RESEARCH THEMES 2012
FOR MSc STUDENTS

Research Master Health Sciences
& Research Master Clinical Research
for Medical Students
Research Themes for MSc-students
Edition 2012

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& 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!

Professor Albert Hofman, MD PhD
Scientific director Health Sciences

Professor Aart Jan van der Lely, MD PhD
Scientific director Clinical Research
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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.W.J. Koper, Dept. of Internal Medicine; Section of endocrinology, Prof. Dr. E.P. Krenning, Dept. of Nuclear Medicine; Prof. Dr. S.W.J. Lamberts and Prof. 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
  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)
  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
  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
  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.

  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

How often is a genetic defect in brain thyroid hormone action the cause of psychomotor retardation? The thyroid produces largely an inactive precursor (T4) that is converted in different tissues by ‘outer ring’ deiodination to the active hormone T3. Both T4 and T3 are converted by ‘inner ring’ deiodination to inactive metabolites. The three deiodinases involved in these reactions (D1-3) are unique selenoproteins located in the cytoplasm. D2 and D3 are particularly important for regulation of T3 levels in brain. The action of T3 is large exerted by binding to nuclear receptors. Therefore, both action and metabolism of thyroid hormone are intracellular process that require transport of T4 and T3 across the plasma membrane by specific transporters.

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 genes, such as those coding for MCT10, D2 and D3.

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 (Friesema et al., Nat Clin Pract Endocrinol Metab, September, 2006).

**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.

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

The aim is
1. to identify novel therapeutic targets and therapies for osteoporosis and to obtain new insights into mesenchymal stem cell differentiation important for tissue engineering, and
2. 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
1. to analyse genes/proteins identified in Research line 1 as risk determinants, and
2. 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 studied that are planned to be performed within the Rotterdam Study. 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.

**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: Hormone signaling and ageing**
Prof. Dr. Ir. A.P.N. Themmen, Prof. Dr. F.H. de Jong, Dept. of Internal Medicine, Section of Endocrinology

**Old age: what have hormones got to do with it?**

Hormones influence organ systems in the body through interaction with specific receptors. Subsequently, the hormonal signal is relayed to the inside of the cells and the appropriate responses are triggered. This process of hormone signaling changes during ageing. In the Hormone signaling
and ageing group, cellular and animal models are developed to measure these ageing-induced changes, to study their mechanism and, if possible, to counteract the negative aspects of hormonal changes in response to ageing. The emphasis of our studies is on the major milestone in female ageing, i.e. menopause and on age-related changes in steroid production in the adrenal cortex.

Three levels of approach are used
1. Molecular: determine the relationship between the molecular structure and function of hormones and hormone receptors
2. Physiology: effects of ageing and changing hormone signaling on physiological processes in mouse models
3. Epidemiology: associations of hormone and receptor gene variants with disease endpoints in patients

During the last 15 years, new markers to predict menopause and female fertility have been developed. In addition, several mutations of hormone receptors and steroidogenic enzymes have been discovered that cause severe sex steroid hormone disbalance in men and women. MSc. students can choose to participate in several lines of investigation in the group
- Studies on associations of hormone receptor gene variations and disease endpoints in several large patient cohorts (breast cancer, infertility patients)
- The development of markers that predict healthy female ageing
- Mutational analysis of luteinizing hormone receptor function
- Analysis of mutations leading to defects in steroid hormone production

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 dia-betes (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:
1. 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’.
2. On molecular mimicry between auto-antigens and environmental antigens as another important cause of autoimmune diseases, such as GBS.
3. 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

Prof. dr. H.A. Drexhage, 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 in-inflammatory disorder we also focus on special descendents 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 previous 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 afore-mentioned diseases.

Subtheme 2: Pathogenesis of the Guillain-Barré syndrome
Dr. B.C. Jacobs (Dept 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 pa-resis. Patients with GBS have a rapidly progressive immune-mediated neuropathy result-ing in severe paresis of limb and respiratory muscles, from which patients may die. Re-search 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-ooligosaccharides 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 anti-bodies? 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 immuno-globulins? 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 (meningo-encephalitis), 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 in-teraction of yet poorly identified genes (e.g. HLA) with environmental factors (viral infec-tions, specifically EBV, vitamin D and perhaps smoking).

Aim of this program is to enhance our understanding of 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 the 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 ophthalmpathy, 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 in-inflammatory process. In certain immune pathological conditions these interactions are aber-rant and result in abnormal inflammation and fibrosis, e.g. during systemic sclerosis and endocrine ophthalmpathy. 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 ophthalmopathy) 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 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.

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, 12 different medical Departments participate. The research school comprises about 300 scientists, and publishes over 400 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. Research is currently organized in 6 themes. On the following pages, more detailed information per research theme is presented.

THEME 1: CARDIAC AND VASCULAR BIOLOGY, AND PHARMACOLOGY


Basic and preclinical translational cardiovascular research is aimed at unraveling biological processes in the normal cardiovascular system and to understand the mechanisms leading to cardiac muscle- and vascular dysfunction, damage and repair. Understanding these (mal)adaptations, which contribute to the pathogenesis of atherosclerosis, hypertension, peripheral- cerebral- (stroke and migraine), and coronary artery disease (infarction), heart failure and cardiac arrhythmias, is of critical importance to further optimize the prevention and treatment of cardiovascular disease.

Research within this Research theme occurs principally in the laboratory setting. For this purpose a wide variety of experimental techniques is employed, ranging from molecular, biochemical and histological techniques to in vivo animal models (including pigs and genetically modified mice), for integrative physiological and pharmacological studies. In addition, integrative physiological studies of cardio-pulmonary homeostasis in critically ill patients and in patients undergoing anesthesia constitute a clinical project for students that prefer a more clinically oriented research project. Thus, the Research Master student will have the choice of a wide variety of research projects, including:

1. Atherosclerosis
   - Molecular basis of atherosclerosis
   - Shear stress and atherosclerotic plaque vulnerability

2. Microvascular (dys)function
   - Molecular basis of angiogenesis and vasculogenesis in health and disease
   - Regulation of coronary and cerebral blood flow in health and disease
   - Role of the renin-angiotensin system in the pathogenesis of hypertension and heart failure

3. Myocardial infarction, cardiac remodeling and heart failure
   - Strategies to limit cardiac ischemia-reperfusion damage
   - Molecular basis of cardiac remodeling and heart failure
   - Cell-based therapy of ischemic heart disease

4. Cardiopulmonary homeostasis in critically ill patients and patients undergoing surgery
**THEME 2: VASCULAR MEDICINE, INCLUDING ATHEROSCLEROSIS, THROMBOSIS AND HEMOSTASIS, AND STROKE**

Prof. dr. P.J. Koudstaal, prof. dr. M.L. Simoons, dr. A.H. van den Meiracker, dr. F.W.G. Leebeek, MD, PhD.

Atherosclerotic lesions typically occur at specific predilection places, such as the origins of arterial side branches and at vessel curvatures. Apparently, biomechanical factors like wall and shear stress interact with risk factors. This process is investigated both at the level of gene expression and inflammation.

Hypertension-induced changes of the arteries and the heart result in abnormal mechanical properties of these organs. Studies exploring whether, and if so, to what extent these mechanical properties are functional and can be influenced by various classes of antihypertensive agents are being conducted. Extensive research is being performed on the role of natriuretic peptides in disorders like heart failure, renal insufficiency, hypertension and thyroid dysfunction. Other studies explore the role of new enzymes in the pathogenesis of hypertension, including the interaction between the renin-angiotensin and the sympathetic nervous system.

Research into the contribution of genetic factors to progression of atherosclerosis is in preparation, using a DNA databank of over 10,000 patients. The scientific program regarding stroke (both ischemic and hemorrhagic) is directed towards establishing the most effective therapy for these patients. Further, the role of new imaging techniques, such as CT perfusion, is under study. We also investigate novel genetic, hemostatic and cardiac causes of stroke, and new options for stroke prevention. A multicenter study is aimed at demonstrating the most effective treatment of aphasias after stroke.

Studies on the role of hemostatic risk factors in the pathogenesis of arterial vascular disease focus on platelet glycoprotein receptor polymorphisms, coagulation factors and proteins involved in the regulation of fibrinolysis. Two large case-control studies are used to further identify and study newly discovered genes and proteins involved in regulation of hemostasis. Further, laboratory studies on monitoring new antithrombotic and antiplatelet drugs, using recently developed assay systems, are carried out.

**THEME 3: CARDIOVASCULAR IMAGING AND DIAGNOSTICS**

Prof. dr. P.J. de Feyter, prof. dr. P.M.T. Pattynama, prof. dr. A.F.W. van der Steen

This theme is concerned with the study of all imaging modalities and related diagnostic methods, invasive and non-invasive, to examine the cardiovascular system in healthy subjects and in patients with (suspected) cardiovascular disease. Its scope ranges from fundamental research of new diagnostic modalities to their evaluation in clinical practice. The strong interrelation between fundamental research and clinical application ensures minimal lag time to introduce new promising methods into the clinical arena. By the same token, such cooperation provides feedback to improve the effectiveness in the developmental study groups.

Development of new or improved diagnostic techniques within cardiovascular medicine is a core activity of COEUR biomedical engineering Developments range from fundamental to clinical applications:
- Improved intravascular diagnosis of the vascular wall, including morphological imaging, functional imaging and vulnerable plaque detection.
- Ultrasound contrast agents for myocardial perfusion imaging, enhanced boundary detection and local drug delivery.
- Development of ultrasound transducers for real-time 3D imaging, transoesophageal imaging and nonlinear imaging (superharmonic imaging).
- Three-dimensional imaging of the coronary arterial lumen and wall and determination of blood velocity profile. This new technique allows the study of vessel wall composition, vasomotion and arterial remodeling, wall shear stress, accuracy of stent placement as their long term functioning.
- Finally, a camera is being developed for real-time imaging of oxygenation of the myocardium during thoracic surgery.

Study topics in clinically applied imaging and diagnostics include, amongst others, the noninvasive imaging with magnetic resonance (MR) imaging and multidetector computed tomography (MSCT) of the heart, the vessels and the vessel wall (plaque composition characterization, imaging of the ‘vulnerable’ plaque). Other, more experimental imaging modalities include intravascular MR imaging, MR spectroscopy, Raman spectroscopy, optical coherence tomography and invasive temperature mapping of the vessel wall.

**THEME 4: SURGICAL-, INTERVENTIONAL- AND DEVICE THERAPY OF CARDIOVASCULAR DISEASE**


Technology for surgical, interventional and device therapy is evolving rapidly. Current emphasis is on development of vascular biological tools to improve healing after vascular injury, as well as development, validation, and evaluation of new catheter-based techniques to study and treat vulnerable atherosclerotic plaques. The research line ‘Experimental interventional cardiology’ is a typical example of the constant interplay between preclinical lab and clinical interventional cardiology.

Projects in the catheterization laboratories are aimed at finding new methods of percutaneous revascularization for patients with coronary artery disease. Acute occlusion and late restenosis are the most important current clinical problems and form the basis for clinical and experimental research. These problems are approached as follows:
- Systemic pharmacological studies;
- The testing and evaluation of new revascularization techniques;
- Improved diagnostics and imaging (optical coherence tomography, intravascular MRI, intracoronary ultrasound);
- Development and evaluation of coated stents; and
- Local drug or stem cell delivery.

Treatment of arrhythmias by ablation and/or device therapy is moving very rapidly. The department of Clinical Electrophysiology addresses the following research topics:
- Improved ablation of atrial arrhythmias with cryo-therapy
- Management of atrial fibrillation
- Evaluation of biventricular pacing in patients with impaired conduction
- Evaluation of implantable cardioverter defibrillators in patients with heart failure, including candidates for heart transplantation

The surgical projects are dedicated to clinical research in support of the introduction and development of innovative cardiac and vascular surgical techniques. The role of new ultrasound methodology (transesophageal and 3-dimensional echocardiography) is evaluated in allograft-, autograft- and reconstructive valve surgery during and after the operation. Outcomes-research focuses on the late results of mechanical valve surgery, hypertrophic cardiomyopathy, diseases of the aorta, as well as to sophisticated computer-assisted clinical decision making.

THEME 5: CONGENITAL HEART DISEASE
Prof. dr. A.J.J.C. Bogers, prof. dr. W. Helbing

Congenital heart disease results from multifactorial causes, including genetic alterations, and may lead to important structural abnormalities. These abnormalities may result in increased cardiac pressure and/or volume load, which may be accompanied by chronic hypoxemia. Abnormal loading conditions and/or chronic hypoxemia may persist after surgical therapy and/or catheter intervention. Management of congenital heart disease has improved significantly in the last decades, which has resulted in improved survival into adulthood of patients with congenital heart disease, and thus in a growing number of adult patients. Many of these patients have residual cardiac loading abnormalities, the prognosis of which is often unclear. In particular, abnormal loads are commonly imposed on the right ventricle. Residual abnormalities may cause heart failure, rhythm disturbances and may affect quality of life. Evidence based medical treatment of impending heart failure in congenital heart disease is often lacking. Guidelines for timing of catheter intervention and surgical therapy lack sufficient evidence and often are not generally accepted. The lack of evidence is in part caused by problems to assess cardiac function in the normal right ventricle and in structurally abnormal hearts with conventional imaging techniques.

The theme has the following aims:
- Increase in knowledge of the molecular basis of right ventricular failure in chronic ventricular overload and/or hypoxemia and improvement in medical therapy of heart failure in structurally abnormal hearts.
- Improvement of techniques and timing for catheter intervention and surgery.
- Improved imaging of right ventricular anatomy and function using (3D) echocardiography and MRI.
- Assessment of the long-term effects of catheter intervention and surgery in congenital heart disease, including the effects on quality of life.

THEME 6: CARDIOVASCULAR CLINICAL EPIDEMIOLOGY

During the last decades, our understanding of cardiovascular diseases has considerably increased, and major improvements have been achieved in patient management and outcome. One of the challenges for contemporary cardiovascular medicine is to rationally implement the available diagnostic tests and therapies in clinical practice, in the appropriate patients at the appropriate time (evidence-based medicine). Predictive thinking and individual risk assessment play an essential role in this respect. Before certain therapy will be initiated, a physician must consider the probability that the patient will improve or deteriorate without therapy, the chances of improvement if the therapy is initiated, the risks of adverse events due to therapy, and, last but not least, the therapy-related costs. Experience with clinical risk/benefit assessment, however, has shown that predictions can rarely be certain and need, therefore, to be qualified in probabilistic terms. The improvement of the physicians’ ability to make these predictions can be recognized as a primary motivating force behind cardiovascular clinical epidemiological research.

This theme covers projects aiming to:
- Study the short- and long-term prognosis of (subgroups of) patients with acute or chronic cardiovascular diseases in relation to applied treatment;
- Develop diagnostic and prognostic stratification models for asymptomatic individuals at suspected high risk of cardiovascular diseases, as well as for patients with established cardiovascular diseases;
- Develop clinical decision models that aim at optimal diagnostic workup and subsequent treatment of patients with established cardiovascular diseases, tailored to estimated benefits, risks and costs;
- Study the relation between the application in clinical practice of treatment guidelines and outcome in patients with established cardiovascular diseases;
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


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/knockin 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 photobleaching).

THEME 2: TRANSPLANTATION AND GENETIC MODIFICATION OF HEMATOPOIETIC STEM CELLS


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 (cured 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), 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. Raaljmakers

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 (± 300 cases) the involvement of novel, “leukemia disease” genes identified by retroviral insertional mutagenesis. Novel disease genes based on the mouse and primary AML screen and, which predict unique disease 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**


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


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 hematopoietic 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, Gentuzumab 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 hemat-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


‘Cancer develops through an accumulation of (epi) genic alterations. The selection of cells with crucial defects allows survival and growth advantage. This ultimately 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, that is the ultimate threat to the patient, as is therapy failure.’

Our successful discovery of predictive markers 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 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 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, i.e. 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 breast cancer which will lead to tailored treatment of patient with cancer. As a consequence the program covers a range of programs from basic to clinically applied research.

Research programs:
- Translational Pharmacology (E. Wiemer, W. Loos, R. Mathijssen, R Debets, J. Verweij)
- Palliative and Supportive care (K. v der Rijt)

The Department of Medical Oncology (see website for actual research and teaching programs) 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, Gynaecologist

Are hormonal and reproductive factors associated with the risk of ovarian- and other hormone-related cancers in later life? Are 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 of women and offspring have limited previous studies of fertility treatment.

The Dutch study OMEGA is a large-scale nation-wide historical cohort study of 19,840 women diagnosed with subfertility problems between January 1st 1980 and January 1st 1995 (follow up 15-30 years) identified in all twelve IVF hospitals that have legal permission to provide IVF-treatment in the Netherlands. The control group consists of 6,558 subfertile women 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.

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.

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

Research theme 1. ‘Hormonal stimulation treatment and women, and health in later life
A. Ovarian cancer and other hormone-related cancers.
B. Cardiovascular disease and metabolic syndrome
C. Menopause

Research theme 2. ‘Hormone exposure and health and disease risk in later life
A. Reproductive health and capacity
B. Cardiovascular disease and metabolic syndrome
C. Hormone-related cancers

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6. Pediatric Research

**THEME 1: CHILDHOOD ASTHMA - A MULTIFACETED DISEASE. THE PIAMA AND GENERATION R BIRTH COHORTS**

Prof. dr. J.C. de Jongste (Erasmus MC-Sophia), dr. H.A. Smit (RIVM), B. Brunekreef (Institute for Risk Assessment and Julius Center, University of Utrecht)

The PIAMA (Prevention and Incidence of Asthma and Mite Allergy) study was initiated in 1996. Over 4,000 subjects were enrolled, making the PIAMA study one of the largest asthma/allergy birth cohorts with almost 90% follow-up until age 8. The cohort has been followed for 8 years because only at that age, a reliable diagnosis of asthma and allergy is possible. Data have been collected on asthma and allergy endpoints on a yearly basis using questionnaires, and in sub-populations with objective measurements at ages 1, 4 and 8. Data have been collected on a wide range of environmental, dietary and lifestyle exposures, using yearly questionnaires in the full cohort, and using measurements of indoor and outdoor pollutants in large subpopulations. This will allow us to identify novel prevention strategies that are applicable in usual health care settings in the Netherlands, by systematically evaluating the extent to which combinations of simple questionnaire items can be used to identify high-risk groups; and predict the development of asthma and allergy over an 8-year period.

The ‘Generation R’ birth cohort study has enrolled almost 10,000 children, who are being followed from early pregnancy into adulthood. At present, the cohort is 5-6 years old. The multidisciplinary Generation R study includes a broad scope of projects, and covers the normal and pathological development of children’s physical and psychological maturation. Important focus is early determinants of disease, including asthma and allergy. Children undergo extensive examinations including lung function and exhaled nitric oxide at 5 years. Some specific research questions that are presently being addressed are:

- Which (combinations of) modifiable risk factors or protective factors are the most promising targets for prevention?
- What are the determinants and the predictive value of exhaled nitric oxide, a noninvasive marker of asthmatic airway inflammation in asthma?
- What are the genetic factors associated with the asthmatic/atopic phenotype?
- What is the effect of air pollution on respiratory symptoms in early childhood?

In addition, separate research lines focus on life style determinants of health and disease, and on the interaction of genetic and environmental factors in the pathogenesis of disease. For a NIHES fellowship, a suitable question will be selected and analysis performed of existing databases, for PIAMA in close co-operation with the dept. of epidemiology and public health of the RIVM and the Institute of Risk Assessments (IRAS) of Utrecht University.

**THEME 2: CLINICAL DECISION-MAKING IN PEDIATRIC EMERGENCY CARE**

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. Hardly any research, however, has been performed on the validity in pediatric patients.

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 ongoing study, data on triage, initial patient evaluation, diagnostics, treatment and follow-up are available for nearly 20,000 children.
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?
- What is the balance between over and under-triage compared to the reference standard?
- How can we modify the system for pediatric patients at the emergency department?

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 in this ongoing study?
- What is the actual impact of the implementation of clinical decision rules with the use information technology (clinical decision support system) in clinical practice.

THEME 3: BIOLOGICAL DETERMINANTS OF LEUKEMOGENESIS AND OUTCOME AND DEVELOPMENT OF TARGETED THERAPIES IN CHILDHOOD LEUKEMIA


The pediatric oncology research program has the following aims:
- Developing clinically and biologically relevant classification of leukemia. This is done by genome-wide screening techniques on DNA level (array CGH), gene expression profiling and microRNA profiling and protein profiling of serum, cerebrospinal fluid and leukemic cells.
- Especially the role of gene silencing of tumor suppressor genes by methylation is analysed.
- Identification of molecules associated with chemotherapy resistance. New resistance genes are identified by comparing gene expression profiles of therapy resistant and sensitive patients, which is confirmed by other techniques. New strategies to modulate the effects of these resistance genes are developed by functional studies.
- Identification of new therapeutic targets and development of new treatment strategies for children with cancer. New targets are identified and confirmed by techniques described above in specific subgroups of patients. This is followed by validation studies to define the effect of inhibition of the target genes, a.o. by RNA interference. The efficacy of new drugs directed against these targets are tested in preclinical models.
- Following this preclinical phase, new drugs are tested in 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.
- The clinical part of the program includes also: (1) Phase III studies in pediatric oncology; (2) Improvements in supportive care, essential because of the intensive treatment; (3) Late effects of treatment, important because of the quality of life with the improved cure rate (70%) of childhood cancer.

The ultimate goal of the research program is to develop targeted therapies for children with cancer. This should lead to more effective and less toxic treatment strategies. The program is mainly directed to children with leukemia but also to brain tumors and solid tumors.

THEME 4: 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*, Dr. N. Exalto, Prof.dr. J.S.E. Laven, Prof. dr. E.A.P. Steegers
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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 the 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 subfertility, congenital malformations, miscarriages, pre-eclampsia, fetal growth restriction and low birth weight.

Studies: To investigate this topic, we started in November 2010 the new Predict Study. In this periconception birth cohort study 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 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 designing 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.


THEME 1: 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, 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:
A) What are the effects of preconception lifestyles (interventions; M-health tool www.SlimmerZwanger.nl), environmental exposures and genes on:
   a1) the causes of subfertility
   a2) the fertility parameters: semen, oocyte and embryo quality
B) What is the influence of grandparent health on fertility of their children?
C) Prediction of fertility outcome parameters with the Rotterdam Reproductive Risk Score (R3-score).
**THEME 2: 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 (SPINABIFIDA 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:
A) What are the effects of periconception lifestyle (intervention; M-health tool www.SlimmerZwanger.nl), environmental exposures and genes on:
   a1) the occurrence of congenital malformations determined by ultrasound examination?
   a2) the DNA methylation patterns in offspring and in several tissues?
B) What is the influence of the grandparent health on the risk of congenital malformations in their children?
C) Prediction of the risk of the 4 congenital malformations with the Rotterdam Reproductive Risk Score (R3-score).

**THEME 3: 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:
A) What are the effects of periconception lifestyle (interventions; M-health tool www.SlimmerZwanger.nl), environmental exposures and genes on:
   a1) first trimester growth (embryo, fetus, yolk sac, placenta) determined by repeated ultrasound measurements?
   a2) pregnancy complications (miscarriage, placental related vascular diseases, IUGR, low birth weight etc.)?
   a3) the DNA methylation patterns in offspring and in placental tissue?
B) What is the influence of the grandparent health on the risk of maternal and perinatal complications in their (grand)children?
C) 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 subspecialities in Urology (oncology, functional urology, andrology, pediatric urology, stone disease). Each of these subspecialities 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 Luider, 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 BLA DDeRS

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:
- Donor specific effector mechanisms and immune tolerance
- 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-g 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-1a, 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+CD25+brightFoxp3+ 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 immuno therapy.
- Studies to unravel the mechanism by which the immune system via cytokine pathways trigger graft acceptance. Furthermore, trails 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 E.J. Kuipers, 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
Prof. dr. H.L.A. Janssen, 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.
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 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
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 (R(E)search 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 centres 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 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; lean 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 GPs 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 PTAs.
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 Agatson-score, calcium mass and volume. Multiple studies show the Agatson-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 of 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 thoracic 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: ASSESSMENT OF LIFESTYLE INTERVENTIONS**

Dr. Sandra Spronk, 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 8: 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 extent 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 9: 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, borderlin 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 10: 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 also be conducted.

The student 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-authorship. Minimally 1 publication as first author will be guaranteed.

THEME 11: 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 12: 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 nation wide 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 13: EFFICACY OF RFA IN THE TREATMENT OF LIVER TUMORS
Prof. dr. J.N.M. IJzermans (Hepatobiliary 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 radiofrequency 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 14: 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 kind of interventional of 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 en 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 15: 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 live 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 can not 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 ultrasound 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 patient 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 16: 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 disorder, 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 report 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 cooperation 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:
- Back and pelvic pain
- Hip- and knee disorders
- 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 mechanisms 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 studies.

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 i) enhance reliable measurements with MRI of tissue changes over time in (early) osteoarthritic joints, by validation of quantitative scores that will be developed; ii) quantify pathological characteristics of tendon in the hand; iii) find pathological characteristics that can be used to identify the status of osteoarthritis; iv) 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 en 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 tumour 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 ambulatory patients to other medical disciplines for outpatient or inpatient care. these GPs and its environment. 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 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 ambulatory patients to other medical disciplines for outpatient or inpatient care. these GPs and its environment. 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 ambulatory patients to other medical disciplines for outpatient or inpatient care. these GPs and its environment. 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 ambulatory patients to other medical disciplines for outpatient or inpatient care. these GPs and its environment. 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 ambulatory patients to other medical disciplines for outpatient or inpatient care. these GPs and its environment. 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 ambulatory patients to other medical disciplines for outpatient or inpatient care. these GPs and its environment. 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 ambulatory patients to other medical disciplines for outpatient or inpatient care. these GPs and its environment. 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 ambulatory patients to other medical disciplines for outpatient or inpatient care. these GPs and its environment. the GPs address approximately 90% of the medical problems presented to them. The information systems of

**THEME 3: BIOSEMATICS**  
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 area focuses on the etiology of neuro-degenerative and cerebrovascular diseases, including dementia and Alzheimer’s disease, Parkinson’s disease, stroke and cerebral white matter lesions. The research emphasizes the role of vascular factors in the etiology of these diseases, with use of state of the art neuroimaging techniques.

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, screening of asymptomatic individuals to identify and treat those with high CVD risk and screening and treatment of abdominal aortic aneurysms. The studies performed include systematic reviews and meta-analyses, prediction rules, 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, and to estimate prognosis on the basis of 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: RISK FACTORS FOR CORONARY HEART DISEASE AND HEART FAILURE
Prof. dr. Jacqueline C.M. Witteman

Cardiovascular epidemiologic research focuses on the determinants of atherosclerosis and coronary heart disease in the elderly, and on cardiovascular diseases in women. The research is based on the Rotterdam Study and addresses inflammation markers and hemostasis as determinants of cardiovascular diseases in the elderly, and the effects of menopause, endogenous hormones and hormone replacement therapy in women.

THEME 5: CARDIOVASCULAR EPIDEMIOLOGY GROUP (WITHIN THE DEPARTMENT OF EPIDEMIOLOGY, ERASMUS MC)
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 are exported from the laboratory to the epidemiology field, allowing population-based studies 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 subclinical atherosclerosis and endothelial function in cardiovascular risk prediction.

THEME 6: 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 7: FETAL AND CHILDHOOD GROWTH, DEVELOPMENT AND HEALTH: THE GENERATION R STUDY
Dr. Vincent W.N. Jaddoe, coordinator, Departments of Pediatrics and Epidemiology & Biostatistics, prof. dr. Albert Hofman, Department of Epidemiology & Biostatistics, prof. dr. Johan P. Mackenbach, Department of Public Health, prof. dr. Henriette A. Moll, Department of Pediatrics, prof. dr. Eric A.P. Steegers, Department of Obstetrics & Gynecology, prof. dr. Frank C. Verhulst, Department of Child & Adolescent psychiatry

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 multilethnic 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). A few subthemes are mentioned below.

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

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 on obesity. We also study risk factors of pregnancy complications in mother and child, such as preeclampsia and preterm birth. Research is performed in close 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 — the Generation R birth cohort**

Prof. dr. J.C. de Jongste, drs. C. Gabriële prof. dr. H.A. Moll

‘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. The Generation R Study**

Prof. dr. H.A Moll, Prof A van Belkum, Prof H Hooijkaas

Several bacterial species including Staphylococcus aureus, Streptococcus pneumoniae, Moraxella catarrhalis and Haemophilus influenzae are bystander residents of the healthy nasopharynx and can be the cause of morbidity (e.g. acute otitis media) in children. The prevalence and patterns of bacterial carriage changes dramatically in the first years of life. S. aureus carriage decreases, while the prevalence of S. pneumoniae, M. catarrhalis, H. influenzae increases. Adhesion to mucosal receptors, host immunity and exposure have been implicated in colonisation. Detailed information, however, on colonisation dynamics during the first years of life is consistently missing. Environmental factors as well as host characteristics might influence the risk of being colonized in childhood. The relation between active colonisation, local bacterial interference, the local and systemic host (immune) response to these colonising agents and frequency and severity of paediatric infectious diseases is not conclusively determined.

This study is embedded in the Generation R Study, a population-based prospective cohort study from fetal life until young adulthood and the first longitudinal study assessing microbial colonisation in concert with infections in young children. Because of limitations in available vaccines, new strategies to prevent infectious diseases must be developed.

**Aim:**
This project aims to study bacteriological and immunological determinants of nasopharyngeal carriage of S. aureus, S. pneumoniae, M. catarrhalis and H. influenzae in young children and to assess their consequences for infectious diseases. The following specific research questions will addressed:
- What are the environmental and host determinants of bacterial colonisation of the nasopharynx?
- What is the role of interference between the major pathogenic bacterial species and their genetic variability in the dynamics of colonisation?
- What is the relation between colonisation, host immune response and infectious diseases in young children?

Clinical and scientific relevance for the future: This project will contribute to the detailed understanding of the immunological and bacterial determinants of carriage and infections in young children and hence facilitate development of future preventive strategies.

**Subtheme 4: Behavioural and cognitive research in young children: The Generation R Study**

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 8: ASSESSMENT OF INTEGRATIVE MEDICINE
Dr Ineke vd Berg, 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, and relaxation. Patients actively participating in their health care and healing process have a better prognosis and a better quality of life.

THEME 9: 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.

In addition to these health sciences activities, the department has an experimental research branch focused on dermatological immunology and inflammatory pathways in psoriasis. The Center for Optical Diagnostics and Therapy (COT) 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. Esther de Vries, drs. Loes Hollestein, drs. Sophie Flohil, Prof. dr. Jan Willem Coebergh, 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. Currently, we are approaching cancer survivors for more detailed information to expand our research activities.

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.


Introduction
Of the approximately 30,000 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 wit 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
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.

C. Risk factors of intrinsic and extrinsic skin aging
Drs. Leonie Jacobs, dr. Fan Liu, Prof. dr. Manfred Kayser, 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 skin aging
Identification of common variants associated with skin aging

Methods:
This research theme is part of Netherlands Consortium of Healthy Aging (NCHA) and at the Erasmus MC it is a collaboration between dermatology and molecular forensic biology. 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. Esther de Vries, 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. The 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.

Methods:
This is primarily a postal survey to cancer survivors registered in the Dutch cancer registry. 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.
Drs. Loes Hollestein, Prof. Ron Herings, Prof. dr. Bruno Stricker, 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. Ellen de Haas, drs Kai Munte, dr. Dominic Robinson, Prof. dr. Martino Neumann

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 trails 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.

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 C00T 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.

H. Photodynamic therapy for the treatment of skin (pre)malignancies
Dr. Dominic Robinson, dr. Riette de Bruijn, Prof. dr. Dick Sterenborg, dr. Ellen de Haas

Photodynamic therapy (PDT) is a well established therapy for non-melanoma skin cancer and its pre-malignancies. It is based on the administration
of a photosensitiser (or a pre-cursor) and a subsequent illumination with visible light. In dermatology PDT normally utilizes topical porphyrin pre-cursors such as aminolevulinic acid (ALA) and its esters. Pre-clinically we are investigating the mechanisms of action underlying the response to PDT in skin (pre-) malignancies with the goals of optimizing efficacy, maximizing patient satisfaction and extending the use PDT to a wide range conditions in the skin and other associated organs. We are developing photosensitisers and photosensitiser formulations based on the use of nanotechnology to actively target cells and tissue and avoid damage to and the prolonged photosensitivity in normal skin.

I. Optical Spectroscopy and skin (pre-)malignancies
Dr. Arjen Amelink, dr. Dominic Robinson, Prof. dr. Dick Sterenborg

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
Dr. Emmilia Dowlatshahi, 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 obcardiovascular events.

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 psoriasis
Dr. Bing Thio, Prof. dr. Errol Prens, dr. Tamar Nijsten

Introduction:
Psoriasis is a chronic inflammatory skin disease that affects 2% of the population. It affects people life's substantially and requires life long therapy. About 10% of psoriasis patients require phototherapy and/or systemic therapy. In addition to conventional systemic drugs, recently, the biologics have been introduced in the treatment of psoriasis.

Aims:
evaluate new psoriasis therapies in fase IIb and III clinical studies
evaluate the effect of fumaric acids in the treatment of psoriasis.
evaluate daily practice effectiveness

Methods:
We participate in many international fase III RCTs evaluating new drugs coming to the market. Also, we have several investigator initiated clinical studies that, for now, focus on the effectiveness of fumaric acids. This drug is not registered in The Netherlands, but is very effective in reducing psoriasis severity. We are involved in the process of registering this drug. We are also setting up a patient registry of psoriasis patients treated with systemic therapy to evaluate daily clinical practice data and long term safety. This registry is being set up in collaboration with Nijmegen and Amsterdam.
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, 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
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.
15. Genetic Epidemiology

Our understanding of the structure of the 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 genes in the etiology of disease. Examples of these 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, students 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 students 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.

THEME 2: CLINICAL AND PUBLIC HEALTH GENOMICS
Dr. A. Cecile J.W. Janssens,

Multifactorial diseases such as type 2 diabetes, osteoporosis, and cardiovascular disease are caused by a complex interplay of many genetic and nongenetic factors, each of which conveys only a minor increase in the risk of disease. Enormous progress in the identification of susceptibility genes is currently made and novel developments are expected from the large-scale genome-wide association studies (see Theme 1: Gene discovery). One of the greatest promises is that the unravelling of the genetic origins of common diseases will lead to individualized medicine, in which prevention and treatment strategies are personalized on the basis of the results of predictive genetic tests. The question however is: How predictive is our DNA?

Research in clinical and public health genomics investigates the potential for applications of genetic testing in preventive and clinical health care. Examples of research questions include: how good can recently discovered type 2 diabetes genes predict the disease in individuals who have no symptoms? Do genetic polymorphisms have added value in the prediction of cardiovascular disease beyond traditional risk factors as blood pressure, cholesterol level and smoking? What is the scientific basis of the genomic profiles (genetic tests that consider more than one gene) used to assess health risks and personalize health interventions that are offered by companies via the internet? Projects on clinical and public health genomics are conducted within the clinical epidemiology research group.
16. Public Health

THEME 1. HEALTH BEHAVIOUR AND HEALTH PROMOTION
Dr. Carlijn Kamphuis, dr. Frank 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 lead 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 behaviour, 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 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. 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, 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-Sahara Africa (worm infections and HIV/AIDS), China (SARS and avian influenza), Bangladesh (leprosy) and Indonesia (tuberculosis). 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’s 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.

Recent Examples of public health research that have impact in practice

Our section is partly responsible for the continuing follow-up of the European Study of Screening for Prostate Cancer. As many of the tumours that are detected by prostate cancer screening have a relatively benign character (indolent cancers), the question is when is treatment necessary, and when can treatment be replaced by active surveillance or watchful waiting. A model was developed to predict indolent cancer, based on characteristics that are available before surgery. This model may help to distinguish the indolent cancers from the aggressive ones for which immediate treatment is the best option.

In 2006, implementation trials have started in the Netherlands for colorectal cancer screening. We will use the simulation model Miscan to conduct a cost-effectiveness analysis that will support decision makers in their choice concerning various screen tests and screening frequencies. Recently, a...
new test has been developed to identify the DNA of developing cancer in a person’s stool. This test is considered for reimbursement by the Centers for Medicare & Medicaid Services in the USA. We were asked to determine the costs at which this test is a cost-effective alternative to currently recommended tests in the USA. We helped develop an interactive website to assist policymakers. The site provides a modeling tool that projects future trends in colorectal cancer mortality and evaluates how alternative cancer control strategies may affect future mortality trends.

Ongoing projects:
- Evaluation of the nation-wide breast cancer screening programme in the Netherlands
- Prospective cohort study of MRI-screening for women at high risk for breast cancer and cost-effectiveness
- Full information for informed participation in breast and cervical cancer screening
- National evaluation of cervical cancer screening in the Netherlands
- Quality of life evaluation in cervical cancer screening
- Cost-effectiveness of HPV-vaccination in the Netherlands
- Prevention of cervical cancer by vaccinations against human papillomavirus (HPV); parental intention and uptake of HPV-vaccinations in adolescents
- Dutch-Belgian randomised controlled lung cancer multi-slice CT screening trial
- Smoking cessation in lung cancer screening
- Genetic screening policy model for colorectal cancer
- Effects and cost-effectiveness of colorectal cancer screening with different fecal occult blood tests
- Quality of life and informed decision making in lung cancer screening
- European Randomized Study for Screening on Prostate Cancer (ERSPC)
- Implementation of compliance improvement methods in amblyopia prevention
- A new programme for prenatal screening for Down’s syndrome in the Netherlands: informed participation and non-participation
- Screening on child abuse at emergency departments, implementation of an optimal protocol CISNET: Colorectal Micro-simulation modelling
- CISNET: Modeling breast cancer incidence and mortality in the USA; the spectrum of disparities
- CISNET: A trial-based Miscan model for prostate cancer screening
- CISNET: Surveillance of Lung Cancer Trends in the U.S. with MISCAN.

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 predictive 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 cost-effectiveness analysis, where we consider the balance between costs and health impact of an intervention compared to an alternative. 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), surgical interventions, and acute diseases (e.g children presenting at the emergency department, patients with brain injury). The research is done in close collaboration with various clinical groups at Erasmus MC.
**THEME 6: OCCUPATIONAL HEALTH**
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. There is a clear need to evaluate health interventions among workers for their long-term effects on work participation and occurrence of disabling diseases. We seek interested students to conduct a health impact assessment on primary preventive interventions, using spreadsheet tools to model the potential gains in health and labour force participation. These assessments will be use to prioritize health management in occupational populations. As part of the project we anticipate to conduct some feasibility tests of the developed models in several companies.

**THEME 7: CANCER SURVEILLANCE**
Esther de Vries PhD (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, cancer among migrants), Prof Jan Willem Coebergh MD PhD 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
- gastrointestinal 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**
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**
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.
Colophon

Editing
Dr. Astrid Vrakking

Design and layout
Bureau mdm.

Publication
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