MolecularMedicine (MM)

Clinical and experimental neuroendocrinology
Regulation of calcium and bone metabolism
Regulation of the bioactivity of thyroid hormone
Signalling in reproduction and ageing
Localisation, detection and radionuclide therapy of various diseases
Regulation of follicle development, oocyte and endometrial embryo quality
Pathophysiology of pediatric endocrine, metabolic and renal diseases
Malignant transformation of hematopoietic stem cells: pathophysiology and development of therapy
Hematopoiesis: regulation of the proliferation and differentiation of hematopoietic progenitor cells
Molecular determinants of therapy response and outcome in childhood cancer
Lymphoid differentiation and immunodeficiencies
Immune regulation and autoimmunity
Diagnosis, classification and treatment evaluation of leukemias and malignant lymphomas
Solid tumors between bench and bed
Molecular Medicine (MM)

Improving accuracy and therapeutic ratio in radiation oncology
Hyperthermia: a treatment for cancer
Photodynamic therapy
Neuro-oncology and pain
Pathophysiological aspects and treatment of gastro-intestinal diseases
Surgical trauma and the development of tumour recurrence
Innovative tumor model development/tumor vasculature/tumor targeting/locoregional control
Clinical and experimental aspects of urological tumors
Gynaecological oncology; basics, epidemiology and clinical aspects
Developmental biology; pathophysiology of the newborn
Experimental therapeutical approaches in inflammatory dermatoses and cutaneous oncology
Tumour endocrinology, genetics, prognostic factors and experimental therapy of cancer
Biological and clinical aspects of drug-resistance and -sensitivity of malignancies
Clinical and experimental immuno(-gene) therapy
MolecularMedicine (MM)

Neoplastic lesions and chronic inflammation of the gastrointestinal tract
Liver-specific immunopathology; mechanism and therapeutic modulation
Human virus infections: immunity, therapy and epidemiology
Infections due to bacteria, fungi and parasites: diagnosis, molecular mechanisms, epidemiology, therapy and prevention
Clinical research in infectious diseases in adults
Renal insufficiency and organ transplantation
Cell biological and pathophysiological investigations on pulmonary diseases
Neuromuscular and degenerative diseases of the nervous system
Organ transplantation
Genitourinary tract disorders in children
Disorders of the gastrointestinal tract in childhood
Clinical, epidemiological and basic research of infectious diseases and immunological diseases in children
Sexually transmitted diseases
**Programme design in brief**

A. Studies on the regulation of hormone secretion by the normal pituitary gland as well as by human pituitary tumours in vivo and in vitro.

B. An integrative approach to the endocrinology of ageing. Hormonal factors related to the ageing process are investigated in population studies. Intervention studies with hormones (growth hormone, dehydroepiandrosterone) are carried out.

C. An integrative approach to factors determining glucocorticoid sensitivity in man. Molecular studies of mutations in the glucocorticoid receptor and in the translational regulation of glucocorticoid action are carried out in cells obtained from patients with glucocorticoid resistance and from patients with transient changes in glucocorticoid sensitivity.

D. Studies on the expression of peptide receptors in cancer, and in immune cells. The regulation of the growth and activity of immunological and of tumour cells in vitro by manipulation of the expression of peptide receptors is studied in relation with the potential endocrine manipulation of immune diseases and cancer growth in vivo.

E. An integrative approach of clinical and surgical endocrinology is used in studies aimed at improving patient care.

F. Evaluation of the (metabolic) role of natural and synthetic growth hormone secretagogues in peripheral tissues in vitro and in vivo.

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**Key figures**

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**Theses**


**Article/Letter to the editor**


Part of book - abstract


EMC MM-01-39-02 - Regulation of calcium and bone metabolism

Programme design in brief
Research focus is skeletal and calcium homeostasis and development and progression of related disorders with particular emphasis on ageing. Increasing life span is accompanied by an increase in age-related diseases such as osteoporosis. Osteoporosis is an important common disease with a large impact on quality of life as well as health care budget. Development of pharmaceutical and life style interventions as prevention or as treatment is important and requires an optimal knowledge in aetiology and mechanisms of development of osteoporosis. Current therapies for osteoporosis are directed to inhibit bone loss and thereby its progression. There is, however, a major need for anabolic therapies which stimulate bone formation because bone loss has already occurred when the consequences of osteoporosis have become overt. Directly coupled to this improvement in early diagnostics. The overall aim of this research line is to develop better diagnostics and therapies for skeletal disorders and disturbances in calcium homeostasis by a combination of molecular, cellular, animal, epidemiological and eventually clinical studies. Four integrated lines of research can be identified
1) Characterisation of molecular mechanisms of bone cell differentiation and bone formation and degradation using human bone cell models by bioinformatic and systems biological analyses of gene, protein and enzyme activity profiles
2) Identification of risk determinants for osteoporosis and osteoarthritis on basis of genetic epidemiological and serum proteomic studies within a.o. the Rotterdam Study
3) Calcium homeostasis and skeletal metabolism in relation to ageing by analyses of experimental animal models, e.g. premature ageing mice, as well as human population research.
4) Development of medium/high throughput screenings procedures to quickly screen therapeutic targets and to evaluate novel therapeutic compounds

Key figures

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Theses
Velde, N. van der (2007, mei 23). Falls in old age: pills, the heart and beyond; Withdrawal of drugs and screening for cardiovascular causes in older fallers. EUR. Prom./coprom.: Prof.Dr. B.H.C. Stricker, Prof.Dr. H.A.P. Pols & T.J.M. van der Cammen.


Article/Letter to the editor


Patent
EMC MM-01-39-03 - Regulation of the bioactivity of thyroid hormone

Programme design in brief
The prohormone T4 is converted by outer ring deiodination to the active hormone T3 and by inner ring deiodination to the inactive metabolite rT3. The three deiodinases (D1-3) involved are expressed in different tissues, where they play different roles in systemic and local control of T3 levels. The deiodinases are located in cell membranes with their active site exposed to the cytoplasm, while the T3 receptors reside in the nucleus. Uptake of thyroid hormone across the plasma membrane is thus required for thyroid hormone action and metabolism, and is mediated by specific transporters. Recently, our group identified an important T3 transporter (MCT8) which was shown to be mutated in patients with severe psychomotor retardation and grossly elevated serum T3 levels. This project concerns the characterization of the deiodinases and transporters in human tissues as well as their importance in the regulation of the bioactivity of thyroid hormone in health and disease.

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Article/Letter to the editor


Programme design in brief

Glycoprotein hormones and members of the TGFβ/activin family of growth and differentiation factors play a central role in development and functioning of the organism throughout life. This program focuses on the effect of variations in signal transduction of glycoprotein hormones (including LH, hCG, FSH and TSH) and TGFβ family members (including anti-Mullerian hormone, BMPs, inhibins and activins) during foetal and postnatal development and subsequent ageing of the organism. Furthermore, effects of mutations or single nucleotide polymorphisms in enzymes involved in biosynthesis or catabolism of steroid hormones are investigated.

Variations in signalling through these pathways affect the early make-up of physiological response systems that can have effects during adult life and in the ageing process. Signal transduction variations of ligand-receptor interaction, signal transduction, gene expression, proliferation and apoptosis are studied not only at the molecular and cellular level, but also at the level of the whole body in animal models of ageing and in populations of ageing men and women. Specific areas are:

1. The role of TGFβ family members in female ageing, oestrogen effects and age at menopause
2. The role of LH and LH receptor variations in female ageing
3. The influence of polymorphic gene variants in female and male physiology
5. Causes and effects of changes in steroid biosynthetic pathways
6. Evaluation of the (metabolic) role of natural and synthetic growth hormone secretagogues in peripheral tissues in vitro and in vivo

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Article/Letter to the editor


Part of book - abstract


Localisation, detection and radionuclide therapy of various diseases

Programme design in brief
Detection of disease:
(Pre)clinical development and use of radiolabeled pharmaceuticals (e.g. peptides, anti-sense molecules, 18F-deoxyglucose (FDG)) to localize and detect various diseases (e.g. tumour and heart imaging). Comparison of results with those of conventional imaging modalities (e.g. MRI, CT, US) and cost-benefit analyses. Investigation of predictive value of scintigraphy for success of various treatment modalities, e.g. unlabelled peptides versus cytostatic drugs.

New radiolabelled peptide-analogues, such as of Bombesine, CCK, Substance P, neurotensin and adhesion molecules have been introduced for lesion visualization. As tumour cells have receptors on their surface for different peptides, many receptor-positive tumours may then be localized, possibly followed by therapy with unlabelled compound or by radionuclide therapy.

Treatment of disease:
As a new modality of cancer treatment, we introduced radionuclide therapy of somatostatin receptor-positive lesions by repeated administration of chelated somatostatin analogues (octreotide, [Tyr3]octreotide, [Tyr3]octreotate) radiolabelled with high doses of therapeutic radionuclides, like the auger electron emitter 111In, the high energy beta particle emitter 90Y and the low energy beta particle emitter 177Lu. Different phase1 studies have been started on radionuclide therapy of human tumours using these radiolabelled peptide analogues.

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Theses


Article/Letter to the editor


Part of book - abstract


EMC MM-01-52-07 - Regulation of follicle development, oocyte and endometrial embryo quality

Programme design in brief
General objectives: The ability of a primordial follicle to undergo folliculogenesis constitutes the very foundation of the expression of the menstrual cycle. During its growth important changes occur within the oöcyte, as well as in its granulose- and theca-cells. These changes include proliferation, differentiation and as well as growth and apoptosis. Hormones (steroid as well proteins) and growth factors control the early (gonadotropin-independent) and late (gonadotropin-dependent) follicle development. Regulation of follicle recruitment and dominant follicle selection as well as ovarian dysfunction is studied in the human model both in vivo and in vitro using morphometric, molecular and genetic techniques.

Clinical studies involve a) Genetic (genotype - phenotype association) and environmental determinants of anovulatory infertility, especially polycystic ovary syndrome (PCOS) and premature ovarian failure (POF). b) Development of new ovulation induction strategies and optimization of fertility treatment and outcome in patients with ovarian dysfunction. c) Prevention of long-term health implications of reproductive, metabolic and cardiovascular components of ovarian dysfunction especially PCOS and POF. d) Gamete and embryo quality using genetic (preimplantation genetic aneuploidy screening) and molecular techniques in subfertile patients as well as in patients with anovulatory dysfunction.

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Theses

Article/Letter to the editor


Programme design in brief

Human growth and development including sexual differentiation and puberty and individual organ systems such as the kidney and bone are regulated by the concerted action of a large number of endocrine, paracrine and autocrine factors. This programme aims at:

a. Studying normal growth and development and the role of growth hormone and growth factors in congenital and acquired growth disorders by means of epidemiological investigations and clinical trials as well as laboratory studies using various in vitro techniques.

b. Long term goals are to unravel in molecular detail the factors involved in the etiology of type 1 diabetes. We want to develop techniques to predict and prevent this disease, eventually applicable in the general population. Immunological, genetic and beta-cell factors are studied. These aims and goals should allow to develop concomitant strategies to cure or improve the current treatment of those who have already developed the disease. The search for the pathogenesis of type 1 diabetes mellitus the optimal treatment and ultimately its prevention is highly relevant for longterm morbidity, prognosis and socioeconomic consequences at adulthood.

c. Studying normal and abnormal renal development as well as therapeutic options by means of multicenter clinical trials.

d. Studying intermediary metabolism of patients with inborn errors of aminoacids, organic acids, lipids and defects of cellular organelles, some of them by newborn screening. Development of therapeutic options by dietary intervention or enzyme replacement therapy in nationwide and international collaboration. Special attention is focused on congenital defects of glycosylation, a recently detected group of inborn errors.

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Theses


Vorst, M.M.J. van der (2007, juni 07). Optimal furosemide therapy in critically ill infants. EUR. Prom./coprom.: Prof.dr. A.J. van der Heijden & Prof.Dr. D. Tibboel

Article/Letter to the editor


Part of book - abstract

Other output
EMC MM-02-41-03 - Malignant transformation of hematopoietic stem cells: pathophysiology and development of therapy

Programme design in brief
In this project we investigate abnormalities in the cellular responsiveness to hematopoietic growth factors, the expression, structure and function of hematopoietic growth factor receptors as well as alterations of signal transduction and transcription that may contribute to the development of hematological malignancies. The abnormalities may influence the survival, cell cycle regulation, commitment or maturation of hematopoietic progenitor cells. The investigations on the genetic abnormalities of hemato-oncologic diseases extend towards the development of a specific diagnosis and the detection of minimal residual disease, as well as new therapeutic interventions of hematological malignancies. With respect to the development of new treatment strategies aimed at eradicating malignant hematopoietic progenitor cells, we address questions related to their sensitivity to chemotherapy, the response to novel drugs that target specific genes and the clinical development of stem cell transplantation. The modalities are explored in relevant animal models as well as in clinical studies.

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Theses
Broers, A.E.C. (2007, november 28). Interleukin-7 and hematopoietic stem cell transplantation: beyond the thymus. EUR. Prom./coprom.: Prof.Dr. J.J. Cornelissen & Prof.Dr. B. Lowenberg.

Holt, B. van der (2007, september 21). Translational studies in elderly patients with acute myeloid leukemia. EUR (153 pag.). Prom./coprom.: Prof.Dr. P. Sonneveld & Prof.Dr. B. Lowenberg.


Article/Letter to the editor


melphalan compared with myeloablative treatment in multiple myeloma: long-term follow-up of the Dutch cooperative group HOVON 24 trial. Haematologica, 92(7), 928-935.


EMC MM-02-41-04 - Hematopoiesis: regulation of the proliferation and differentiation of hematopoietic progenitor cells

Programme design in brief
In this program we investigate the regulation of blood cell formation, i.e. hematopoiesis, in health and disease. Hematopoiesis is differentially regulated at the levels of primitive stem cells and more differentiated progenitor cell subsets and we study specifically the intrinsic characteristics of hematopoietic stem/progenitor cells and the extrinsic interactions with cells of the tissue microenvironment. The studies on intrinsic characteristics of stem/progenitor cells include the analysis of genetic determinants that control replication, replicative senescence, differentiation commitment, maturation, cellular dependence on humoral and stromal regulators and expression of specific hematopoietic growth factor receptors and differentiation specific genes. The focus of the experimental stem cell transplantation program is on improving immune reconstitution and induction of allo-antigen specific tolerance following transplantation. Specific projects deal with the development of tools and conditions that allow efficient gene transfer into the most primitive stem cells with long-term in vivo repopulation ability, eventually for the development of gene therapy, presently focused on inherited disorders, including immunodeficiencies, inherited anemias and metabolic diseases.

In direct connection to the studies on hematopoiesis in healthy circumstances, the program has a focus on hematopoiesis in disease conditions. These diseases are characterized by quantitatively insufficient hematopoiesis resulting from disturbances at intrinsic or extrinsic levels of regulation in stem/progenitor cells. Conditions studied include idiopathic and congenital neutropenia and accelerated aging of stem cells following cytotoxic treatment. Models that include transgenic mice and subhuman primates have been developed to allow for the dissection of these conditions at the molecular level.

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Theses

Article/Letter to the editor


EMC MM-02-54-03 - Molecular determinants of therapy response and outcome in childhood cancer

Programme design in brief
This translational research programme is focussed on the role of molecular genetic abnormalities on leukemogenesis and outcome in childhood malignancies, especially leukemia. Specific goals are:
- Molecular classification of childhood leukemias to redefine leukemias into biological subclasses. This is done by genome-wide screening techniques at the DNA level, extensive gene expression profiling by micro-array analysis and protein expression profiling.
- Identification of (epi)genetic abnormalities important for development of childhood leukemias and lymphomas. Expression of tumor suppressor genes and oncogenes in various types of childhood leukemias and lymphomas are studied. The value of epigenetic silencing mechanisms such as methylation are studied.
- Identification of molecules associated with cellular drug resistance and clinical therapy response. New resistance genes for specific classes of cytotoxic drugs are identified by micro-array analyses of drug resistant and sensitive patients and confirmed by other techniques. New strategies to modulate these new resistance genes are developed.
- Identification of new targets for therapeutic intervention. New specific targets are detected in specific genetic subgroups of childhood leukemia by micro-array expression analysis. The presence of potential new drug targets is confirmed by other techniques and validation studies are performed. RNAi is being developed for ALL cells for this purpose. New agents directed against the newly discovered targets are evaluated in preclinical models for their activity in childhood leukemias.
- Development of new treatment protocols: the targets and new compounds studied in the preclinical setting as described above are used in phase I/II studies. Central goal of the clinical program is the development of targeted therapies for children with hematological malignancies.
- The clinical part of the research programme also studies: (1) Effectiveness of therapy in paediatric oncology, which are mainly done in national and international collaborations; (2) Improvements in supportive care in paediatric oncology, which are essential because of the high intensity of most treatment protocols; (3) Late effects of disease and treatment, which is important in the light of the improved cure rates of children with cancer.

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Article/Letter to the editor


EMC MM-02-72-01 - Lymphoid differentiation and immunodeficiencies

Programme design in brief

One of the most intriguing features of the specific immune system is the generation of mature B and T lymphocytes that carry immunoglobulin (Ig) molecules and T-cell receptors (TCR), which are highly specific for antigens, even when these cells have not encountered the antigens before. The generation and selection of a diverse and flexible specificity repertoire by lymphocytes is dependent on a series of developmental cell fate decisions, including the induction and regulation of Ig and TCR gene rearrangements. These decisions are implemented by the activity of specific transcription factors and enzyme systems and occur at specific checkpoints, controlled by signaling pathways downstream of antigen receptors and their immature forms. In particular, the research aims of this program comprise:

- To study the role of lymphoid-specific transcription factors that control the in vivo developmental program of lymphoid cells.
- To investigate signal transduction routes that are crucial to stem cell self-renewal and differentiation into lymphoid cells.
- To unravel the essential steps in the induction and execution of Ig/TCR gene rearrangements in precursor-B and -T cells, e.g. using immunodeficiencies as model.
- To characterize the signal transduction pathways downstream of the antigen receptors, which are essential for survival, selection and developmental progression of lymphoid cells.
- To investigate how defects in the regulation of differentiation and proliferation steps during lymphoid development result in immunodeficiencies or lymphoid malignancies.
- To translate the obtained knowledge on normal lymphoid differentiation and gene defects into novel diagnostics and opportunities for gene therapy in patients with primary immunodeficiencies (PID).

Key figures

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Theses

Prom./coprom.: Prof.Dr. J.J.M. van Dongen, Prof.Dr. G. Wagemaker & Dr. F.J.T. Staal.


Article/Letter to the editor


Patent


EMC MM-02-72-02 - Immune regulation and autoimmunity

Programme design in brief
Chronic inflammation and autoimmune disease are leading causes of morbidity, psychosocial burden and economic loss in Western societies. In view of the central role of the innate and adaptive immune system in these diseases, detailed insight into immune regulation is a requirement for rational development of diagnosis and (immuno)therapy. The Postgraduate School Molecular Medicine has an extensive and active programme in immune regulation and autoimmunity, consisting of a close collaboration between clinical and pre-clinical departments. Specifically, the departments of Neurology (workgroup leaders Dr. R.Q. Hintzen, B.C. Jacobs, Prof. Dr. R.A. van Doom), Dermatology (Prof. Dr. H.A.M. Neuman, Prof. Dr. E.P. Prens), Rheumatology (Prof. Dr. J.M.W. Hazes, E. Lubberts, Dr. R.J.E.M. Dolhain) and Internal Medicine (Dr. P.M. van Hagen) have structurally integrated their immunological research groups within the department of Immunology. There is additional close collaboration on the role of microbial compounds in immune regulation with the departments of Virology (Prof. Dr. A.D.M.E. Osterhaus), Medical Microbiology and Infectious Diseases (Prof. Dr. H.A. Verbrugh, H.P. Endtz, Dr. A. van Belkum). Furthermore, the departments of Internal Medicine (Prof. Dr. A.J. van der Leijl, Prof. Dr. T.J. Visser) and Immunology collaborate on thyroid autoimmune disease and diabetes in schizophrenia, and with the department of Psychiatry (Prof. Dr. M.W. Hengeveld, Dr. V. Bergink, Prof. Dr. J.M. van Beveren) on immune aberrancies in major affective disorders and schizophrenia. The departments of Immunology and Hematology have initiated a program for the experimental treatment of type 1 diabetes. The contribution of immune response gene polymorphisms to inflammation and autoimmune diseases is investigated in collaboration with the department of Pediatrics (Dr. M. Emonts). Selected diseases of interest are type I diabetes, thyroiditis, affective disorders and schizophrenia (all having a major immuno-neuro-endocrine component), rheumatoid arthritis (RA) and the related disorder Sjögren’s syndrome, psoriasis, and the demyelinating diseases multiple sclerosis (MS) and Guillain-Barré syndrome (GBS). In addition, the pathogenic mechanisms leading to atherosclerotic plaque vulnerability are studied in collaboration with the departments of Biomedical Engineering/Cardiology (Prof. Dr. Krams, New Imperial College, London) and Cell Biology (Dr. R. de Crom). The general premise is that the immunological mechanisms driving the multifactorial pathophysiology in the different diseases of interest are highly analogous. These mechanisms include influences of the neuro-endocrine system, basic abnormalities in monocytes/macrophages/dendritic cells, genetic polymorphisms of molecules involved in cellular interaction, microbial infection, as well as the leukocyte effector functions mediating tissue damage. Close collaboration with clinical researchers who are well-trained in immunology allows joint elaboration of scientifically relevant research questions, construction of well-characterized patient cohorts, and evaluation of experimental (immuno)therapy. Combining researchers with different backgrounds (e.g. molecular biology, cellular immunology) working on these different diseases in a single integrated team significantly stimulates scientific discussion and output. The joint expertise allows coverage of a broad area of approaches and technology, 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. Some departments have initiated new research programs on autoimmunity recently, while others have a longstanding international track record (e.g. department of Neurology). The MS research is organized in the MS Centre ErasMS (head Dr. R.Q. Hintzen), supported by a 4 year programme grant from the Dutch MS Research Foundation. The Biomedical Primate Research Centre (Dr. B.A. ‘t Hart and colleagues, Rijswijk) participates in this MS Centre. Research topics in this subtheme include basic immunopathogenic mechanisms (e.g. molecular mimicry in GBS and MS); immune-endocrine interactions (e.g. diabetes, thyroiditis, amelioration of MS, thyroiditis and RA during pregnancy); molecular signaling pathways in chronic autoimmune inflammation (transcription factors in psoriasis, signature mRNA and micro RNA expression in monocytes); experimental immunotherapy (e.g. antibodies against costimulatory molecules and cytokines); immune regulation by external factors (e.g. UV irradiation and skin inflammation, infection and MS activity); immune function and disease activity in MS; and an aberrant immune regulation by an aberrant development and activity of antigen presenting cells (e.g. diabetes, Sjögren’s syndrome, thyroiditis, atherosclerosis, affective disorders, schizophrenia and histiocytosis).

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Theses

Article/Letter to the editor


**Book editorship**
EMC MM-02-72-03 - Diagnosis, classification and treatment evaluation of leukemias and malignant lymphomas

Programme design in brief
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 research program consists of three main projects:

Normal and aberrant V(D)J recombination in leukemias and malignant lymphomas: basic aspects and diagnostic applications. Project leader: A.W. Langerak.

One of the key processes during early lymphoid differentiation concerns the rearrangements of the immunoglobulin (Ig) and T-cell receptor (TCR) genes. This so-called V(D)J recombination process is tightly regulated. Nevertheless, aberrant V(D)J recombination activity can induce aberrant Ig/TCR gene rearrangements, which involve oncogenes. Insight into normal and oncogenic rearrangements can be translated into better diagnosis and classification of lymphoid malignancies. Immunobiology of acute leukemia and treatment evaluation. Project leader: V.H.J. van der Velden.

Although most patients with acute leukemia achieve remission according to cytomorphological and clinical criteria, many patients relapse and die from their disease. Therefore sensitive techniques are needed to monitor the patients for the presence of MRD during and after treatment in order to obtain better insight into the in vivo effectiveness of treatment, with flow cytometric immunophenotyping using aberrant marker expression and detection of tumor-associated proteins or with molecular MRD techniques via PCR analysis of Ig/TCR gene rearrangements and chromosome aberrations. Gene expression profiles in immature lymphoid cells and acute lymphoblastic leukemias. Project leader: F.J.Th. Staal.

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 transcriptional initiation by transcriptional 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 extensively studied and compared to corresponding normal immature T and B cell subpopulations. Results of these comparative studies will be exploited for developing new diagnostic tools.

Key figures

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Theses
Prom./coprom.: Prof.Dr. J.J.M. van Dongen, Drs. A.W. Langerak & F. Heule.

Article/Letter to the editor


**Patent**

EMC MM-03-24-01 - Solid tumors between bench and bed

Programme design in brief
The department of Pathology is the backbone of the Josephine Nefkens Institute (JNI), and thereby committed to translational research of human solid tumors. The focus of the department is to unravel the pathogenesis of solid cancers combining advanced morphological and molecular methods on human tumor material, and animal models. Leading themes are the molecular and (epi)genetic basis of cancer, tumor stem cell biology, and tumor-host interactions. Results are used to develop objective criteria for diagnosis, response prediction and prognosis of human cancers, which will then be implemented in top-referral and routine clinical pathology. This is implemented and stimulated by coupling basic scientists with clinical pathologists around specific cancer types. These activities are also meant to facilitate other Erasmus MC departments research programs by making available its morphologic expertise and giving access to human pathology specimens through the Erasmus MC tissue bank (Dr. P.H. Riegman). The research program of the department forms a substantial part of Main Theme 3, Solid Tumors of the Postgraduate Schools Molecular Medicine. Collaborations within Erasmus MC are formalized in the Postgraduate Schools Molecular Medicine, MGC and NIHES. Here below, the research program of the Department of Pathology is briefly summarized per research group:

- Group Dr. H. van Dekken: molecular markers for diagnosis and progression in esophageal cancer;
- Group Dr. W.N.M. Dinjens: molecular diagnosis of solid cancers;
- Group Dr. L.C.J. Dorssers: molecular mechanisms of hormone independency in breast cancer;
- Group Prof.d.r. R. Fodde: molecular, genetic, and cellular basis of intestinal and mammary tumor initiation and progression: role of cancer stemness and tumor microenvironment;
- Group Dr. A.B. Houtsmuller: kinetics of molecules involved in DNA-repair, and (androgen dependent) transcription, studied in vivo using fluorescent-labeled proteins;
- Group Prof.d.r. J.M. Kros: molecular markers for diagnosis and response prediction in gliomas;
- Group Prof.d.r. R.R. De Krijger: molecular markers for diagnosis and progression in pheochromocytoma;
- Group Prof.d.r. L.H.J. Looijenga and Prof.d.r. J.W. Oosterhuis: pathogenesis of germ cell tumors, and cancer risk of various types of gonadal dysgenesis;
- Group Prof.d.r. J. Trapman and Dr. G.J.J.H. van Leenders: molecular mechanisms of origin and progression of prostate cancer; role of prostate (cancer) stem cells;
- Group Dr. E.C. Zwarthoff: biology and molecular diagnosis of bladder cancer; function of the leukemia-associated MN1TEL fusion gene; molecular pathogenesis of meningioma.

For more extensive descriptions of the work carried out in our department, the reader is referred to the Application for Renewal of the Erasmus Postgraduate School Molecular Medicine 2003- (www.molmed.nl), Oncological Research at the Erasmus MC University Medical Center Rotterdam, Annual Reports 2000-2004-, and recent issues of -Daniel den Hoed Cancer News-.

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Theses
Oers, J.M.M. van (2007, september 05). Activation of the fibroblast growth factor receptor 3 in bladder cancer. EUR. Prom./coprom.: Prof.Dr. T.H. van der Kwast.

Article/Letter to the editor


Programme design in brief

A key field of research in radiotherapy is the clinical application of conformal radiotherapy, and intensity modulated radiotherapy (IMRT), where the treated volume is made to conform to the target volume, thereby limiting the volume of irradiated normal critical tissue. By reducing the probability of normal tissue toxicity, this approach allows for sparing of critical organs and/or radiation dose escalation and improved local tumor control. In collaboration with the AvL in Amsterdam, a randomized clinical trial of dose escalation for prostate cancer is currently underway. Phase II studies of intensity modulated conformal radiotherapy are underway for long cancer and head and neck cancer (to limit damage to the salivary glands and escalate dose). Studies of stereotactic irradiation for eye and brain tumors have been activated. The intraoperative brachytherapy research is focused on the treatment of tumors of the rectum, head and neck, and lung. A program of Ultrasound and CT-assisted brachytherapy for prostate cancer is underway. In collaboration with the Toraxcenter of the University Hospital Rotterdam, patients are being treated with endovascular brachytherapy in the context of ongoing clinical trials. In addition, two trials of radiotherapy for peripheral vascular disease and arteriovenous shunts are rapidly accruing patients. Finally for a number of clinical tumor sites radiation with concomitant chemotherapy radiation protectors is being studied.

The current research in clinical physics is focused on the development and application of tools for conformal intensity modulated therapy. Improved electronic portal imaging (EPI) techniques are being developed and EPI has been clinical implemented for patient set-up verification and correction, in-vivo dosimetry during conformal treatments and for quality assurance measurements of intensity modulated photon beams produced with dynamic multileaf collimation. A program has been started to use implanted radio opaque markers for set-up verification instead of the bony anatomy. The optimization of dose distributions by intensity modulated radiotherapy beams is being actively pursued and algorithm is being developed for automated beam orientation selection.

The research activities of molecular radiobiology are geared gaining an improved understanding of the mechanisms and biology relevance of double-strand DNA breaks repair in relation to genomic instability, carcinogenesis and DNA end joining. In a Dutch Cancer Society funded project, the phenotype of mice with defective homologous recombination repair is currently being analyzed. Recently, dr. Kanaar has been granted a subsidy in the prestigious Pioneer program coordinated by the Netherlands Research Council.

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Theses


Tafel, A.A. (2007, mei 02). Roles of homologues recombination in processing DNA lesions. EUR. Prom./coprom.: Prof. Dr. J.H.J. Hoeijmakers & Prof. Dr. R. Kanaar.

Article/Letter to the editor


Zijtveld, M. van, Dirkx, M.L.P. & Heijmen, B. (2007). Correction of conebeam CT values using a planning CT for derivation of the "dose of the day". Radiotherapy and Oncology, 85(2), 195-200.


Part of book - abstract


Other output

Hyperthermia (HT), i.e. heating tissue to 39 - 44 °C for 60 to 90 minutes, results in a cascade of effects, which all can be exploited to improve tumor response to radiotherapy (RT) and chemotherapy (CT). Currently known effects are: inhibition of radiation-induced damage repair, changes in perfusion, re-oxygenation, effects on macromolecular and nanoparticle delivery, induction of the heat shock response and immunological stimulation. Generally, normal tissue tolerates a hyperthermic treatment of 1 hour up to 44 °C without relevant clinical damage. This makes HT an ideal complementary treatment to both RT and CT. Consequently, HT is always implemented as part of a multimodal, oncological strategy. Its efficacy to improve clinical outcome of radiotherapy and chemotherapy has been demonstrated in multiple randomized phase III trials. At present, HT is part of standard therapy for several tumor pathologies in the Netherlands. The medical program is directed towards the development of the clinical application of HT as adjuvant to RT and CT. The group is internationally recognized for its coordination of the Dutch Deep Hyperthermia Trial, which was also of major importance for the recognition of hyperthermia as regular health care within the frame of the Dutch National Health Service. Currently, we coordinate a national phase III trial investigating RT+HT versus RT+CT in advanced cervical cancer. In close collaboration with the MD's of the departments of Radiation Oncology, Gynecology and Medical Oncology, we explore the feasibility of new clinical studies for tumor sites where treatment with regular RT or CT schedules does not result in a satisfactory probability of local control.

The research in hyperthermia physics aims at improvement and assurance of the quality of the technical application of the hyperthermia treatment. The group has an international recognized guiding position in translating hyperthermia treatment planning towards clinical application. As strong focus of the research program is on the assessment of critical parameters for the application of 3-dimensional treatment planning on-line during loco-regional deep and superficial heating. In direct association to this objective we also invest in research aiming at (quantitative) validation of our treatment planning models for each individual applicator, including the development of new, accurate QA tools and procedures. Additionally, research is directed on the development of new hyperthermia systems to allow application of hyperthermia at tumor sites, which at this moment cannot be treated. The recent development of the HyperCollar for heating head and neck tumors is an compelling example of our work in this area. Finally, to enable prediction of treatment outcome it is important to perform extensive analysis of the relationship between thermal dose and tumor response. Eventually, this information will enable optimization of the treatment based on a probability of a successful treatment outcome.

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### Theses


### Article/Letter to the editor


**External report**


**Other output**


Programme design in brief

Main objective of the research programme is to study the interaction between light and living tissue with the purpose of understanding, optimising and further developing applications of light for diagnosis and treatment of disease. In contrast to other physical modalities used for diagnostic or therapeutic purposes, such as ionising radiation, light has only shallow penetration in living tissue. This apparent limitation renders it excellently suitable for diagnosis and treatment of superficial disease. Fueled by rapid developments in optoelectronics, lasers and fiber optic technology, these techniques can be applied in vivo, in a non-invasive or minimally invasive manner. Research activities comprise ex vivo and animal experiments, as well as clinical studies. Current research activities are centered around two strongly interrelated research lines: photodynamic therapy (PDT) and optical diagnostics (OD).

PDT: Photodynamic therapy is a therapeutic technique that is based on the interaction of a light sensitive drug with light. PDT has been under study for several decades and is now an emerging treatment modality for a range of primarily malignant conditions. It is under clinical investigation for the treatment of cancers of head and neck, bladder, lung, prostate, oesophagus, brain, and skin and several non-malignant indications. For age-related macula degeneration (AMD) and non-melanoma skin cancer PDT is now the gold standard therapy. In the last decade PDT research in my group has focussed on the mechanisms of action of different photosensitisers, light dosimetry, light fractionation and the development of clinical applications. Research activities comprised preclinical work on animal models, phantom studies, theory development, clinical experimentation and clinical pilot studies. Greatest achievements of the reseach group is the improvement of ALA-PDT for basal cell carcinoma to a level at which it outperforms surgery using light fractionation and the development of a very successful approach for PDT of nasopharyngeal cancer.

OD: Early attemps to use optical techniques for detecting cancer date from more than a century ago and were partly inspired by the fluorescent emission from the drugs used in early photodynamic therapy. The dramatic technological developments in optics and optoelectronics that have started a decade ago have enabled the use of a large number of new non invasive non destructive optical sampling techniques to probe inside the body. Sofar, my research group has a history in fluorescence imaging and spectroscopy as well as diffuse reflection spectroscopy. These techniques have been investigated for the diagnosis of cancer and are currently being used routinely in monitoring photodynamic therapy. Over the last few years Differential Pathlength Spectroscopy has been developed in my group, which is a special form of reflection spectroscopy. This technique has been used successfully in the bronchoscopic classification of early cancers, and is currently under investigation for diagnosis of cancer in the esophagus, the oral cavity, the brain and breast. A spin off company has been set up to enable further commercialisation of this technology. In collaboration with Utrecht University we are developing a new in vivo microscopic technique: Non-linear Spectral Imaging.

Key figures

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Theses


Article/Letter to the editor


Programme design in brief
The overall aim of this scientific programme is to study various aspects of cancer involving the nervous system, in close collaboration with many departments, including the departments of Pathology, Immunology, Medical Oncology and Radiotherapy. The program focuses on the following three main topics:

1. Primary Brain Tumors.
   1.1 Identify molecular markers predicting treatment response in glial tumors using FISH, micro-array and high-end mass spectrometry.
   1.2 Develop experimental gene therapy modality for treatment of primary brain tumors.
   1.3 Establish an effective treatment for patients with primary brain tumors. The department participates in phase I trials and is coordinator/initiator of several large international phase II-III trials.

2. Paraneoplastic disorders.
   2.1 Identify the association between paraneoplastic autoantibodies, antigen specific T lymphocytes, clinical neurological syndrome and associated tumor.
   2.2 Clone the target antigen of newly identified paraneoplastic autoantibodies.
   2.3 Study the role of the paraneoplastic autoimmune response in anti-tumor immunity and neurological dysfunction.

   3.1 Study the role of neurotrophic factors in pain transmission in the superficial dorsal horn in animal models.
   3.2 Establish an effective treatment for patients with cancer pain, focusing on neuropathic cancer pain and breakthrough pain. The department has initiated several clinical pain studies and coordinates an international randomized study to evaluate a new treatment modality for breakthrough pain.

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Theses


Dekker, L.J.M. (2007, oktober 10). Proteomics of body fluids. EUR (159 pag.). Prom./coprom.: Prof.Dr. P.A.E. Sillevis Smitt, Prof.dr. C.H. Bangma, Dr. T.M. Luider & Dr.ir. G.W. Jenster.


Article/Letter to the editor


Part of book - abstract

EMC MM-03-47-02-A - Pathophysiological aspects and treatment of gastro-intestinal diseases

Programme design in brief
A major objective of this project is to investigate the impact of recently developed modalities for the diagnosis and treatment of gastro-intestinal diseases.

The etiology of functional disorders such as constipation, disordered defecation and fecal incontinence will be evaluated using new diagnostic tools such as conventional anorectal manometry, 24-hours ambulant anorectal manometry, electromyography, barostat-measurements and laser Doppler flowmetry. New immuno-histochemical techniques using monoclonal antibodies will be used to investigate the histopathological characteristics of slow transit constipation. The efficacy of new therapeutic options such as anterior rectopexy, enterocoele repair and sacral neuromodulation will be evaluated in clinical trials. Treatment of fecal incontinence and obstructed defecation by means of neuromodulation with pacemakers is a major topic for the next years. Medical treatment of anal fissures by local application of drugs, such as exogenous NO-donors and botulin-toxin, will also be evaluated. New surgical procedures, such as the Iwadare-technique, will be implemented in the treatment of complex, high transspincteric fistulas.

Pathophysiological aspects of inflammatory bowel diseases such as Crohn's disease and ulcerative colitis will be studied. Another objective of this project is to evaluate the functional results following ileo-anal anastomosis in patients with IBD and FAP and following colo-anal anastomosis in patients with rectal cancer.

New radiological tools such as endorectal ultrasound and magnetic resonance imaging of the anal sphincters and pelvic floor using an endo-anal coil, will be used for the preoperative localisation and classification of perianal fistulas, sphincter defects and rectal cancer.

The role of laparoscopic techniques will be evaluated in patients with acute peritonitis and colorectal cancer. The potential benefit of endoscopic intersection of the splanchnic nerves for patients with severe abdominal pain due to chronic pancreatitis will be studied.

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Theses


Halm, J.A. (2007, januari 31). Experimental and clinical approaches to hema treatment and prevention. EUR. Prom./coprom.: Prof.Dr. J. Jeekel & Prof.Dr. J.F. Lange.


Kate, M. ten (2007, januari 19). The influence of surgical trauma on the development of distant tumour. EUR. Prom./coprom.: Prof.Dr. J. Jeekel.


Raa, S. ten (2007, april 25). The consequences of surgical trauma on intra-peritoneal tumour recurrence and/or adhesion formation. EUR. Prom./coprom.: Prof.Dr. J. Jeekel.

Article/Letter to the editor


EMC MM-03-47-06-A - Surgical trauma and the development of tumour recurrence

Programme design in brief
Locoregional or distant tumour recurrence of gastrointestinal carcinoma remains as important complication after potentially curative surgical resection. Prevention of this affliction remains the goal of many clinical and experimental studies. Excessive production of reactive oxygen species (ROS) and related tissue injury play a fundamental role in a wide variety of disease processes. Besides chronic inflammatory diseases, ROS are also produced after surgical trauma. The main producers of ROS are inflammatory cells (PMNs) entering damaged tissue after surgical trauma. The purpose of these cell products is to destroy invading organisms and damaged tissue. Despite this beneficial effect, the overwhelming oxidative potential can result in additional tissue destruction, which enables tumour cells to adhere.

This programme aims at
Characterisation of the adhesion of human tumour cells to meso- and endothelial cells and investigating the influence of growth factors and cytokines.
Identifying pathways of enhanced tumour cell adhesion after surgical trauma and to elucidate the role of PMNs and ROS for this process.
Prevention of tumor recurrence of human pancreatic tumor in nude mice using scavengers and interferons

Insight in the mechanism of enhanced tumour recurrence after surgical trauma and the role of PNMs and ROS in this process may lead to the development of tools, such as scavengers and/or interferons to prevent this common pathway of tumour recurrence in most gastro-enterologic cancers.

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Halm, J.A. (2007, januari 31). Experimental and clinical approaches to hernia treatment and prevention. EUR. Prom./coprom.: Prof.Dr. J. Jeekel & Prof.Dr. J.F. Lange.


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Raa, S. ten (2007, april 25). The consequences of surgical trauma on intra-peritoneal tumour recurrence and/or adhesion formation. EUR. Prom./coprom.: Prof.Dr. J. Jeekel.

Article/Letter to the editor


EMC MM-03-47-11 - Innovative tumor model development/tumor vasculature/tumor targeting/locoregional control

Programme design in brief
The Problem: Surgical treatment of primary tumors, recurrences or metastases may be technically impossible or insufficient to achieve local tumor control. Combination of surgery with infusion or perfusion techniques of organs or extremities, or a combination with peroperative insertion of catheters for peroperative radiotherapy or afterloading can improve the surgical results. The possibility to translate the success of isolated limb perfusions with TNFα + cytostatic drugs in patients with irresectable extremity tumors into its application in new regional perfusion settings (pelvis, liver) is under investigation. Moreover a genetherapy program using various vectors has been developed investigating the efficacy of isolated perfusion and regional infusion techniques for these new treatment modalities. The development of treating metastatic disease with tumortargeting devices such as liposomal encapsulation of TNF + cytostatic or other antiangiogenic drugs is another arm in the overall program. Optimisation of pre- and peroperative diagnostic procedures as well as induction chemo-/ radiation therapy may improve the resectability of tumors and improve the quality of life. These aspects are investigated in preclinical animal models and in clinical trial protocols. An important development is the intravital microscopy models and new in vitro tumor cell mobility assays and innovative invitro tumor models developed in our laboratory as well as the structural participation in the OIC ¿Optical Imaging Center¿of the ErasmusMC. Regional isolated perfusion or infusion of cytokines, in particular TNFα or other "antistromal agents" in combination with cytostatic drugs are the central research item in this approach of biochemotherapy targeting both structural elements of neoplasms.

Key figures

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Article/Letter to the editor


Part of book - abstract
Programme design in brief
The clinical and experimental aspects of urological malignancies are a central issue within the research programme of the Department of Urology, Erasmus MC. The research is concentrated towards identification and characterization of molecular mechanisms that are responsible for cancer development and progression, improvement of the (molecular) diagnostic procedures, aspects of epidemiology and prevention, the development of prognostic factors and the development of innovative approaches to treatment, especially with respect to cancer derived from the prostate, kidney and urinary bladder.

Research related to prostate cancer is most developed at this time. The clinical research programme shows much interaction with the more basically oriented research efforts and offers an opportunity to introduce recent developments in the laboratory directly into early clinical research. The research programme benefits from a large database of prostate cancer patients and of their clinical course, which was set up 20 years ago together with a tissue and serum bank.

Some international projects fall within this programme: The European Randomized Study of Screening for Prostate Cancer (KWF/EUR 98-1657, EMCR 2002-2722; Quality of Life: KWF-EUR-2000-2329, Preventiefonds 0028-22820, ZON/Mw 2200-0106; 5th Frame Work Programme QLRI-2000-01741; FP5 EU Meta-analysis of prostate cancer - Prostate Cancer Trialists’ Co-operative Group (PI O. Dalesio, NKI and F.H. Schröder, Erasmus MC)) is co-ordinated nationally and internationally by the Department of Urology. The programme includes participation and co-ordination of multiple clinical trials (EORTC, etc.). Furthermore, an international project on the Development of Prostate Cancer Gene Therapy is incorporated in the programme activities (5th Frame Work QLK6-CT-2000-00271 and 6th Frame Work GIANT) and an EU sponsored project on the development of serum markers (6th Frame Work P-MARK).

Elucidation of the mechanisms of androgen-regulated growth and loss of hormonal responsiveness of prostate cancer cells is a major goal of this project. A panel of xenografts and in vitro cell lines, comprising sublines that are different with respect to their hormone responsiveness, are analyzed for differential gene expression in order to identify the various genes involved in these processes. The study also includes the investigation of the possible role of intercellular interactions, epithelial-stromal as well as epithelial-epithelial. A further aspect is the investigation of the role of the androgen receptor in prostate development and prostate cancer.

The prostate cancer xenografts and human serum bank are also being utilized for our search for novel diagnostic and prognostic markers. Using Fourier Transform mass spectrometry, we have identified serum proteins associated with presence of prostate cancer and serum proteins derived from xenografts.

As far as carcinoma of the kidney and bladder is concerned, the activities are concentrating on clinical studies. Regarding bladder cancer, molecular diagnostics, non-invasive spectrometry, and development of non-viral genetic transfer to injured urothelium are a focus. These fundamental studies should lead to new diagnostic and therapeutic clinical applications.

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Theses


Article/Letter to the editor


Programme design in brief

Elevated levels of steroid hormones like estradiol and progesterone are important factors in the development of endometrial, breast and probably also ovarian cancer. Nevertheless, some medical interventions like hormone treatment for In Vitro Fertilization (IVF), Hormone replacement Therapy (HRT) after menopause, and tamoxifen-treatment of breast cancer cause significant increases in steroid signaling.

Questions we are trying to answer are: Is temporarily administration of gonadotropins significantly correlated with an increased risk of ovarian, endometrial, breast and thyroid cancer in women treated with In Vitro Fertilization? Furthermore, are women who have a poor response to IVF more prone for gynaecological and breast cancer? Furthermore, in our laboratory we are investigating the molecular mechanism behind the question why steroids are sometimes causing cancer development (increases estrogen signaling can cause endometrial cancer), while in other cases steroids seem to protect against cancer growth (progesterone inhibits estrogen induced carcinogenogenesis in the endometrium). In these investigations Wnt signaling plays an important role.

The life-time risk for infection with HPV is around 80%. Fortunately most women are able to clear this infection, and less than 10% of women infected with a high-risk HPV develop a persistent infection, which is one of the leading causes of preneoplastic and neoplastic lesions in the female genital tract, including cervical and vulvar intraepithelial neoplasia (CIN and VIN). Acquisition and clearing of HPV infection, viral load and persistence, T-cell response, cytokine expression, changes in cellular genome, viral oncogene proteins E6 and E7, role of human tumor suppressor genes p53 and Rb, loss of heterozygosity and telomerase activation are all factors that are studied to understand HPV-induced carcinogenesis. In addition to these molecular studies we are also investigating clinical aspects like the consequences of a national based primary screening program for cervical cancer and the role of HPV testing in the management of women with premalignant cervical lesions. Furthermore, in a number a randomized clinical trials alternative treatments, to otherwise mutilating surgery for VIN, are evaluated.

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Theses


Article/Letter to the editor


characteristics, survival and prognostic factors of hereditary breast cancer from BRCA2-, BRCA1- and non-BRCA1/2 families as compared to sporadic breast cancer cases. European Journal of Cancer, 43(5), 867-876.


Seters, M. van, Kate, F.J.W. ten, Beurden, M. van, Verheijen, R.H.M., Meijer, C.J.L.M., Burger, M.P.M. & Helmerhorst, T.J.M. (2007). In the absence of (early) invasive carcinoma, vulvar intraepithelial neoplasia associated with lichen sclerosus is mainly of undifferentiated type: new insights in histology and aetiology. Journal of Clinical Pathology, 60(5), 504-509.


Part of book - abstract


Book editorship

External report


EMC MM-03-54-04-A - Developmental biology; pathophysiology of the newborn

Programme design in brief

Growth and development of the fetus, the transition of the fetus to the newborn and growth, and development of the newborn infant are among the most critical periods in human life. Perturbations of the normal development in these critical periods can cause temporary or persistent effects. Knowledge of the normal development is essential for the evaluation of an abnormal pattern of development. Abnormal growth and development is mainly seen in groups of infants like preterm infants.

Our research therefore focuses on these infants, but also on normal and sick term infants and infants with inherited metabolic disease.

1. Substrate utilization, metabolism, nutrition and body composition of the preterm and term newborn.
2. Intestinal development in rodents, mammals and preterm infants
3. Neonatal neuroimaging, neurology and long-term development
5. Neonatal pharmacology; developmental and neonatal pharmacology.

Key figures

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Article/Letter to the editor


EMC MM-03-61-05-A - Experimental therapeutical approaches in inflammatory dermatoses and cutaneous oncology

Programme design in brief
The Department of Dermatology will focus its scientific efforts on inflammatory dermatoses and cutaneous oncology. At present time we are exploring clinically related basic research possibilities. Our first step towards the research target consists mainly of in vivo, ex vivo and in vitro studies of psoriasis and non-melanoma skin cancer. With these studies we will aim to gain more insight in the immunopathological aspects of psoriasis and the protective immunological mechanisms during tumor growth of basal cell carcinoma. Furthermore the signal transduction pathways will be explored together with micro-array studies. In addition various therapeutic approaches in psoriasis and in non-melanoma skin cancers will be investigated regarding to their mode of action and immunomodulatory potential.

Key figures

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Theses

Article/Letter to the editor


Part of book - abstract
EMC MM-03-86-01 - Tumour endocrinology, genetics, prognostic factors and experimental therapy of cancer

Programme design in brief
Hormones and growth factors play an important role in the growth regulation, diagnostics and the treatment of a large number of tumor types. New endocrine and molecular targeted therapies (will) are being developed on the basis of detected tumor characteristics and are directed on factors involved in the regulation of growth and metastasis of cancer. Research is performed regarding the antitumor effects, mechanisms of action and mutual interaction of various treatment modalities in different types of cancer. In addition to the performance of clinical trials tumor cell-lines, experimental animal models and human tumor tissues are used in preclinical studies. Prognostic factors play an important role in the selection of patients for (new) endocrine and anti-growth factor therapies. For a better selection of patients, the value of recently detected cell biological parameters and gene signatures (determined by micro arrays) as prognostic and predictive factor will be investigated. As a whole the research is strongly directed on clinical application. Finally, research is carried out in the field of familial cancer syndromes, genomics, early diagnosis and (chemo)prevention

Key figures

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Theses


Article/Letter to the editor


Patent


Part of book - abstract


EMC MM-03-86-08 - Biological and clinical aspects of drug-resistance and -sensitivity of malignancies

Programme design in brief
The limited sensitivity of cancer to drug treatment is a major problem. For the time being cytotoxic drug treatment is still the mainstay in the medicinal approach to cancer. Yet there are only a few malignancies that are curable by cytotoxic treatment alone. Germ cell tumors, malignant lymphomas and various forms of childhood cancers can serve as examples. An increasing group of malignancies has been shown to have initial sensitivity to cytotoxic drugs and as a consequence they can offer patients palliation and prolongation of life. However ultimately these tumors become resistant to the drugs applied. Unfortunately, the molecular mechanisms underlying this drug unresponsiveness are still largely unknown. The present concept indicates that for cytotoxicity a cytotoxic agent should interact with intracellular target molecules, and that this interaction triggers a cascade of programmed events, ultimately resulting in cell death. We perform mechanistic, prognostic and therapeutic studies aimed at the improvement of systemic therapy with anticancer drugs. The induction and activity of known drug resistance proteins towards novel chemotherapeutic agents is examined. In addition we search for novel genes and biochemical pathways involved in sensitivity and resistance using yeast as a model system for human cells. In clinical studies we examine the relevance of the newly identified genes and other factors to the outcome of treatment, by including pharmacokinetic, -dynamic and -genetic aspects of drug-target and drug-drug interactions, in order to enable dose-intensification and optimization and to achieve individualised dosing. We also apply novel, basically non-cytotoxic, agents that are targeted against one or several components of signal transduction pathways. In cells and tissues signal transduction events are crucial for cell proliferation, cell differentiation, angiogenesis etc. In cancer cells signal transduction pathways may become critical for tumor growth by molecular changes in one of the transduction molecules. A wide variety of novel agents is being developed that specifically target these critical pathways. In our clinical programme with these agents we also focus on pharmacokinetic, -dynamic and -genetic aspects.

Results
It is our hypothesis that in cancer cells drug resistance is the result of gene (over)expression or alternatively, lack of expression of drug sensitivity genes by gene disruption or gene silencing. Our specific aim is the identification of novel drug resistance and sensitivity genes / biochemical pathways. We mainly focussed on the use of the simple eukaryotic model organism Saccharomyces cerevisiae by systematically screening the sensitivity of 4700 independent yeast disruption strains (knockouts) for chemotherapeutics. Using a semi-high-throughput screen we examined the growth inhibitory effects of the widely used cytotoxic drugs, doxorubicin and cisplatin, on the parental yeast strain BY4742 and each of the individual knockout strains. About 550 knockout strains have a clearly aberrant drug sensitivity profile identifying genes whose disruption causes resistance or sensitivity. The vast majority (93%) shows increased sensitivity to cisplatin and/or doxorubicin implying that the genes involved have protective roles against these toxic substances. Only in 7% of the cases a gene disruption results in a resistance phenotype. Using the Cytoscape and the Biomodules plug-in software (collaboration with Dr. T. Galitski, Inst. for Systems Biology) we integrated our quantitative data with yeast protein interaction data, metabolite mediated interaction data and protein-DNA interaction data thus establishing a graphic network model. Within the molecular network we were able to identify biological modules (biomodules) i.e. associations of preferred molecular partners that interact to perform a collective function thereby highlighting biochemical pathways governing sensitivity / resistance to cisplatin and/or doxorubicin. The existence of human orthologs for ~25% of the selected yeast genes and the conservation of the biochemical pathways that we identified will enable us to investigate whether these genes / biochemical pathways play a determining role for drug sensitivity / resistance in human cancer cells.

We previously identified a number of genes in yeast using random gene disruption by transposon insertion and subsequent phenotypic selection. One of the genes we identified encodes a serine-rich protein specific kinase (SKY1) which causes cellular resistance to cisplatin, carboplatin, and anthracyclines upon disruption. Interestingly, this knockout is hypersensitive to the antimetabolite 5-FU and has a mutator phenotype, indicative for microsatellite instability. Heterologous expression of the human SKY1 homologue SRPK1 (5'-RNA- and protein-specific kinase) in the skyl1 disruption mutant yeast cells restored cisplatin sensitivity. Subsequently we showed that downregulation of SRPK1 also conferred resistance to cisplatin in human cancer cell lines. These observations prompted us to investigate the possible relevance of SRPK1 in human cancer particularly germ cell tumors (GCTs) that are routinely treated with cisplatin based-chemotherapy. We showed that high SRPK1 expression might be an important prognostic indicator for the responsiveness of non-seminomatous GCTs towards platinum-containing chemotherapy, while its absence or low expression might predict resistance. Currently we are investigating the prognostic significance of SRPK1 expression in stage III colorectal cancers that are treated with for 5-FU neoadjuvant chemotherapy. Attempts are made to further dissect the biochemical pathway to which SKY1 belongs by identifying the upstream and downstream signalling components and elucidate the molecular mechanism of the aberrant drug sensitivity phenotype in the absence of SKY1.

Imatinib mesylate is a selective tyrosine kinase inhibitor that is used for the treatment of gastrointestinal tumors and chronic myeloid leukemias. The drug is taken orally on a daily basis over prolonged periods of time. However, the vast majority of patients will eventually progress while on therapy. Prolonged exposure (up to 9 months) of the colon carcinoma cell line CaCo to Imatinib, which is non-toxic to these cells, led to the induction of two ABC transporters: P-glycoprotein and the breast cancer resistance protein. Although P-gp was already indicated in imatinib transport BCRP was not. We were the first to demonstrate that Imatinib is also substrate of BCRP. The fact that these transporters, that are highly expressed in the gut, pump Imatinib may have consequences for the bioavailability of the drug and lead to pharmacokinetic resistance. Currently we are investigating the bioavailability of Imatinib in conditional BCRP knockout mice (collaboration with Dr. A. Sparreboom, National Cancer Institute).

Vaults are large ribonucleoprotein particles in mammalian cells whose expression correlates with chemoresistance in primary tumors and cancer cell lines, but whose role in the drug resistance phenotype was not understood. In a collaborative study with the group of Dr. A.M. Bennett (Yale University School of Medicine) we presented evidence that vaults function as scaffolds for signalling proteins and as such play a role in survival signalling and contribute to a
that are evolutionarily conserved riboregulators modulating gene expression. MiRNAs have been shown to play a role in cancer and possibly the development and maintenance of drug resistance. MiRNAs are small RNAs (21–22 nucleotides) involved in various important developmental processes in plants and animals and are involved in apoptosis, differentiation, cell proliferation, stem cell division and undoubtedly many other cellular processes. It is currently believed that thousands of genes are under control of miRNAs. The expression of miRNAs in human cancer cells was monitored using newly developed detection techniques including miRNA arrays and RT-PCR procedures suitable for the quantitative detection of genes involved in drug resistance. In addition we showed vaults functionally interact with an E3 ubiquitin ligase COP1 which regulates the stability of c-jun and p53 suggesting vaults are involved in carcinogenesis. Based upon in vitro studies on the repair of DNA damage induced by platin derivatives, we are studying the potential of interval shortening between treatment courses as a method of dose intensification. The approach of interval shortening yielded positive results in locally advanced head and neck cancer and show a substantial increase in response rate to chemotherapy for ovarian cancer and NSCLC. In addition we study the possibility of individualised dosing guided by pharmacodynamic parameters. If this way of dosing is not considered useful or feasible we study the application of simplified methods of dose-calculation.

Our research with new drugs focuses on new classes of cytotoxic agents that might not be involved the classical mechanisms of resistance. We have performed or participated to several of the pivotal studies with taxanes (paclitaxel, docetaxel) and topoisomerase I inhibitors (CPT11, topotecan). Presently, we are focussing on totally new classes of cytotoxic agents (ES-285, F60008, RO 4403726, PH-739538), receptor tyrosine kinase inhibitors (Imatinib, BIBW 2992, GW 2016, AZD0530, antibodies targeted at different receptors (2C4, TRM-1) angiogenesis inhibitors (KRN951, ABT-510, BAY-579352, GW 786034) and multitargeted tyrosine kinase inhibitors (SU 11248, SU 14813).

Current oncological practice calls for normalizing the doses of chemotherapeutic drugs to a uniform standard, typically body-surface area (BSA). Our recent results from retrospective and prospective investigations indicate that this approach is mostly invalid, and that other approaches should be evaluated to control for the degree of interpatient variability. Some examples currently under investigation are the development of new dosing strategies for anticancer agents based on:

1. Pretreatment patient physiologic characteristics (CPT11), extent of organ dysfunction (Navelbine), and age (paclitaxel).

2. Enzyme phenotyping using CYP3A4 probes (cortisol, midazolam, and erythromycin) in collaboration with Dr. Sharyn D. Baker at Johns Hopkins Oncology Center in Baltimore, USA and Dr. Alex Sparreboom (NCI, Bethesda, USA) (CPT11, docetaxel, Imatinib).

3. Detection of inherited metabolic disorders in collaboration with Dr. Alex Sparreboom (NCI, Bethesda, USA) and Dr. Ron van Schaik at Erasmus MC and Dr. Howard McLeod at Washington University in St. Louis, USA (UGT1A1, hCEs, CYP3A4, CYP3A5, CYP2C8, MDR1, cMOAT, MRP1, and BCRP polymorphisms in relation to pharmacokinetics of taxanes, camptothecins, epipodophyllotoxins and Vinca alkaloids).

Future
The results of our genome-wide yeast screen led to the identification of 550 yeast genes a number of which can be classified in biochemical pathways that play a determining role in drug sensitivity. We now focus on the human orthologs to these yeast genes / pathways examining whether these genes play a role in clinical drug resistance. Expression of these genes is investigated in selected sets of human tumor samples and/or cell lines using oligonucleotide arrays and correlated to responsiveness to chemotherapy and/or drug resistance profiles. In addition mammalian gene knockdown by the siRNA approach will be initiated to obtain direct proof of the relevance of these genes for human cancer. With our whole-genome approach, we expect that we will be able to identify complete pathways, instead of single molecules that are involved in drug response.

A novel approach that is currently explored concerns the involvement of microRNAs (miRNAs) in the pathogenesis of cancer and possibly the development and maintenance of drug resistance. MiRNAs are small RNAs (21–22 nucleotides) that are evolutionarily conserved riboregulators modulating gene expression. MiRNAs have been shown to play a role in various important developmental processes in plants and animals and are involved in apoptosis, differentiation, cell proliferation, stem cell division and undoubtedly many other cellular processes. It is currently believed that thousands of genes are under control of miRNAs. The expression of miRNAs in human cancer cells was monitored using newly developed detection techniques including miRNA arrays and RT-PCR procedures suitable for the quantitative detection of miRNAs. It is our intention to monitor the full complement of miRNAs expressed in human cancer cells, about 400 human miRNAs have been described and correlate their expression to known clinical parameters. A next step is the functional characterization and identification of mRNA targets of selected miRNAs.

The clinical new drug development will also in future studies focus on drugs with new mechanisms of action. The use of pharmacological approaches to drug dosing, as opposed to using BSA as the only independent variable, offer exciting potential for the future, not only for the practical aspects of improving the safety of administered chemotherapy, but also as a means of targeting populations that might be able to tolerate dose intensification of the agent in question.

### Key figures

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**Theses**


**Article/Letter to the editor**


Part of book - abstract

Verweij, J., Seynaeve, C. & Sleijfer, S. (2007). GIST as the model of paradigm shift towards targeted therapy of solid
tumors: update and perspective on trial design. In F. Colotta & A. Mantovani (Eds.), Targeted therapies in cancer (pp.
144-154). Italy: Springer.
Programme design in brief

MAIN OBJECTIVE:
Immunogene therapy of cancer in general, and the therapeutic use of T lymphocytes genetically endowed with cancer-specificity in particular.

MAIN RESULT:
Successful generation of tumor-specific T lymphocytes following genetic introduction of genes encoding tumor-specific receptors, design and testing of strategies to improve efficacy and safety of TCR gene therapy, and the current continuation of a phase I study to treat metastatic renal cancer with gene-modified T lymphocytes, the first clinical study of its kind in Europe.

MAIN FOCUS:
1. GMP T cell processing and conduct of clinical immuno(gene) therapy
   - A more than 15-year track record in clinical trials of immunotherapy of solid tumors.
   - Gene transduction and T cell expansion procedures at clinical scale that meet good clinical practice (GCP) criteria.
   - A phase I immunogene therapy trial to treat metastatic renal cell cancer with autologous gene modified T cells, the first clinical study of its nature in Europe (P00.0040C/DDHK 97-29).
2. Immunological monitoring of therapeutic interventions
   - Laboratory activities have been accredited by CCKL, the Dutch foundation for quality improvement of laboratory studies and accreditation of laboratories active in health care.
   - Experimental and clinical custom-tailored (immune) monitoring packages are set up and validated, and are offered to external parties (i.e., 'contract research').
   - Routine services to immune phenotype leukemia and lymphoma or quantify minimal residual disease (see also under 6).
   - Immune monitoring techniques: up to 6-color flow cytometry and real-time PCR to assess absolute numbers, phenotype and function of patient T lymphocyte subsets (including assessment of the phosphorylation state of key molecules in T cell signalling), and in vitro technologies to measure general and antigen-specific T cell functions, such as cytokotoxic activities, cytokine production, cell proliferation and apoptosis.
3. Monitoring circulating tumor and endothelial cells (CTC and CEC)
   - CTC are enriched by immunomagnetic cell selection using the CellSearch instrument, followed by counting using the CellTracks Analyzer and followed by further characterisation (in collaboration with the Laboratory for Genomics and Proteomics).
   - CEC are enriched and enumerated using the same instrumentation as CTC, but using different reagents. CEC counts are under study as markers for vascular damage and tumor progression.
4. Experimental immunogene therapy
   a. TCR gene therapy directed against MAGE antigens
      - Molecular engineering of TCR to enhance efficacy and safety of TCR gene therapy.
      - Genetic strategies that enable T lymphocytes to counteract the immunosuppressive milieu of tumors.
      - Mouse models include: (a) transplantation of tumors onto mice transgenic for Human Leucocyte Antigens (HLA molecules) and (b) spontaneous melanoma.
      - Real-time non-invasive in vivo monitoring of gene-modified T lymphocytes via advanced intravital fluorescence microscopy (in collaboration with Laboratory of Experimental and Surgical Oncology, Erasmus MC).
   b. Selection and validation of antibodies from phage-display library. We generated a non-immune phage Fab display library allowing selections of antibodies directed against any antigen (including pMHC) of interest (repertoire about 8x10^9). Isolated antibodies are characterized for binding and can be molecularly modified to genetically direct T cells, viral and non-viral vectors, and cytotoxic drugs.
   d. Anti-tumor effect of novel molecules and their receptors. Develop and test strategies to direct potential anti-tumor activities of native molecules (i.e. members of the IL-1 and IL-10 family) as well as synthetic molecules with known pro-apoptotic and/or anti-angiogenic activities to the site of the tumor cell (i.e. via T lymphocytes or adenoviruses).
   e. Development of novel technologies
      - Development of (new) T cell transduction, selection and expansion methods.
      - Design and generation of multimeric complexes (> 4 monomers) consisting of tumor-specific receptors to facilitate killing of tumor cells (patent: International Application Number: PCT/NL2005/000878).
      - Design and testing of a ligand-addition system to target therapeutics (i.e. adenoviruses or polymer-coated drugs) to tumors (patent filed).

Key figures

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Theses


Article/Letter to the editor


Patent

Part of book - abstract
Programme design in brief
Programme design in brief: The research of the Department of Gastroenterology & Hepatology is centered around the themes premalignant lesions and chronic inflammatory processes of the gastrointestinal epithelium. The main focus is on molecular, immunological and optical detection of the development, the diagnosis, and treatment of chronic inflammatory and neoplastic diseases of 1) esophagus, 2) stomach, and 3) colon.

Ad 1) Esophagus: Reflux induced chronic inflammation is thought to be the main initiating factor for the development of Barrett's esophagus, a precursor lesion for adenocarcinoma of the esophagus. Concerning Barrett's esophagus, the investigations aim at:

a) the understanding of the inflammatory inducing factors in reflux esophagitis and Barrett's esophagus;
b) the determination of prognostic parameters in Barrett's epithelium, that predict development of malignancy, c)

c) uncovering of optical and molecular techniques for detection of dysplasia in Barrett's, and

d) development of minimal invasive treatment strategies for early malignancy.

Ad 2) Stomach: endoscopic surveillance of patients with pre-malignant gastric lesions may provide a basis for gastric cancer prevention. current surveillance in routine practice often relies on histological assessment of random biopsies obtained during conventional endoscopy. However, the appropriate biopsy strategy is unclear. Research aims to:

a) improve detection of precursor lesions that precede development of early gastric cancer;
b) to assess the predictive value of clinical, histological and serological parameters

c) to develop guidelines for clinical management of patients at increased risk for gastric cancer

Ad 3) Colon: Colon research concerns effective screening, and interventions strategies in sporadic colorectal cancer (CRC), familial and hereditary cancer syndromes and idiopathic chronic inflammation. The investigations aim at:

a) mediators of inflammation in Crohn's Disease and Ulcerative Colitis
b) mutual interaction and the effects of drugs hereon

c) uncovering of optical and molecular techniques for detection of dysplasia in members of familial and hereditary colon cancer families
e) to develop strategies for population based screening for colorectal cancer

Key figures

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Theses


Tuyl, B. van (2007, juni 01). Videocapsule endoscopy. EUR (155 pag.). Prom./coprom.: Prof.Dr. E.J. Kuipers & M.F.J. Stolk


Article/Letter to the editor


**Part of book - abstract**


**Book editorship**
EMC MM-04-20-02-A - Liverspecific immunopathology; mechanism and therapeutic modulation

Programme design in brief
The mission of the research program is to unravel the mechanisms underlying inadequate immunological reactions which lead to liver damage, and the development of effective diagnosis and treatment of these disorders. On the one hand, an insufficient immune response to hepatitis viruses causes persistence of the viruses leading to chronic hepatitis and hepatocellular carcinoma, on the other hand over-reactivity of the host immune system to antigens presented in the liver is the primary cause of hepatobiliary auto-immune diseases and of rejection after liver transplantation. The program is performed by integrated pre-clinical and clinical research. The pre-clinical research is focused on intra-hepatic immunological reactions between Antigen-Presenting Cells and T-cells in the liver of patients. The clinical research is focused on medicinal modulation of these interactions by cytokines, anti-viral-, and immunosuppressive drugs. Cohorts of patients with chronic hepatitis B, chronic hepatitis C, primary biliary cirrhosis, primary sclerosing cholangitis and vascular liver disease are the basis from which investigator-initiated randomised controlled trials are organised. Numerous global multicenter studies on antiviral therapy in chronic viral hepatitis have been coordinated by the liver group. The effects of these treatments on the intrahepatic immune reactivity are studied by sophisticated methods developed in the laboratory, such as the fine needle liver aspiration biopsy.

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Theses

Article/Letter to the editor


Man, R.A. de (2007). Hepatitis B and C: in view of the treatment options, priority should be given to reaching the groups at risk. Nederlands Tijdschrift voor Geneeskunde, 151, 2365-2366.


**Part of book - abstract**


Book editorship

Inaugurale rede
Programme design in brief
The role of virus specific immune responses in the (immune) pathogenesis of, and protection against virus infections is studied in humans and in animal models for human virus infections. Special attention is paid to infections with morbilli-, lenti-, herpes-, influenza- and hepatitis viruses. The role of virus specific antibodies in neutralization and/or enhancement of virus infectivity and the kinetics of the emergence of these antibodies, is subject of study in different systems. Similarly, also the evaluation of the role of virus specific T helper- and cytotoxic T cells is carried out. The knowledge generated in this way is used to design novel strategies of intervention in viral spreading and pathogenesis, like e.g. vaccination, diagnosis and post-exposure treatment. In this framework novel antiviral therapeutic strategies, based on immunological and non-immunological principles, are also developed. Finally, epidemiological research questions, related to infections with the aforementioned viruses and "exotic" viruses, are addressed.

Besides the continuation of the above mentioned activities, studies concerning the epidemiology and epizootiology of influenza viruses of man and animals will be extended in the next year, with a special emphasis on possibly emerging influenza pandemics. Research concerning the possible development of an HIV vaccine based on the use of Rev and Tat will be intensified. This will also be the case for research concerning the immunopathogenesis of chronic infections with HBV, HCV, EBV, CMV and HIV, with special attention for problems with multiple infections and infections in immunocompromised and transplantation patients. Finally, a focus will be on virus infections if wild and threatened animal species as well as exotic and zoonotic virus infections.

Morbillivirus, lentivirus, herpesvirus, hepatitis virus, pathogenesis, immunopathogenesis, neutralizing antibody, enhancement, cytotoxic T cell, T cell phenotype, antiviral, epidemiology, zoonosis

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Theses


Article/Letter to the editor


EMC MM-04-28-01 - Infections due to bacteria, fungi and parasites: diagnosis, molecular mechanisms, epidemiology, therapy and prevention

Programme design in brief
The project is focused on the infectious complications caused by bacteria, fungi and parasites related to recent developments in clinical medicine, such as new therapeutic modalities or resistance, an increased use of medical devices, frequent diagnostic and therapeutic intervention, and an increasing number of immunocompromised patients. As a consequence, a growing number of patients are prone to severe (nosocomial) infections that are often difficult to treat. These infections are a major cause of morbidity and mortality in these patients, which is partially enforced by failure of antibiotic treatment despite the availability of potent antibiotics. The focus of this programme is on the molecular mechanism of infection, the epidemiology, the early diagnosis using molecular techniques, the prevention of infections, as well as treatment using alternative methods. The approach is partly fundamental/animal-experimental and partly clinical/epidemiological

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Theses


Article/Letter to the editor


Kasteren, M.E.E. van, Mannien, J., Ott, A., Kullberg, B.J., Boer, A.S. de & Gyssens, I.C.J. (2007). Antibiotic prophylaxis and the risk of surgical site infections following total hip arthroplasty: Timely administration is the most important factor. Clinical Infectious Diseases, 44(7), 921-927.


Part of book - abstract

Book review


Newspaper article
Verbrugh, H.A. (). Indonesia must be smarter in handing out antibiotics. The Jakarta Post.
EMC MM-04-28-04 - Clinical research in infectious diseases in adults

Programme design in brief
The programme focuses on problems of diagnosis, prevention and therapy of infections in immunocompromised adult patients including HIV, and co-infections such as hepatitis B. Inpatients are mainly studied in the department of haematology and in the intensive care setting. Catheter-related infections, infections in neutropenic patients and HIV-infected patients are topics of specific interest. The programme explores the value of novel tools like vibrational spectroscopy in the diagnosis of infections by bacteria and fungi. In these infections that are often difficult-to-treat, new management strategies of antimicrobial drugs or inflammation modulators are expected to result in a better outcome.

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Article/Letter to the editor


Kasteren, M.E.E. van, Mannien, J., Ott, A., Kullberg, B.J., Boer, A.S. de & Gyssens, I.C.J. (2007). Antibiotic prophylaxis and the risk of surgical site infections following total hip arthroplasty: Timely administration is the most important factor. Clinical Infectious Diseases, 44(7), 921-927.


Part of book - abstract
EMC MM-04-39-05 - Renal insufficiency and organ transplantation

Programme design in brief
This program concerns various methods of renal replacement haemodialysis, peritoneal dialysis and transplantation. In the clinical setting we try to find optimal treatment modalities for acute renal failure i.e. continuous dialysis techniques (CAVHD, CVVH) and for haemodynamic instability during intermittent dialysis. In CAPD patients we study the effect of dialysis fluids on nutrition, while in patient on hemodialysis we characterize their inherent immuno deficiency. The main topic of the program is immunological monitoring of kidney- and heart transplant recipients. We study the cascades of immunological factors that lead to acute and chronic rejection. In attempt to find strategies to prevent and treat these processes.

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Theses


Article/Letter to the editor


EMC MM-04-42-02 - Cell biological and pathophysiological investigations on pulmonary diseases

Programme design in brief
Investigations of immunological, cell biological processes in inflammation, infection, transplantation and malignancies in the lungs are performed to get insight into the contribution of inflammatory cells and mediators. Emphasis is on I) the antigen presenting cell as a major contributor to the inflammatory process in obstructive and interstitial pulmonary diseases and as target and tool for therapy II) the role of transcription factors and signal transduction pathways that are essential for development and function of lymphocytes. Pathophysiological investigations are performed to increase our understanding of structure function relationships in the lungs. In this programme investigations are done in animal models and in humans. The effects of therapeutic interventions on cell biological processes and structural and functional properties of the lungs are also under investigation.

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Article/Letter to the editor


EMC MM-04-44-02 - Neuromuscular and degenerative diseases of the nervous system

Programme design in brief

This research programme aims to study various aspects of immune-mediated and degenerative disorders of the central (multiple sclerosis, encephalitis, fronto-temporal dementia, progressive supranuclear palsy/PSP, epilepsy) and peripheral (Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, mitochondrial myopathy, Pompe’s disease) nervous system. Studies are conducted in close collaboration in particular with the Departments of Immunology, Medical Microbiology and Infectious diseases, Virology, Genetics, Epidemiology, Rehabilitation of the Erasmus MC, as well as with neurological, neuroimmunological and genetic centers around the world. Clinical neurophysiological research focuses on development and application of non-invasive EMG techniques to assess motor unit function in neuromuscular disorders. The Rotterdam MS center ‘ErasMS¿ for MS and CNS inflammation integrates research and care. The Paediatric Neurology Department coordinates the long-term follow-up of the Dutch Study of Epilepsy in Childhood and participates in the ‘Generation R¿ project, and in national and international collaborative groups for the identification of genes and genotype-phenotype correlations in mitochondrial disorders, epilepsy and congenital affections of the nervous system.

The programme is focused on the following topics:

Neuromuscular disorders / neuroimmunology - peripheral nervous system.
1. Immunological, microbiological and genetic determinants leading to Guillain-Barré syndrome (GBS) and Miller Fisher syndrome.
2. Clinical trials and laboratory studies with intravenous immunoglobulin (IVIg) and other immunomodulatory drugs in GBS and the chronic inflammatory demyelinating polyneuropathy (CIDP).
3. Non-invasive EMG techniques to monitor changes in motor unit function.
6. Mitochondrial disorders leading to neuromuscular disorders, visual system disorders and encephalopathies.

Multiple sclerosis / neuroimmunology - central nervous system.
1. Immunological, genetic and infectious determinants on the disease course in Multiple Sclerosis (MS) and Acute Disseminated Encephalomyelitis (ADEM).
2. Determinants of ADEM and MS in childhood.
3. Gene discovery in MS families.
4. Immunomodulatory treatment of central nervous system (CNS) inflammatory disease.
5. The Rotterdam ‘ErasMS¿ multiple sclerosis center, including research in animal models.
6. Retinal measurements as a tool to monitor CNS inflammation.

Neurodegenerative disorders of the CNS (dementia, Parkinson and PSP)
1. Genetic factors and genotype-phenotype correlations in frontotemporal dementia, Alzheimer disease, and hereditary cerebellar ataxia.
2. Prevalence, familial aggregation and genetic factors in progressive supranuclear palsy.
3. Incidence and determinants of ALS disease in a population-based study (Rotterdam study).
5. Genetic and environmental factors in cognitive function of healthy individuals in a genetic isolated population (ERF-study).
6. The role of TDP-43 protein in the FTD and Motor Neuron Disease with neuronal ubiquitin-positive inclusions.

Epilepsy and other neurological disorders in childhood
1. Incidence and determinants of epilepsy and other paroxysmal disorders in childhood (Generation R study).
2. Course of childhood epilepsy in cohort studies with prospective long-term follow-up, developing prognostic models and evaluating modified treatment strategies.
3. Initiating and conducting therapeutic trials in childhood epilepsy.
4. Genes and genetic mechanisms in childhood epilepsy and in families with epilepsy.
5. Monitoring techniques, diagnosis and treatment modalities in neonatal seizures.
7. Molecular genetics and cognitive aspects of cerebellar dysfunction in Williams syndrome.
8. Treatment of migraine and other headaches in childhood.
10. Continuous EEG monitoring in neonatal asphyxia.

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Article/Letter to the editor


Programme design in brief

Ischemia reperfusion injury, chronic transplant dysfunction after transplantation, and hepatic steatosis are the main focus of the experimental studies on liver surgery and allotransplantation. Effects of ischemia reperfusion injury are studied in small animal models, including well defined renal, lung and hepatic models. Current experimental research focuses on the molecular mechanisms by which ischemia reperfusion injury leads to organ failure and, in the kidney allotransplantation model, to chronic transplant dysfunction. In addition, the contribution of ageing to this process is being studied. Accumulation of oxidative damage to DNA is thought to play a major role in organismal aging by compromising cellular function, triggering cell death and limiting the proliferative capacity of regenerative tissues. Clinical observations suggest an inverse relationship between ischemia time and long-term transplant success, leading to the hypothesis that this injury leads to processes also activated during premature aging of organs.

Use of knockout mice that are defective in DNA repair pathways are used to study the effects of ischemia reperfusion injury after liver resection and organ transplantation. Transcriptional profiling will be used to understand the molecular basis of the injury process. These studies are being conducted in close collaboration with the Department of Cell Biology (Prof. Dr. J. Hoeijmakers) and the Department of Immunology (Prof. Dr. R. Benner). The role of the angiotensin system in renal ischemic damage is studied in collaboration with Dr. T. Walther of the Department of Pharmacology, University Hospital Charité, Berlin, Germany.

Ischemia reperfusion injury in the lung is used to study therapeutic options to ameliorate reperfusion injury with the aim to decrease the incidence of acute respiratory distress syndrome and chronic deterioration of lung function following lung transplantation. This is done in collaboration with Prof. Dr. B. Lachmann, Department of Experimental Anaesthesiology, and Prof. Dr. B. Lambrecht, Department of Pulmonary Diseases.

Additional studies on hepatic steatosis in relation to resection and transplantation are being studied in close collaboration with Prof. Dr. J. Folkman, Department of Surgery, Childrens Hospital, Harvard Medical School, Boston, USA. Specifically, the roles of matrixmetalloproteinases in the process of hepatic lipid metabolism are being evaluated in rodent models of dietary-induced hepatic steatosis.

Research on xenotransplantation has been hampered by potential risks of viral transmission from the animal donor to the human recipient. Progress has been made on genetic modification of donor animals, including elimination of Gal-epitopes and introduction of complement-regulating factors. Using larger animal models the effects of these modifications are being studied in collaboration with Prof. Dr. D. Cooper at the Thomas Starzl Transplantation Institute, Pittsburgh, USA. Studies involving the induction of immunological tolerance are conducted in close collaboration with Prof. Dr. D. Sachs, Transplantation Biology Research Center, Harvard Medical School, Boston, USA.

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Theses


Article/Letter to the editor


EMC MM-04-49-03-A - Genitourinary tract disorders in children

Programme design in brief

Experimental and clinical investigation of normal and pathological function and recovery of the urinary tract and reproductive tract.

Antenatal diagnostics, detection of congenital disorders before birth and the resulting postnatal evaluation and treatment. Bladder dysfunction, neurogenic and structural. The mechanisms that connect loss of bladder and renal function to changes in bladder structure plus new treatments are investigated in an animal model for infravesical obstruction. Raman spectroscopy is applied for in vitro and in vivo analysis of the bladder wall-structure (also in bladder cancer). In cooperation with the centre for optical diagnostics and therapy, Dr. G.J. Puppels.

Gonadal dysgenesis. The chromosomal changes occuring in gonadal tissue of patients with gonadal dysgenesis are studied to improve its diagnosis, to gain insight into its development and to discover early markers of testicular cancer. Joint KWF project with the laboratory of experimental pathology and oncology, Dr. L.H.J. Looijenga.

Hypospadia, possible causes of hypospadias like androgen receptor and the effect of hypospadias correction on urodynamics are investigated.

Inborn errors predisposing to stone formation. The role of inborn errors in renal metabolite handling for urinary stone formation is studied.

Obstruction and reflux, of the pyelo-ureteric junction, ureter with (functional) obstructions, vesicoureteric reflux and infravesical obstruction in prospective studies. In co-operation with the department of Nuclear Medicine, Prof. Dr. H.Y. Oei.

Urinary tract infection. Proteomics and bacterial DNA analysis are used to study bacterial populations in the urinary tract and to improve diagnosis of UTI. Specific complications like bladder stone formation are analysed. New bladder rinsing fluids are developed. In co-operation with departments of medical microbiology and infectious diseases, Prof. Dr. A van Belkum, Center for Biomics, Dr. T.M. Luider and obstetrics, Dr. T Schneider.

Urodynamic investigations, in connection to the other projects the value of urodynamic evaluations is investigated in cooperation with FURORE.

Key figures

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Article/Letter to the editor


**Part of book - abstract**
Programme design in brief
The digestive tract is under constant attack by bacteria, viruses and other noxious agents in the lumen of the gastrointestinal tract. The gastrointestinal mucosa, consisting of the epithelium and the underlying immune cells in the lamina propria, forms an important line of defence against these potential harmful agents. Mucosal damage may lead to malabsorption and diarrhea, since the gastrointestinal epithelium is essential for the digestion and uptake of nutrients and for the maintenance of the liquid balance in the human body. Many types of gastrointestinal diseases lead to mucosal damage.

The mission of the research program is to unravel the mechanisms underlying normal function and disorders of the gastrointestinal tract including the liver, in childhood 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. In particular, research is focussed on mechanisms responsible for damage and subsequent regeneration of the gastrointestinal tract in 1. Inflammatory bowel diseases (Crohn and ulcerative colitis), 2. Infectious diseases (rotavirus or norovirus, E. coli) 3. Inherited diseases (cystic fibrosis, Crigler Najjar), and 4. after chemotherapy. The relevance is perhaps best illustrated by the high incidence of each of the studied diseases. Possibilities are evaluated of intervention using dietary components, probiotics, or drugs, either to prevent mucosal damage or to stimulate the recovery of mucosal functions after an insult.

Key figures

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Article/Letter to the editor
Programme design in brief

This programme aims to enhance the understanding of the (molecular) pathogenesis, pathobiology, epidemiology, diagnosis, therapy and prevention of infectious diseases and immunological disorders in children by means of clinical and basic research.

Infectious diseases are the major cause of morbidity in children and contribute substantially towards mortality in children needing top clinical care including those with AIDS, meningococcal sepsis and immunocompromised children with sepsis. Primary and secondary (acquired) immunodeficiencies as well as immunodysregulations, in particular auto-immunity, are frequent diagnostic and therapeutic challenges and often complicated by (serious) infections. The studies carried out within this project aim to increase the understanding of interactions between host and micro-organisms and to improve the diagnostic, therapeutic and preventive modalities of infectious diseases and immunological disorders.

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Article/Letter to the editor


Book - monograph - book editorial

Part of book - abstract


**Programme design in brief**

The investigation into the bacteria and viruses causing sexually transmitted diseases (STD) is focused on the detection, the identification of pathogenic factors, the regulation of the immune response during the infection and its relevance in the clinical practice. The insight that is so obtained must lead to improved diagnostic and screening methods which may broaden the insight into the epidemiology of STD. Optimising the therapy (including the possibilities for vaccination), particularly directed at more effective and patient friendly treatments has received continuous attention. Areas of accent are infections caused by Chlamydia trachomatis, Treponema pallidum and STD caused by human papilloma virus (HPV), herpes simplex virus (HSV), hepatitis B virus (HBV) and human immunodeficiency virus (HIV).

**Key figures**

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**Article/Letter to the editor**


