detailed information on the vessel wall, such as plaque composition, elastic wall properties, and even biochemical processes that take place in the plaque. In addition, dynamic and perfusion imaging can provide functional information, e.g. for determining the perfusion or motion of the heart, or to study tumor activity. Owing to the growing complexity and sheer size of cardiovascular data, in combination with the large increase in the number of studies in clinical practice and biomedical research, there is a strong and increasing interest in robust, automated processing tools to aid in the analysis of these data. This research line aims to develop and evaluate novel image processing techniques for visualization, quantification and integrated analysis of multimodal anatomical and functional cardiovascular imaging data.

#### Subtheme 2: Cellular and Molecular Image Analysis

Dr. Erik Meijering

Advances in imaging technology have revolutionized medicine and biology in the past decades and have opened the door to studying the structure and function of cells and even single molecules. Biomedical imaging experiments in this area nowadays generate vast amounts of multiparameter spatiotemporal image data containing much more information than can be analyzed by human observers. The goal of our research is to develop advanced image processing and analysis methods to enable efficient, accurate, and reproducible quantification and characterization of cellular and molecular processes. In particular we develop novel methods for image restoration, enhancement, super-resolution, image segmentation, registration, detection, object tracking, and motion analysis. Promising solutions are implemented as user-friendly and publicly available software tools."

#### Subtheme 3: Neuro Image Analysis

Dr. Henri Vrooman

Advanced MR brain imaging is widely used in scientific research and clinical practice, as it is a technique that non-invasively provides both anatomical and functional information of the human brain. Nowadays, research is focusing on large imaging population studies to build models of the aging brain. Using robust, standardized image processing pipelines, several imaging biomarkers, i.e. quantitative information about volume, shape, and functionality of specific brain regions and brain structures, are collected from healthy and diseased subjects. The collected information gives more insight in neurodegenerative diseases and can also be used as reference data on neuro-imaging workstations implemented in the clinic, to give clinicians the possibility to compare patients with memory complaints or cognitive disorders with healthy subjects from the same age and sex. In this way, this research area aims to assist radiologists and referring physicians, yielding a more accurate, better differentiated and earlier diagnosis of brain diseases, such as multiple sclerosis and dementia.

#### Subtheme 4: Oncological Image Analysis

Dr. Jifke Veenland

One out of three persons develops cancer. Worldwide, much effort is put in developing new treatments and individualizing treatments. For this purpose, markers are being developed to predict and monitor the response of the tumor to the treatment. With MRI it is possible to non-invasively depict the tumor during treatment. In our research we focus on the development and validation of MRI-based image markers for cancer treatments. These markers can be used for tissue characterization, treatment planning, response monitoring and response prediction. Since markers can differ per type of tumor and per treatment, different types of tumors and different types of treatments are studied.



## **Subtheme 5: Image Guidance in Interventions**

Dr. Theo van Walsum

Minimally invasive interventions have distinct advantages for patients. Image guidance is often essential in these interventions, to visualize the target anatomy and the instruments. Current interventional modalities have limitations, which may hamper effective image guidance. E.g. ultrasound imaging often is only 2D, is hard to interpret, and does not always give appropriate contrast between tissues. X-ray imaging is a projection imaging modality, uses harmful ionizing radiation, and requires contrast agents to visualize the vasculature. By incorporating information from pre-operative, diagnostic imaging, is expected to improve image guidance.

This research line aims to develop and evaluate novel image processing techniques for better image guidance, by registering information from e.g. preoperative imaging to the interventional scene. We focus on motion and deformation modeling, and integrating these models in the registration and tracking of target anatomy and instruments during the intervention.

## **Subtheme 6: Model-based Medical Image Analysis**

Dr. Marleen de Bruijne

The "Model-based Medical Image Analysis" research group develops novel techniques for quantitative analysis of medical images, with a focus on statistical learning in large scale image-based studies. An important theme is the application of so-called supervised learning techniques in differential diagnosis and prognosis of disease. Using statistical models learned from a database of images for which the diagnosis has already been established, or for which the future course of the disease is known from clinical follow-up, such techniques are more widely applicable and often give better results than conventional image analysis methods. Our main applications are in computer-aided diagnosis of neurodegenerative, cardiovascular, and pulmonary disease.

## **Subtheme 7: Image Registration**

Dr. Stefan Klein

Image registration is the task of aligning medical images, such that pixel-by-pixel comparison becomes possible. This is necessary when combining information from different modalities (MRI, CT, Ultrasound), when comparing baseline and follow-up scans, and when comparing the anatomy of different patients. Accurate image registration enables quantitative measurements of tissue atrophy, fully automated motion analysis in 4D (3D+time) datasets, fusion of anatomical and functional imaging data, and it can even be used to create an "average human" based on images of multiple individuals. In our research, we aim to develop fully automatic algorithms for image registration and to use these in various medical imaging applications, such as the analysis of atherosclerotic plaque, the early diagnosis of dementia based on MRI brain scans, and the quantification of tumor response to anti-cancer drugs.

## **Theme 2: Observational Databases**

Prof. dr. Miriam C.J.M. Sturkenboom

In the Dutch health care system general practitioners (GPs) play a central role. They practice in the community outside the hospital, referring ambulatory patients to other medical disciplines for outpatient or inpatient care. These other medical disciplines report their findings and actions back to the concerned GPs. The GPs address approximately 90% of the medical problems presented to them. The information systems of the GP, the electronic patient records, are an important source of data due to the unbiased and prospective collection of these data and the detailed insight in patient care. The Integrated Primary Care Information (IPCI) project is a longitudinal collection of electronic patients records from Dutch general practitioners into a central research database. This research area focuses on clinical epidemiological, pharmaco-epidemiological and pharmaco-economic studies based on this database.

### Theme 3: Biosemantics

Dr. Jan A. Kors

The explosion of textual information now available to life scientists has an almost overwhelming effect. It has become entirely impossible to read all relevant literature and interpret all available data in anyone's discipline. Predictions for the near future are staggering: in biomedical sciences alone, one new article will be produced every minute in 2007 and this number is likely to increase in the decade to come. This research area focuses on developing innovative tools for sharing the wealth of data sources world-wide. More specific, we develop tools for massive concept mining, enrichment of thesauri and ontologies and meta-analysis of large amounts of distributed resources. We distinguish four major categories of activities: A: Knowledge creation, discovery and analysis, B: Knowledge validation and annotation, C: (re-)distribution of Knowledge and D: Software and tool development. In close collaboration with many partners, tools are designed, implemented and evaluated to speed up and improve the validation and annotation process, to disambiguate textual variations and to enrich ontologies and thesauri. The second major subject of the group is the meta-analysis of large numbers of papers. Scientists have been meta-analyzing various literature resources and have come up with new insights through intelligent combination of concepts and their interrelationships. Computational tools that assist the researcher in this combination process have already resulted in new hypotheses. Different technologies will be further developed to allow for massive meta-analysis of hundreds of thousands of database records at a time. The approach is expected to cause a quantum leap in our ability to handle and mine massive amounts of information.

## 14. Clinical Epidemiology

### Theme 1: Causes of major neurological diseases

Dr. M.A. Ikram

This research line focuses on the etiology of neuro-degenerative and cerebrovascular diseases, including dementia and Alzheimer's disease, Parkinson's disease, ischemic stroke, hemorrhagic stroke, leukoariosis, microbleeds, and polyneuropathy. The research utilizes a multimodal approach to study causes, determinants, and prognosis of these diseases. A particular focus is on interacting pathologies, including vascular disease and neurodegenerative diseases. The research revolves around three main areas: 1) biomarkers, which includes genetics, serum markers, and metabolomics; 2) neuroimaging, which includes conventional as well as advanced MRI (e.g. diffusion tensor imaging, fMRI, perfusion imaging); and 3) subclinical signs and symptoms, including cognition, gait, and activities of daily living. Research is carried out at the Department of Epidemiology in the setting of the Rotterdam Study and Rotterdam Scan Study. Major collaborations are set up with the departments of Neurology, Radiology, Neurosciences, Medical Informatics, Internal Medicine, as well as external national and international partners.

### Theme 2: Assessment of Radiological Technology (ART)

Prof. dr. Myriam.G.M. Hunink

This program focuses on the assessment of medical imaging technology, both diagnostic imaging and minimal invasive (image-guided) therapies. The clinical problems studied are mainly related to cardiovascular disease (CVD) and include imaging for suspected coronary artery disease, imaging of carotid artery disease, imaging and treatment of peripheral arterial disease, and screening of asymptomatic individuals to identify and treat those with high CVD risk. Other areas of research are identifying the best management strategy in patients with incidental findings on imaging studies (performed clinically or as part of population-based studies) and the choice of image-guided therapy vs surgery vs conservative therapy (for example, for intra-cerebral aneurysms). The studies performed include systematic reviews and meta-analyses, prediction models, decision modeling, randomized controlled trials, and cost-effectiveness analyses. The goal is to assess the added value of imaging, to determine the appropriate indications for specific imaging technologies, to estimate prognosis on the basis of imaging findings and to define the best treatment based on the imaging findings.

### Theme 3: Effects and side effects of drugs

Prof. dr. Bruno H.C. Stricker

The focus is on intended effects of medications, and the effects of medication use under common circumstances in large populations. There are several drug-related research projects in the Rotterdam Study, a large prospective cohort study that is being conducted since 1990 to investigate cardiovascular, locomotor, neurological, and ophthalmological diseases.

### Theme 4: Cardiovascular Epidemiology Group (within the Department of Epidemiology, Erasmus MC)

Prof. dr. Oscar H. Franco MD DSc PhD FESC

Cardiovascular disease is the most common chronic illness in both developed and developing countries, causing approximately one-third of the total deaths worldwide and the greatest impact on morbidity. The Cardiovascular Disease Epidemiology group aims at interdisciplinary research across several established disciplines within the group and integrates knowledge on all aspects of the cardiovascular disease; including biology, behavior and lifestyle, imaging, prediction, treatment, and prevention. The large population-based Rotterdam Study, as well as the long-standing collaborations with a number of other large cohort studies around the world, provide a rich environment for the conduct of cutting edge research. Within the group, the following main research teams, working closely and in parallel, are designed to cover the whole spectrum of research on cardiovascular disease:

### **Subtheme 1: Biomarkers for cardiovascular disease**

Within this discipline, current advances in molecular biology and genetics including genomics, epigenomics, transcriptomics and metabolomics are exported from the laboratory to the epidemiology field, allowing a molecular epidemiologic approach towards investigation of clinical and pre-clinical cardiovascular disease. This working theme aims to recognize the importance of molecular and genetic approaches to cardiovascular disease and most importantly, utilize this knowledge to conduct prevention and treatment research that directly improves the health of individuals.

### **Subtheme 2: Lifestyle factors and primary prevention**

Existing and developing knowledge regarding risk factors for cardiovascular disease, especially modifiable risk factors, suggest that it may be possible to curtail the explosion of global disease. To this end, this work theme is focused on evaluating the role of lifestyle factors and interventions for preventing cardiovascular disease among healthy populations. The research focuses on the individual as well as the collective contribution of lifestyle factors; including physical activity, dietary factors, alcohol consumption, smoking habits, wellbeing, sun exposure and sleep, to the prevention of cardiovascular disease. It also aims to address the lacking knowledge on the interaction of lifestyle factors with genetic, metabolic, and inflammatory markers as well as medications.

### **Subtheme 3: Cardiovascular risk prediction**

Clinical decision making for detection, management and prevention of cardiovascular disease relies on accurate identification of individuals at risk of developing the disease. This research team, working closely with the departments of public health and biostatistics, appreciates the role of emerging markers in cardiovascular disease risk prediction and aims on augmentation of the standard cardiovascular risk scoring systems with novel measures. Enhancements in ascertaining the risk status of individuals for developing cardiovascular disease secure windows of opportunities that could permit early preventive interventions and personalized care.

### **Subtheme 4: Atherosclerosis imaging**

Atherosclerosis imaging research contributes to the understanding of the natural history of cardiovascular disease and the processes leading to the progression and stabilization of the disease, as well as the assessment of disease burden and therapeutic efficacy. This research team within the cardiovascular disease epidemiology group works in close collaboration with the departments of cardiology and radiology and focuses on the application of imaging technology to cardiovascular disease prevention. Current research projects within this discipline are focused on evaluating associations between various risk factors and vascular structure and function, as well as evaluating the role of non-invasive assessment of sub-clinical atherosclerosis and endothelial function in cardiovascular risk prediction.

### **Theme 5: Common psychiatric disorders**

Dr. H. Tiemeier

Depression and anxiety are both leading cause of the global disease burden and among the five most leading causes of disability worldwide. In the past, researchers identified psycho-social risk factors but we now realize that most psychiatric disorders are the result of an interplay between functional and structural brain changes, genes, cognitive and psychological processes and social factors. Our research on common psychiatric disorders is embedded in the Rotterdam Study. Main areas of interest next to depression and anxiety are insomnia and sleeping problems in the elderly and smoking cessation. Studies addressing vascular factors, stress and thyroid hormone secretion, and inflammation are possible. A more recent focus lies on and genetic risk factors and their interaction with social determinants. Our aim is not only to explain how biological or social factors cause psychiatric disorders. Rather we also investigate how psychiatric problems or diseases impact on physical health. Here are some examples of research questions and the approach:

- Why do people with short sleep duration die younger? We monitored sleep in many persons for 6 nights by actigraphy.
- Does stress influence the vascular or the immune system? We study diurnal cortisol patterns assessed by repeated saliva sampling.
- Do first-ever and recurrent depression have the same causes? We collected unique data of more than 5000 persons over 10 years with continuous monitoring of depressive symptoms.
- Are people with a silent, non-clinical MI or TIA more likely to have depression? For this research we will collaborate with the cardiovascular group.
- Do genes modify the ability to quit smoking after a severe health event? For this question we will make use of genome wide association analyses.

## Theme 6: Fetal and childhood growth, development and health: the Generation R study

Prof. dr. Vincent W.V. Jaddoe, coordinator,

The Generation R Study is a large population-based cohort study from fetal life until young adulthood in 10,000 children. The Generation R Study is a collaborative project in which several departments in the Erasmus MC participate. The study is designed to study growth, development and health in a contemporary population-based multiethnic cohort of urban children from fetal life until young adulthood. The study focuses on four primary areas of research: (1) growth and physical development; (2) behavioral and cognitive development; (3) diseases in childhood; and (4) health and health care for pregnant women and children. Special interest in these areas of research is on identification of early causal pathways leading to both normal and abnormal growth, development and health in childhood and adulthood.

The general aims are:

- To describe normal and abnormal growth, development and health from fetal life until young adulthood in a multiethnic population-based cohort;
- To identify biological, social and environmental determinants of normal and abnormal growth, development and health from fetal life until adulthood;
- To examine the utilization and effectiveness of current strategies for prevention and early identification of groups at risk.

Eventually, this study will contribute to the development of strategies for optimizing health and health care for pregnant women and children.

An extensive data and biobank has been generated. With an integrated strategy of basic, clinical and epidemiological research various research questions are addressed focused on growth, development and health from fetal life to young adulthood. MSc student are actively participating in one of the 4 main research programmes in the Generation R Study ([www.generationr.nl](http://www.generationr.nl)). A few subthemes are mentioned below.

### **Subtheme 1: Early growth, obesity and cardiovascular development**

Prof. dr. V.W.V. Jaddoe, Prof dr. E.A.P Steegers

This research is embedded in The Generation R Study and focused on environmental and genetic exposures related to fetal and postnatal growth, early cardiovascular development, insulin resistance en obesity. We also study risk factors of pregnancy complications in mother and child, such as preeclampsia and preterm birth. Research is performed in closed collaboration between the departments of Pediatrics, Epidemiology, Obstetrics, Pediatric Cardiology and Pediatric Nephrology.

Examples of research topic are:

- Development of growth curves
- Maternal life style habits in relation to pregnancy complications
- Genetics of fetal and postnatal growth
- Maternal and childhood nutrition in relation to cardiovascular and metabolic development
- Biomarkers of preeclampsia and pregnancy induced hypertension

MSc student are actively participating in one of the research projects, actively participate in the research Group (data collection, cleaning, scientific meetings) and normally produce one to two papers that will be submitted for publication.

## Subtheme 2: Early determinants of respiratory morbidity

Prof. dr. J.C. de Jongste, Dr L. Duijts.

'Generation R' is a multidisciplinary project, aimed at recruiting a 10.000 children birth cohort in Rotterdam, with follow-up from the first trimester of pregnancy until 20 years of age. The project wants to establish prospectively the importance of prenatal and early life events for later health, to ultimately improve children's health and education by defining factors which affect growth and development, and determine risk of disease in order to stimulate preventive strategies..

The prevalence of chronic respiratory symptoms among children of various ethnic minorities in the Netherlands is unknown. In major North-American cities the prevalence of childhood respiratory disease including asthma and allergy is increasing, especially in non-caucasian children. There is evidence that ethnic differences in prevalence cannot only be explained by differences in socio-economic class. In Europe, several birth cohort studies have addressed respiratory morbidity during the first years of life. These have focused on known risk factors for respiratory morbidity, including socioeconomic status, exposure to allergens and pollutants, family history of allergy and/or asthma, and examined relationships with respiratory symptoms. However, few have focused on ethnic differences. In Swedish and German studies differences in atopic disease prevalence were reported between Western European and Turkish immigrant children, suggesting that environmental and genetic factors are involved which may affect the risk of infection, allergy and asthma in different ethnic groups. In the Netherlands, the ongoing PIAMA study follows a large birth cohort. A relatively high prevalence of respiratory symptoms was found in non-Dutch ethnic groups, which could be largely attributed to socioeconomic differences, suggesting that environmental factors had strong impact on respiratory morbidity in the first 2 years. However, numbers were small and biased, as only Dutch questionnaires were used. No epidemiologic birth cohort study has specifically been designed to include different ethnic groups by approaching them in their own language, and evaluate the differences in symptomatology together with biological, medical, psychosocial and environmental factors in order to establish and understand differences in respiratory morbidity, especially asthma, and allergy between ethnic groups living in the multicultural urban society.

Question:

Are respiratory morbidity and allergy different between ethnic groups and, if this is the case, can differences be explained by pre- and/or postnatal environmental factors? The project is focused on describing respiratory and allergic morbidity of the Generation R cohort during the first 2 years of life.

Question/aim:

- This project aims to address the impact of ethnicity and environmental factors on respiratory morbidity in the first 2 years of life by answering the following questions:
- Is ethnicity a risk factor for respiratory morbidity and allergy in the first two years of life?
- Do medical consumption (drug prescription, visit to the general physician, hospital admission), perception of disease and quality of life of infants and preschool children with chronic respiratory symptoms and/or allergy differ between ethnic groups?
- To what extent can environmental pre- and postnatal factors explain differences in respiratory morbidity and allergy between ethnic groups?

For a NIHES fellowship, a suitable question will be selected For a NIHES fellowship, a suitable question will be selected and analysis performed of existing databases, in close co-operation with the dept. of pediatrics, epidemiology and public health of the Erasmus MC.

## Subtheme 3: Immunological and bacterial determinants of nasopharyngeal carriage of opportunistic pathogens and infections in young children.

Prof. dr. H.A Moll, Dr M van Zelm, Prof H Hooijkaas

After infection, T and B lymphocytes are able to mature into highly specific memory lymphocytes, which is the basis for adaptive immunity. The adaptive immune system matures in the first years of life through host pathogen interactions. However, it is unclear how the adaptive immune system in young children is shaped to create highly specific immunity to a wide variety of pathogens. Although the immune system is able to generate strong immunological responses, complete eradication of pathogens is not always achieved. Several viruses are known to evade clearance and persist in a dormant state. In latency, the virus is not detectable anymore in serum, but antibodies against these viruses are. Common persistent viruses are Epstein-Barr virus (EBV) and Cytomegalovirus (CMV). The prevalence of persistent CMV and EBV infections is estimated to range from ~50% in children to >90% in adults.

Reactivation of these viruses when immunity is suppressed can result in major complications, e.g. in transplantation settings, suggesting that these viruses can only be controlled by a constantly active immune system. We hypothesize that this constant viral pressure puts a heavy load on the immune system, and will affect normal immune maturation. One parameter that reflects the maturation of adaptive immunity is the extent of differentiation of lymphocytes in the peripheral blood. We hypothesize that persistent viral infections have adverse effects on the diversity of the broad immune repertoire, thereby impairing immunity to other pathogens. The aim is to:

1. Study determinants of CMV and EBV infection in children at 5 years of age;
2. Study the buildup and diversity of the immature adaptive immune system by studying the phenotypic differentiation of lymphocytes in children with and without persistent infections with EBV or CMV at 5 years of age.
3. Study the consequences of the diversity of the adaptive immune system for atopic and immune mediated diseases
4. Determine how development, diversity, and reactivity of the adaptive immune response in healthy and allergic children, are affected by the intestinal microbiota.

Clinical and scientific relevance for the future: This project will contribute to the detailed understanding of the development of the immune system and their consequences for atopic and immune mediated diseases in children.

#### **Subtheme 4: Behavioral and cognitive research in young children:**

Prof. dr. Frank C. Verhulst, dr. Henning Tiemeier

Whereas most somatic disorders are quite rare, behavioural and learning disorders in children are frequent. About one in ten children will develop a mental health disorder and many more have behavioural or cognitive problems that are a burden to child, families and society. Behavioural problems can be caused by social factors (e.g. bullying or poverty), psychological factors (e.g. bad parenting or poor emotion recognition) and biological factors (e.g. genetic variation or altered stress hormones). Aetiological research has demonstrated that many child psychiatric disorders are neurodevelopmental in origin, i.e. they have their onset early in life and affect the functioning of the nervous system. Furthermore, child psychiatric research has been leading the field of gene-environment interaction studies.

This understanding has guided the behavioural and cognitive research in Generation R. We are thus investigating the importance of fetal development for behaviour and cognition later in life, and have assessed neurodevelopment with brain-ultrasound, neurological examinations, and will soon start MRI imaging. Moreover, we are conducting genome wide analyses and candidate studies to detect genetic risk factors and vulnerabilities. Together with several EUR and external partners we have introduced many innovative child assessments, which are unique to large-scale behaviour studies. These include the Strange Situation Procedure, HOME environment assessment, executive function, parent-child interaction tasks or tasks of moral development.

The topics and possible themes for research in Generation R cover a wide area; selected but prototypical questions addressed in the coming years include:

- Do low thyroid hormone or vitamin levels in pregnant women cause cognitive problems in the offspring? (Neurodevelopmental research)
- Does father-child interaction matter in respect to the emotion development of the child? (Med Psychology)
- What do teacher, father and 5-year child self report add to maternal report of behavioural problems? (Methods)
- Do daycare, bullying in kindergarten, television watching or unstructured parenting affect certain children predisposed to behavioural problems? (Social Psychiatry)
- Are altered cortisol secretion patterns cause or consequence of behavioural problems? (Psychobiology)
- Does prenatal cannabis exposure affect the brain development? (Psy. Imaging)
- Can we identify the genetic basis of child resilience to family adversity (Psy.Genetics)

## Theme 7: Assessment of Integrative Medicine

Prof. dr. Myriam G.M. Hunink

The human body has an enormous self-healing potential which is probably underused in medicine. There is an increasing interest among patients and healthy individuals to harness the effects of this self-healing potential as demonstrated by the growing interest in mind-body-medicine and integrative medicine in general. An integrative approach to medicine implies a change of attitude – rather than seeing patients as a bag of biochemicals we need to recognize the complexity of the multidimensional human being interacting with his/her environment. For the majority of diseases there is no magic bullet to cure and care and prevention. Health and well-being require a multidimensional approach: apart from medical interventions the patient needs to pay attention to diet, exercise, healthy habits, relaxation and self-care that can promote health. Patients actively participating in their health care and healing process have a better prognosis and a better quality of life. In this line of research we focus on mind-body interventions, in particular mindfulness and music as medicine.

## Theme 8: Dermatology

The department of dermatology (Erasmus MC) is the largest training hospital for dermatology in The Netherlands. The three main research themes are: (1) oncology, (2) inflammation and (3) phlebology. The research focuses on common skin diseases that have a large impact on both patients and society. Since we study common diseases, most of our research is translational, and involves patient data.

The epidemiology and clinical research group supports the three research focus points of the department of dermatology. This research line collaborates closely with other Erasmus MC departments such as Epidemiology and Public Health. We work with large existing datasets including national cancer registries (IKNL), national pathology database (PALGA), pharmacy based databases (PHARMO RLS Network) and are integrated in the Rotterdam Study. In addition to database research, we are involved in many clinical studies and trials in the field of dermato-oncology, psoriasis and varicose veins. Together with Public Health and department of primary care we are investigating the possibilities of shifting care to the GP's and assess patients preferences and its economic impact.

In addition to these health science activities, the department has an experimental research branch focused on dermatological immunology and inflammatory pathways in psoriasis. The Center for Optical Diagnostics and Therapy (CODT) is also part of the department of dermatology. Its members are investigating Raman, reflectance, and fluorescence spectroscopy for the diagnosis of skin diseases and the therapeutic use of light in translational research on photodynamic therapy (PDT).

### Research theme 1: Skin cancer

#### A. Prevalence, incidence, mortality and survival of cutaneous malignancies in The Netherlands and Europe.

Dr. Loes Hollestein, drs. Joris Verkouteren, dr. Luba Pardo, Prof. dr. Tamar Nijsten

##### Introduction

The basic of epidemiology is measuring the frequency of disease occurrence. The Dutch cancer registry is one of the few population based cancer registries that includes basal cell carcinoma (BCC) and is one of the most reliable sources on the incidence of BCC worldwide. Together with the department of Public Health and the cancer registries, we have a long track record in this specific field. Recently, we have studied the occurrence of multiple skin cancers emphasizing the concept of field cancerization. We are approaching cancer survivors for more detailed information to expand our qualitative research activities including establishing a skin cancer specific QoL questionnaire. In addition, focus on health services research among skin cancer patients at the different levels of care in The Netherlands. We investigate the diagnostic, therapeutic and follow up interventions and to do so, we use claims data, cancer registry data and IPCI data.

Linking data from other European cancer registries allows us to compare incidences across Europe and detect trends in incidence, mortality and survival by cancer type, stage, etc.

##### Aims:

- To study incidence, prevalence and trends of all cutaneous malignancies in The Netherlands.
- To compare trends in incidence and mortality of melanoma and nonmelanoma skin cancer across European countries.



- To study survival of melanoma patients in a population-based setting
- To study the association of risk of skin cancer with other cancers

#### Methods

The Dutch cancer registry (IKNL) has collected tumor data since 1989 and has shown to be highly reliable. The IKNL collects all skin malignancies including BCC that is registered in one of four regions (IKZ). In the network of cancer registries, datasets from different countries are merged and can be compared and studies with regards to incidence, age, tumour characteristics (morphology, topography), treatment and for melanoma, co-morbidity at the moment of diagnosis. Follow-up for vital status is available and specific studies can be designed to obtain additional patient information

### **B. Prevalence of skin cancer and its associated (genetic) risk factors. Dr. Luba Pardo, drs. Joris Verkouteren, Dr. Leonie Jacobs, dr. Loes Hollestein, Prof. dr. Tamar Nijsten**

#### Introduction

Of the approximately 35,000 Dutch citizens that develop a basal cell carcinoma (BCC) annually, a substantial proportion develops multiple BCCs in the years after their first BCC. A meta-analysis of studies from the USA and Australia suggest that about 40% of BCC patients will have one or more BCCs after their first BCC. The likelihood to develop another melanoma after having been diagnosed with a first is less well documented. Some relatively smaller studies suggest this is about 5%. Several high-penetrance loci have been identified for skin cancer. In addition to these mutations, recent genome-wide association studies (GWAS) have identified a number of common genetic variants associated with the development of sporadic skin cancers. The identification of high risk patients is clinically relevant because it may affect the follow up regimen after diagnosis. Also, studying high risk skin cancer patients in detail may increase the understanding of carcinogenesis.

#### Aims:

- To study incidence of multiple basal cell carcinoma.
- To study incidence of multiple melanomas
- To identify genes associated with the development of skin cancers and premalignancies
- To study environmental and patient-related factors and potential gene-environment (GE) interactions related to skin cancer

#### Methods:

To study the incidence of multiple skin cancers in large databases, we use the national pathology database (PALGA) and the national cancer registry (IKNL). Both these datasets allow us to estimate the frequency of occurrence of multiple skin cancers and assess whether age and gender are related to a higher risk of developing more than one skin cancer. For a detailed risk factor analysis, the approximately 2,000 people with skin cancer in the Rotterdam Study are analyzed. In addition to patient and tumor characteristics and environmental exposures, we are interested in the genetic component of developing (multiple) skin cancers. Therefore, GWAS and candidate-gene approaches and pathway analysis will be performed in collaboration with the Harvard cohorts and deCODE..

### **C. Risk factors of intrinsic and extrinsic skin aging**

Drs. Leonie Jacobs, Drs. Merel Hamer, Dr. Fan Liu, Prof. dr. Manfred Kayser, Prof. dr. Tamar Nijsten

#### Introduction:

Skin changes such as wrinkling, hyperpigmentation and hypervascularity and skin sagging around the eyes and cheeks are part of skin aging. The effect of patient characteristics such as age (including hormonal status), gender and body mass index, sun exposure and smoking status are well documented risk factors for more pronounced skin aging. Skin aging is not only a cosmetic concern, but is also a risk factor for skin cancer development. Moreover, loss of cutaneous elasticity (i.e., skin wrinkling and sagging) may be a predictor of more systemic aging. Little is known about the genetic contribution to skin aging and whether it is associated with other diseases.

Aims:

- To study the association between classic (life-style, dietary, environmental, and hormonal) risk factors and different components of skin aging (wrinkling, pigmentation spots and teleangiectasia)
- Identification of common variants associated with skin aging
- Investigate the genetics of perceived age.

Methods:

This research theme was part of Netherlands Consortium of Healthy Aging (NCHA) and at the Erasmus MC it is a collaboration between Erasmus MC's dermatology and genetic identification and LUMC. The data used is primarily derived from the Rotterdam Study, but also from other international genetic consortia interested in these phenotypes. Different aspects of skin aging are scored by dermatologists on thousands of standardized 3 dimensional photographs. Also, biological, calendar and estimated age will be assessed. These skin-related outcomes will then be used to identify classical risk factors including a food-frequency questionnaire and genetic polymorphisms associated with (components of) skin aging.

#### **D. Impact of skin cancer on patients' lives.**

Prof. dr. Lonneke van der Poll, drs. Rik Waalboer, dr. Loes Hollestein, Prof. dr. Tamar Nijsten

Introduction:

Except for a relatively small proportion of melanoma patients, skin cancer (i.e., basal cell carcinoma, squamous cell carcinoma) is a non-life threatening disease. In contrast to other solid and hematological malignancies, the long term (treatment induced) sequelae after the surgical removal of skin cancer are fairly mild. Nevertheless, most skin cancers are located in the face and scars after surgery may have cosmetic and functional consequences. Moreover, patients' lives are affected by a diagnosis of skin cancer. They have an impaired health related quality of life (HRQOL) often due to sun avoidance issues, anxiety to develop other cancers and being anxious of the skin of their family and loved ones.

Aims:

- Estimate the impact of different skin cancer on patients' lives.
- Estimate the trend of quality of life impairment in melanoma patients over time
- Self knowledge of patients' diagnosis.
- Create and validate a skin cancer specific QoL questionnaire (BASIQOL)

Methods:

This is primarily a postal survey to cancer survivors registered in the Dutch cancer registry. However, a new skin cancer specific HRQOLL instrument needs to be developed via the established methodology including focus groups. The self completed questionnaire includes items on patient characteristics, validated disease specific and generic HRQOL instruments, a EORTC questionnaires assessing level of information about patients' cancer and very specific and practical questions relevant to patients with a prior skin cancer.

#### **E. Drug use and skin cancer risk.**

Dr. Loes Hollestein, Prof. Ron Herings, Prof. dr. Bruno Stricker, Prof. dr. Tamar Nijsten

Medication use can influence the risk of several malignancies including skin cancers. Pharmacological companies try to monitor potential adverse effects (pharmacovigilance), but medications can also have a chemopreventive effect on (skin) cancer. Chemoprevention in skin cancer is not yet as well documented as for colon cancer and other solid cancers. For now, acitretin is the only available drug that lowers the risk of developing skin cancer. Other interesting drugs are aspirin, NSAIDs and statins because their risk profile is well known, they have other important health effects and observational studies suggest that they may be effective in skin cancer. In addition to cancer occurrence, drug exposure might influence progression of cancer.

Aims:

- investigate the association between prescription medication and skin cancer development.

- investigate potential effects of the use of certain medications on progression and mortality of melanoma

Methods:

In the southeastern part of the Netherlands, there is an area where data on prescription medication use is available from the PHARMO database and detailed information on cancer diagnosis and prognosis from the Eindhoven Cancer Registry.

This linkage of two large databases can be used to study a multitude of questions related to the above mechanisms.

## **F. Clinical research in the treatment of skin cancer**

Dr. Renate van den Bos, dr. Gerwin Puppels

Introduction:

The department of dermatology has a longstanding experience in the treatment of patients with skin cancers. We perform many surgical procedures including micrographic Mohs surgery (MMS) in which we are a centre of excellence. The department develops the MMS technique and expands the types of skin cancer that can be treated with MMS. All the patients treated with digital MMS are entered in a database which is suitable for research as well as clinical trials in skin cancer patients. The clinical research varies from prospective comparative trials to open case series. Nonsurgical treatments such as PDT are also subject of research at our department in developmental stages as well as in comparative studies.

Aims:

- innovation in skin cancer treatment
- optimize patient care and surgical techniques
- development of new nonsurgical treatments.
- Evaluate existing management strategies and treatments (such as Mohs surgery)

Methods:

Retrospective and prospective clinical studies as well as preclinical studies are being done to improve surgical techniques with a focus on MMS. The existing database of MMS treated patients (>1,500) is a source for many interesting study objectives. Besides are we involved in the development, use and research in new medical devices and bandage equipment, an example is the plaster we can use instead of using stitching techniques.

Clinically, photodynamic therapy using ALA is routinely used as a treatment for actinic keratosis, squamous cell carcinoma in-situ and basal cell carcinoma. We are investigating the use of light fractionation to enhance efficacy and using low intensity illumination to reduce pain and enhance patient satisfaction. We are involved in a number of large scale randomized trials to assess the efficacy and cost effectiveness of PDT. We are also investigating the use of PDT using porphyrin pre-cursors and pre-formed photosensitizers in the skin of the genitourinary system.

## **G. Raman spectroscopy and skin cancer**

Dr. Gerwin Puppels, dr. Peter Caspers

Introduction:

Melanoma is the most lethal skin cancer. Worldwide 200.000 patients are diagnosed with cutaneous melanoma each year. If melanoma is recognized in an early stage patients can be cured by complete surgical resection with a 95% 5-year survival rate. Diagnosis at a later stage results in drastically lower survival rates.

Aims:

To development instrumentation and methodology for objective real-time identification of suspicious pigmented skin lesions using Raman spectroscopy.

Methods:

Raman spectroscopy is a non-invasive method to obtain detailed information about molecular changes in tissues by illuminating the tissue with laser light and analyzing the light that is scattered back.

The CODT houses state-of-the-art Raman equipment for in vivo and in vitro Raman measurements on tissues. The equipment will be used to create an annotated (clinical evaluation, histological pathology) database of Raman spectra of suspicious pigmented lesions. This database will be used for the development and validation of diagnostic algorithms.

## I. Optical Spectroscopy and skin (pre-)malignancies

Dr. Dominic Robinson,

White light reflectance spectroscopy and fluorescence spectroscopy can be used to quantify concentrations of absorbing (e.g. blood, bilirubin, melanin) and fluorescent (e.g. collagen, photosensitizers) compounds in living tissues. We are investigating the use of quantitative spectroscopy for monitoring PDT in superficial skin (pre-) malignancies so that treatments can be optimized. In addition, reflectance spectroscopy is sensitive to the scattering properties of tissue, which are related to tissue architecture and nano-scale mass-density fluctuations within cells. We are currently investigating methods to quantify the optical scattering properties of turbid media such as tissue, and aim to relate these scattering properties to cellular ultrastructure and tissue architecture in pre-clinical models and to use these scattering properties as optical biomarkers of e.g. pre-malignant disease states.

## Research theme 2: Inflammation

### A. Psoriasis and comorbidities

Drs Emilia Dowlatshahi, drs. Ella van der Voort, dr. Marlies Wakkee, dr. Tamar Nijsten

Introduction:

Psoriasis is a chronic inflammatory skin disease that may be associated with psoriatic arthritis (~10% of patients). In the last decade, multiple studies have demonstrated that psoriasis patients are at an increased risk of developing metabolic syndrome, cardiovascular disease (including acute myocardial infarction and stroke) and several other systemic diseases. It has been hypothesized that this link is due to increased levels of inflammatory cytokines in the circulation in psoriasis patients compared to control populations and/or to a genetic predisposition of psoriasis patients to develop other metabolic and cardiovascular diseases. However, most of these observational studies have been conducted in routine medical databases (pharmacy dispensing data, primary physician databases and claims data) and suffered from several important classical biases such as surveillance bias and residual confounding. None of the studies have investigated the genetic predisposition.

Aims:

- To study the association between psoriasis and cardiovascular disease.
- To study the genetic predisposition of psoriasis patients to obesity, diabetes and cardiovascular events.
- To study the association between liver diseases and psoriasis.

Methods:

About 350 participants of the Rotterdam Study suffer from psoriasis (confirmed by their medical records and history of drug prescriptions). Because cohort members have all been very well described and have been screened for all the components of metabolic syndrome and cardiovascular disease, it is an ideal study population to compare the incidence of cardiovascular disease between controls to psoriasis patients after adjusting for the pivotal confounders. Moreover, it allows us to see whether psoriasis patients share genetic risk factors with obese and diabetic patients who are at an increased risk of developing cardiovascular diseases.

B. Clinical trials in immune mediated inflammatory skin diseases including psoriasis, hidradenitis suppurativa, atopic eczema and chronic urticaria

Dr. Bing Thio, Prof. dr. Errol Prens, dr. Martijn van Doorn,

Introduction:

Psoriasis, hidradenitis suppurativa, atopic eczema and chronic urticaria are skin diseases that are part of the 'immune mediated inflammatory diseases' (IMIDs). These IMIDs affect a large percentage of the population and have a large impact on people's quality of life and often require life-long therapy. Many patients require a form of systemic therapy. In addition to conventional systemic drugs, in the last decade, the highly specific biologic drugs have been introduced in the treatment of these IMIDs in dermatology and new drugs are being developed..

Aims:

- To evaluate new (pharmacological) treatments (including biologics) in fase II (cooperation with Centre for Human Drug Research in Leiden) and fase III/IV clinical studies for dermatological IMIDs
- To evaluate the effect of fumaric acid in the treatment of psoriasis.
- To evaluate daily practice effectiveness of systemic treatments
- To evaluate the added value of therapeutic drug monitoring of biologics in IMIDs (collaboration with the department of pharmacy, clinical pharmacology and immunology)

Methods:

We participate in many fase II (Centre for Human Drug Research) and international fase III RCTs evaluating new drugs coming to the market. Also, we have several investigator initiated clinical studies that, focus on the effectiveness of fumaric acids and combination therapies such as fumaric acid with etanercept and methotrexate combined with adalimumab. Therapeutic drug monitoring (measuring through levels and anti-drug antibodies) of therapy with biologics is done in close collaboration with the department of pharmacy and immunology. We are also setting up a patient registry of IMID patients that are treated with systemic therapy (including biologics) to evaluate daily clinical practice data and long term safety. This registry is being set up in collaboration with the Radboud mc and AMC (psoriasis), UMCU (chronic urticaria and eczema) and UMCG (hidradenitis).

MSc. students with an interest in inflammatory dermatoses are encouraged to make further inquiries and are very welcome to join any of the existing or new projects that are taking place in the Erasmus MC or in the Centre for Human Drug Research in Leiden.

#### Research Theme 4: Laser dermatology

Introduction: In our department several dermatological diseases are being treated with Lasers. Laserlight selectively targets water and chromophores such as hemoglobin or melanin in the skin. By absorption of high energy laserlight, skin structures containing these chromophores can be targeted selectively. Skin conditions such as hemangiomas, naevus flammeus, facial or leg teleangiectasias, pigmented lesions, hairs and tattoos can be treated succesfully. Generally many treatment sessions are required to obtain optimal results. The mode of action and the efficacy of lasers and side-effects of laser treatments can be improved. Laser treatment can also be combined with certain (locally active) drugs.

Aims: To investigate optimisation strategies for laser treatment efficacy.

Methods: the efficacy of lasers may be improved in several ways. Laser treatments can be enhanced by combined treatment with certain drugs. For example, the neovascularization after laser treatment of naevus flammeus can be blocked by using angiogenesis inhibiting drugs such as sirolimus. Treatment of lentigo maligna (a potential precursor of melanoma) can more effectively be treated when laser evaporation is combined with a topical immune response enhancing drug such as imiquimod. Alos, the recurrence rate of laser-treated warts can be mimimized by post-laser evaporation addition of topical bleomycin. All these projects are being executed in investigator-initiated trials. MSc. students with an interest in laser therapy are encouraged to make further inquiries and are very welcome to join any of the existing or new projects that are taking place at the department of laser dermatology and Erasmus Aesthetics.

#### Research theme 3: Phlebology

##### A. Clinical studies in treatment of varicose veins

Dr. Renate van den Bos, drs. Anke Biemans, Prof. dr. De Maeseneer, Prof. dr. Martino Neumann, Prof. dr. Tamar Nijsten

##### Introduction:

In the last century, the golden standard in the treatment of varicose veins has been surgical ligation and stripping. In the last decade, new minimal invasive techniques have been introduced that use heat generated by laser light, radiofrequency or steam to ablate the varicose vein. These new techniques are highly effective, have few side effects and are very well tolerated by patients. However, not all of these techniques have been standardized to provide optimal care and the number of comparative and cost effectiveness studies is limited.

## Aims:

- standardize laser parameters to optimize patient care
- evaluate minimally invasive treatment approaches in varicose veins.
- compare the different new therapies including patient reported outcomes and costs.

## Methods

There are several investigator initiated comparative clinical trials running that compare endovenous laser therapy to steam ablation, or laser therapy to radiofrequency ablation or laser therapy to surgical stripping. Some of these trials have finished and are in the analytic stages whereas others are in the recruiting phase. The goal is to include every varicose vein patient who is treated at our department in a clinical trial that is in line with patients' wishes. We have a special focus on patient reported outcomes such as pain experience, health related quality of life and treatment satisfaction in the treatment of varicose veins.

## Theme 9: Major respiratory diseases

Prof. Guy Brusselle, Prof. Bruno Stricker, Dr. Joachim Aerts, MSc. Lies Lahousse

In the Rotterdam Study, clinical epidemiologic studies of the major respiratory diseases in the elderly are performed. The main focus of the respiratory epidemiologic research are obstructive airway diseases encompassing Chronic Obstructive Pulmonary Disease (COPD) and asthma, but also lung cancer is a priority topic for investigation. In COPD, we study the natural history of the disease, the determinants of exacerbations, the association with cardiovascular and cerebrovascular diseases (comorbidities / multimorbidities) as well as the genetic susceptibility in smokers and nonsmokers to develop COPD. In addition, we aim to elucidate the genetic and clinical determinants of lung function measurements in the adult population (both spirometric measures and lung diffusing capacity).

## Theme 10: Assessment of Lifestyle interventions

Prof. dr. Myriam G Hunink

For many diseases there is no magic bullet to cure, care and prevention. Health and well-being require a multidimensional approach: apart from pills and medical procedures, the patient needs to pay attention to diet, exercise, healthy habits, and relaxation. Patients actively participating in their health care through a healthy lifestyle have a better prognosis and a better quality of life. There is an increasing interest among patients and healthy individuals to harness the effects of their own self-healing potential as demonstrated by the growing interest in healthy lifestyle interventions and prevention in general. In this theme we perform randomized controlled trials (RCTs) and systematic reviews of RCTs to evaluate the effectiveness of non-pharmacological lifestyle interventions for the treatment of chronic disorders with a focus on cardiovascular disease.

## Theme 11 Endocrinology, with a focus on thyroidology

The relation between thyroid (dys)function and clinical outcomes of aging  
Dr. L. Chaker, Prof. dr. R.P. Peeters

Thyroid hormone is crucial for normal function of practically all organ systems. Overt thyroid dysfunction is related to various clinical outcomes such as cardiovascular disease, osteoporosis, and cognitive decline. Recent studies have shown that even thyroid function within the normal range may also be related to these clinical outcomes.

This research program focuses on the consequences of variations in thyroid function within the context of the Rotterdam Study, a prospective population-based study of age-related disorders that includes 15,000 persons since 1990. In a large number of subjects we can study different thyroid function parameters (TSH, FT4, TPO antibodies) in relation to detailed follow-up data on cardiovascular and metabolic disease, osteoporosis and fracture risk, cognitive decline and dementia, as well as other parameters of aging.

We study these endpoints in close collaboration with other research groups within the Rotterdam Study but also work together with the Erasmus MC thyroid lab, the Thyroid Study Collaboration and other cohorts within the Charge Consortium.

Specific subtopics within the research line:

1. Thyroid function and cardiovascular complications
  - Myocardial infarction, cardiovascular mortality, heart failure
  - Cardiac function (imaging and non-imaging)
  - Determinants in variations in outcomes (subgroup analyses)
2. Thyroid function and bone parameters
  - Osteoporosis and fracture risk
  - Bone geometry and other imaging modalities
  - Osteoarthritis
3. Thyroid function and neuroepidemiology
  - Cognitive decline, Alzheimer's disease and dementia
  - Cerebrovascular disorders
  - Pre-clinical markers of degenerative disease (imaging)
4. Determinants and course of thyroid function during aging:
  - Longitudinal changes in thyroid function
  - Risk factors for changes in thyroid function
  - Identification of risk groups
  - Assessing the frequency and influence of thyroid medication

Clinical outcomes associated with thyroid function during pregnancy and early childhood.

Dr. T.I.M. Korevaar, Prof. dr. R.P. Peeters, Prof. dr. H. Tiemeier

During pregnancy and early development, TH is crucial for normal growth and development of the child. Over the last two decades it has been shown that even slight alterations in thyroid function may have a profound impact on the course of pregnancy and the development of the child.

The research aim of the Generation R thyroid study group is binomial; First of all, we want to investigate which factors influence the thyroid function during pregnancy and early childhood. This includes a wide range of potential environmental, genetic and inter,- or intra-individual determinants. Secondly, we study to what extent variations in thyroid functioning may effect clinical outcomes. Our main focus lies with pregnancy outcomes, neurocognitive, cardiovascular and bone development. We work in close collaboration with various other research groups but also with the Erasmus MC thyroid laboratory. This allows us to form novel research hypotheses based on basic scientific evidence and translate this to novel clinical research projects.

Specific subtopics within the research line:

1. Determinants of thyroid function during pregnancy and early childhood:
  - Thyroid function in relation to dietary and/or environmental factors
  - Genetic factors influencing thyroid function during childhood
  - Influence of fetal programming on thyroid function during childhood

## 2. Thyroid function in relation to clinical outcomes:

- Development of bone, cardiovascular or neurocognitive parameters in childhood
- Thyroid function and pregnancy hormones or macronutrients
- Thyroid dysfunction during pregnancy and postpartum maternal health

## Theme 12 Nutrition and healthy ageing across the lifecourse

Prof. Oscar H Franco, dr.ir. Josje Schoufour, dr. ir. Trudy Voortman, dr.ir. Jolien Steenweg- de Graaff, dr. Jessica Kieftede Jong

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Projects in this theme are embedded in ErasmusAGR ([www.erasmusage.com](http://www.erasmusage.com)). ErasmusAGE aims to identify nutrition and lifestyle factors that are associated with life course health. Research areas focus on cardiometabolic health, frailty, cognition and behavior, and cancer using several prospective cohort studies (The Generation R Study and The Rotterdam Study) as well systematic reviews and meta-analyses in close collaboration with other departments. The Generation R Study is a birth cohort of children and their parents who are followed from pregnancy onward. The children are currently 10 to 12 years of age. The Rotterdam Study is a prospective cohort study of middle-aged and elderly, focusing on determinants of common age-related diseases such as cardiovascular disease, dementia, diabetes, and cancer.

### **Nutrition and cardiometabolic health in different stages of life**

Lifestyle is the most important modifiable risk factor for cardiovascular disease and type 2 diabetes mellitus. According to the WHO, 80% of premature death from these cardiometabolic diseases could be prevented by a healthy lifestyle, including a healthy diet. This does not only include a healthy lifestyle during adulthood: Although cardiometabolic diseases predominantly become apparent at older ages, the origins of cardiometabolic diseases have been linked to nutrition in early life, for example during early childhood or during pregnancy. The research in this theme therefore focuses on the role of nutritional factors during the life course, i.e., during pregnancy, childhood and older adulthood, in the prevention of adiposity, cardiovascular disease, and diabetes. We study this in the two large cohorts in Rotterdam: The Generation R Study and the Rotterdam Study. Nutritional factors include intake or blood levels of specific nutrients, intake of specific food groups, or overall dietary patterns. In the Rotterdam Study we focus on incidence of type 2 diabetes or cardiovascular disease, and intermediate cardiometabolic risk factors, such as adiposity, dyslipidemia, insulin resistance, hypertension, and chronic inflammation. In the Generation R Study, we examine proxies for cardiometabolic health, such as growth, body composition, blood pressure, blood lipids, inflammatory markers, and insulin levels.

### **Nutrition and frailty**

One commonly used approach to study healthy and unhealthy ageing is via the concept of frailty. Although there are several approaches to conceptualize frailty, followed by a wide range of frailty instrument, researchers generally agree that frailty is a state of increased vulnerability to adverse health outcomes at old age. One commonly used frailty approach is the frailty index. The frailty index is based on the accumulation of health deficits, which include symptoms, signs, diseases, disabilities, laboratory measures or other measures as long as they are health and age related. There is compelling evidence that nutrition and other lifestyle factors play a large role in achieving healthy ageing. Nevertheless, the effect of lifestyle on frailty and trajectories of frailty is poorly understood. Therefore we study the effect of lifestyle, mainly physical activity (sedentary behavior, sports and total physical activity) and nutrition (e.g. dietary patterns, macronutrients, micronutrients) on frailty and changes in frailty status over time.

### **Nutrition, cognition and behavior**

There are now many studies showing the link between good nutrition in the first 1,000 days of life - including the fetal period - and long-term health benefits. The fact that optimal growth and development during this period are also critical to the development of brain and cognition is now well recognized and is the principal basis for targeting nutrition interventions within this critical period. This research theme focuses on pre- and postnatal nutrition (dietary patterns, food groups, and specific nutrients) in relation to child brain, cognitive and behavioral development using data from the Generation R Study. In addition, determinants and consequences of food related behavior (e.g. fussy/picky eating and eating disorders) are studied within this research theme.



### **Nutrition and cancer**

It has been estimated by the World Cancer Research Fund that 4 in 10 cancer cases could be prevented by lifestyle changes such as for example not smoking, physical activity, safe sun exposure, and reduce alcohol intake. This theme focuses on specific nutritional determinants (eg. dietary patterns, dietary endocrine disrupting chemicals, or specific nutrients) of the most common cancers globally: colorectal cancer, prostate cancer, breast cancer, and lung cancer using data from The Rotterdam Study. In addition, since several risk factors for cancer overlap with those of cardiovascular disease, this theme also focuses on how diet may interact with specific cardiometabolic risk factors that may be related to cancer such as for example hypercholesterolemia , body fat distribution and nonalcoholic fatty liver disease.

## 15. Genetic Epidemiology

Our understanding of the structure of human genome is increasing rapidly, yet our knowledge of the function of variations in the human genome and their relationship to common disorders in the general population is still limited. The current developments in the field of genomics will result in large amounts of information on variations in the human genome. One of the most important challenges in epidemiology will be to link these variations to the risk of major disorders in the population. These findings will make a large impact on individualized care of patients as well as public health strategies. This makes genetic epidemiology one of the most exciting fields to work in.

Within the genetic epidemiology unit, we have successfully identified various genes that play an important role in the etiology of major diseases. These genes were sometimes identified through searches through the complete genome. These include genes involved in Parkinson's disease, hemochromatosis, multiple sclerosis, type 2 diabetes, lipid levels and hypertension. Students can participate in such searches. These include searches for a variety of disorders including Alzheimer's disease, type 2 diabetes, ADHD, depression, obesity, among other disorders. Furthermore, we have several studies ongoing targeting the role of specific gene in the etiology of disease. Examples of those are the role of mutations in the HFE gene in various disorders including diabetes, cardiovascular disease, neurodegenerative disorders and the role of genes involved in the RAS system in diabetes, cardiovascular disease, depression and cancer. These are also fascinating projects to work in as part of masters training in epidemiology. Finally, student can participate in translational studies as part of the Clinical and public health genomics module.

### Theme 1: Gene discovery

Prof. dr. Cornelia M. van Duijn, dr. Yurii S. Aulchenko

In recent years, there has been major progress in human genomics, particularly in the identification of the genes which are involved in the pathogenesis of major disorders in Western societies. This progress has been achieved by genome wide association (GWA) analyses in which case-control studies have been characterized by dense arrays of genetic markers. Successes have been achieved for a wide range of disorders varying from macular degeneration, Crohn's disease, multiple sclerosis, rheumatoid arthritis, diabetes and HIV. These developments have led to a stream of novel disease genes, highlighting new aetiological pathways and improving the understanding of the molecular basis of these diseases. The research program of NIHES offers student to participate in this rapidly developing field, performing hands-on analysis of data available with the Genetic epidemiology unit. This may concern genome wide association studies or studies of candidate genes/pathways with multiple outcomes. The research program of the genetic-epidemiology group combines successfully methodological and empirical research. The methodological research program focuses on several aspects of genome wide association studies including meta-analysis and gene interaction. The statistical methods group targets both the design and the analysis of genomic research.

## 16. Public Health

### Theme 1: Health behaviour and health promotion

Dr. Carlijn B.M. Kamphuis, dr. Frank J. van Lenthe

Our society faces an epidemic of unhealthy life behaviours, as evidenced by the strong increase in obese children and adults. An unhealthy lifestyle not only leads to increased morbidity and mortality, but also to adverse consequences among those with a chronic disease. The research in this theme varies from identifying the relative importance of lifestyle and coping strategies on morbidity among different populations, such as school children and elderly persons, developing and evaluating interventions aimed at changing health behaviours, and evaluating the consequences of health behaviour for functioning and participation, for the role of physical activity in frailty among older persons. Projects can accommodate a large variety of interest, such as active data collection on health behaviour and physical activity patterns among elderly persons in relation to the physical environment, studying the role of social and cultural determinants of health behaviour, and investigating how to reach and encourage persons with unhealthy behaviour to participate in health intervention programmes.

### Theme 2: Infectious disease control

Prof. dr. Jan Hendrik Richardus, Dr. Sake J. de Vlas

Infectious diseases are still an important problem worldwide and in many cases systematic preventive control is needed. The theme infectious disease control aims at studying the public health consequences of infectious diseases and evaluating the cost-effectiveness of their control. The core activity is the development and application of simulation models describing the transmission and natural history of infectious diseases in human populations and the impact of control measures. However, we also perform epidemiological data collection or carry out literature reviews.

Most of the research is in collaboration with active control projects, and has a strong focus on global infectious diseases that have a chronic course with secondary complications. Examples of work over the past years concern parasitic worm infections, tuberculosis, leprosy, chronic hepatitis B, visceral leishmaniasis, and HIV/Aids. The research network includes various scientists and scientific institutes in the developing and developed world, including the WHO and the World Bank. Special collaborations exist with sub-Saharan Africa (worm infections and HIV/Aids), China (influenza and HIV/Aids), Bangladesh (leprosy), India (lymphatic filariasis and visceral leishmaniasis) and Indonesia (tuberculosis). The department is a key partner within the Neglected Tropical Diseases Modelling Consortium, funded by the Bill & Melinda Gates Foundation. Within the Huisman Research Centre for Infectious Diseases and Public Health, Erasmus MC and the Municipal Public Health Service of Rotterdam work together in the area of infectious disease surveillance and control in the Rotterdam region. Here, emphasis is on diseases that are closely related to the immigrant population of the city, in particular viral hepatitis, tuberculosis, STDs, and HIV/Aids.

### Theme 3: Screening for disease

Prof. dr. Harry J. de Koning

The development and improvement of screening tests for the detection of asymptomatic disease will continue to lead to an increased use of such tests in hospitals, physician' practices, organized screening programs and individuals. Early detection of diseases may lead to considerable improvement in survival or quality of life. However, early detection also means a longer period of life during which a person is aware of having the disease, and false-positive test results will induce unnecessary diagnostic interventions.

Our research quantifies the health benefits, unfavourable side-effects, impact on quality of life, and the cost consequences of introducing screening. This may lead to advice to introduce, or not introduce, screening for a specific disease, or to introduce it in a specific way, e.g., for selective groups of the population only.

Ongoing projects are the evaluation of the Dutch nationwide breast cancer, cervical cancer and colorectal cancer screening programmes and EU-TOPIA: towards improved screening for breast, cervical and colorectal cancer in all of Europe. We are involved in several randomized controlled trials as for example the ROBINSICA trial, in which screening for cardiovascular disease using the coronary artery calcification score is evaluated, the Dutch-Belgian (NELSON) randomised controlled trial on lung cancer screening by low dose spiral CT in high-risk subjects. Other examples of projects are the prevention of cervical cancer by HPV vaccination, and screening on language disorders in children. In addition, we are collaborating with several modeling groups in the US to model the effects of breast, lung, colorectal, prostate, cervical and esophageal cancer screening and treatment.

## Theme 4: Inequalities in health

Prof. dr. Johan P. Mackenbach

All countries have substantial inequalities in health within their populations. For example, people with a lower level of education, a lower occupational class, or a lower level of income tend to die at a younger age, and to have, within their shorter lives, a higher incidence and prevalence of almost all diseases (cardiovascular, cancer, respiratory, injuries, ...). Other important disparities in health are found between men and women, between ethnic groups, and between people with a different marital status. At the Department of Public Health of Erasmus MC we try to find the specific determinants of these health inequalities, and to evaluate interventions and policies aiming to reduce health inequalities. We are engaged in a number of prospective cohort studies, in international comparative studies of health inequalities, and in a wide range of intervention studies. Our research provides important input into health policy at the regional, national and international level, and offers excellent opportunities for public health research training.

## Theme 5: Medical Decision making

Prof. dr. Ewout W. Steyerberg

Diagnostic and therapeutic options continue to increase, both in number and in complexity. The science of medical decision making considers decision problems in individual patient care. Our research considers diagnostics (what is wrong?), therapy choice (what can be done about it?) and prognosis (what will happen?). Special interest is in prognosis and prediction modeling. We frequently use regression analysis for prediction of the presence of disease (diagnosis) or the outcome of a disease process (prognosis) given patient and/or care characteristics. Recent interest is expanding from development and validation of prediction models to assessment of impact in clinical practice, that is, do patients have better outcomes when decisions are based on a prognostic model than without? A specific issue here is the contribution of novel markers to the improvement of prognostic models. Another line of research is on quality of care, where we consider differences between health care providers, such as differences in mortality between hospitals. We study a wide scope of medical problems, including patients with various cancers (e.g. bladder, prostate, colorectal), cardiovascular disease, neurological disorders (including stroke, Guillain - Barre syndrome), gastrointestinal disease (e.g. Barrett oesophagus), surgical interventions, and acute diseases (e.g. patients with traumatic brain injury). The research is done in close collaboration with various clinical groups at Erasmus MC, in the Netherlands, and internationally.

## Theme 6: Health, work, and participation

Prof. dr. A. Burdorf

With growing life expectancy in developed countries, workers are encouraged to remain in work longer. There is ample evidence that among older workers, especially those 50-65 years, ill health contributes to selection out of the workforce due to early retirement, unemployment, and permanent disability. For chronic diseases, such as rheumatoid arthritis and low back pain, the average working life expectancy may be reduced by up to 4 years. We seek interested students to study the influence of poor health on paid employment and participation in available datasets of cohort studies across European countries, such as SHARE, SILC, and EHIS. With statistical analysis techniques for longitudinal data, we want (i) to determine how particular aspects of health problems, e.g. particular chronic diseases or functional limitations, predict leaving paid employment, (ii) to assess how lifestyle behaviours and working conditions mediate these associations, and (iii) estimate the number for working years lost due to poor health during a working career (life course perspective).

## Theme 7: Cancer surveillance

Esther de Vries PhD ([e.devries@erasmusmc.nl](mailto:e.devries@erasmusmc.nl), skin cancer, cancer in general, international comparisons), Valery Lemmens PhD (cancers of the GI-tract, cancer in general, treatment, quality of care), Melina Arnold ([m.arnold.1@erasmusmc.nl](mailto:m.arnold.1@erasmusmc.nl), cancer among migrants), Prof Jan Willem Coebergh MD PhD [j.coebergh@erasmusmc.nl](mailto:j.coebergh@erasmusmc.nl)

Project : Cancer surveillance examines the various cancer epidemics, elucidating determinants of changes in incidence and prognosis

The Cancer surveillance section at the department of Public Health of Erasmus MC entertains excellent relations with the renowned South Netherlands cancer registries at Eindhoven and Rotterdam, each with impressive extra data-collections on clinical aspects of cancer detection and care, co-morbidity, and strongly involved in a variety of regional, national and European studies of cancer incidence and prognosis. Besides close collaborations across Europe, a.o. with IARC (Int Agency for Research of Cancer in Lyon) there is close collaboration with most clinical oncological departments at Erasmus MC and in the large southern community hospitals where most older cancer patients are being treated.

In our research special emphasis exists on the following topics:

- skin cancer epidemics of melanoma and non-melanoma skin cancer including basal cell skin carcinoma
- gastro-intestinal cancer epidemics with special emphasis on oesophageal and colorectal cancer
- obesity, alcohol and smoking related epidemics of cancer
- cancer in the (very) elderly, allowing for studies of the role of co-morbidity of which there is a unique data collection since 1995
- cancer in migrants

Most likely we can accommodate your own ideas.

## Theme 8: End-of-life decisions

Prof. dr. Agnes van der Heide

During the last decades, the end of life has emerged as a new field of practice and research in health care, due to demographic changes, cultural developments, and medical progress. Advances in medicine have substantially increased the possibilities to prolong the lives of patients with advanced chronic diseases. However, prolongation of life seems not beneficial for all patients with a limited life expectancy and poor quality of life. Care at the end of life therefore often involves decisions about whether or not to use life-prolonging interventions, or about far-reaching interventions to alleviate severe suffering. Empirical research in this field inventorizes epidemiological and clinical aspects of decision making at the end of life and includes observational and experimental studies. Themes to be studied are: determinants and outcome of palliative sedation, limiting treatment, and euthanasia, and how to optimize care for the dying.

## Theme 9: Preventive Youth Health Care to promote healthy growth and development of all babies, children and adolescents

Prof. dr. Hein Raat

Healthy growth and development of babies, even before birth, and of children and youth is essential for public health. Even in the western world, persistent differences in health potential are present between children of various social and ethnic backgrounds. These differences show up in pregnancy and continue during childhood, leaving their marks throughout life. The aim of this theme is to unravel the mechanisms that cause childhood health inequalities, and to contribute to effective prevention in day-to-day practice of professionals dedicated to support parents and to promote child health. Three types of studies are conducted.

Firstly, studies regarding the origins of socio-economic and ethnic differences in growth and development. They primarily use the framework of the Generation R cohort of almost 10.000 Rotterdam children, most of which were included in early pregnancy, with extensive measurements throughout pregnancy and after birth. The theme focuses on assessing how adverse circumstances of the mother affect pregnancy, birth outcomes and child health. Furthermore we have a project on the origins of social and ethnic differences in overweight in childhood.

Secondly, studies that develop and evaluate new preventive interventions in preventive youth health care. For example we developed E-health4Uth, an interactive, web-based approach that supports monitoring and prevention in preventive Youth Health Care (YHC) and with an application for obstetric care. Several applications in day to day practice are being evaluated.

Thirdly, we conduct studies, in collaboration with others, to evaluate established or new Youth Health Care interventions by applying rigorous designs such as large cluster-Randomised Controlled Trials (c-RCTs). Examples are multi-center studies to evaluate the nation-wide protocols for Overweight Prevention, a new Internet-based Home-safety Promotion intervention, and early detection of emotional/behavioural problems.

## Theme 10: International Health

Dr. Tanja AJ Houweling

At the start of the 21st century profound health inequalities persist globally between countries and between socio-economic groups within countries. These inequalities are not due to a lack of technical or medical knowledge on how to improve health. Within countries, they are due to a lack of knowledge on how to reach the most in need with effective interventions. Our projects focus on three main areas: (1) **What works, where, and why to reach the most in need with effective interventions and reduce health inequalities.** We evaluate health interventions --such as participatory women's groups to reduce newborn mortality, and conditional cash transfer and performance-based financing schemes in Asia and Africa-- in terms of (a) the socio-economic groups that these interventions reach and (b) their health impact among lower and higher socio-economic groups. We mainly use observational and experimental study designs, including large randomised trials, but we also explore the role that experiential knowledge of policy makers and practitioners can play in understanding what works, where and why to reach lower socio-economic groups. (2) **Understanding societal contexts that are conducive to reducing or increasing health inequalities.** Building on the work of the WHO Commission on Social Determinants of Health, we use ecological designs, contrasting case studies and natural experiments to study the effects of factors like state strength and rapid economic growth on the magnitude of health inequalities within countries in Asia, Africa, and Latin America. Students can explore these issues using Demographic and Health Survey (DHS) data. (3) **Measurement and monitoring of health inequalities in low and middle income countries.** Socio-economic inequalities in a wide range of health outcomes, in particular for newborns, children and women, can be studied using DHS data and data collected in large demographic surveillance sites in Asia and Africa.

# Colophon

## Editing and layout

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## Cover

Zita

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## Publication

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