

Research Annual Report 2007



Medical Genetics Center (MGC)

Molecular and cellular basis of genome instability in cancer

Bioinformatics

Gene-expression during embryonal development

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Chromatin regulation in development and disease

Pathophysiology and treatment of chloride channel diseases

Forensic molecular biology

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Development disorders and congenital malformations

Reproduction and development

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EMC MGC-01-12-03 - Molecular and cellular basis of genome instability in cancer

Programme design in brief

Preserving the genome is of prime importance to all living systems. However, the integrity of DNA, the carrier of genetic information, is continuously threatened by endogenous and exogenous agents and by intrinsic instability of chemical bonds in DNA itself. Oxidative stress, UV- and X-rays and numerous chemicals induce a wide variety of lesions in DNA. Obviously, this affects proper functioning of the DNA and can lead to cell death, cancer, inborn disorders, and overall functional decline contributing to ageing. To counteract the gradual erosion of the vital genetic information and prevent its pleiotropic detrimental consequences an intricate network of genome care-taking and protection systems has evolved. DNA repair pathways and cell cycle control mechanisms constitute an important component of this genome protection network. The overall objective of this program is to understand the molecular mechanism and the biological impact of the systems designed to preserve the vital genetic material. Our primary objectives are:

1. understanding of the molecular mechanisms, specificity, fidelity and in vivo functioning of major multi-enzyme repair and damage-response pathways: nucleotide excision repair (NER), double strand break (dsb) repair and replication damage tolerance mechanisms, as well as damage-induced cell cycle arrest.
2. elucidation of the molecular defects of genetic disorders with NER (and transcription) deficiencies: xeroderma pigmentosum (XP), Cockayne's syndrome and trichothiodystrophy. These diseases are characterized by sun (UV) sensitivity, frequently neurological abnormalities, poor development, frequently features of premature ageing and in case of XP predisposition to skin cancer. A second goal is to identify human conditions associated with impaired dsb repair, damage tolerance, or cell cycle response.
3. generation of mouse models for human NER, dsb repair and damage tolerance deficiencies to assess the biological impact of these systems. The approaches followed include isolation and functional characterization of mammalian repair genes and proteins, analysis of these proteins in vitro and in living cells, their involvement in human repair syndromes, their use for inducing specific repair defects in the mouse germ-line by gene targeting as well as analysis of defects in these systems at the level of mRNA expression (genomics) and proteins (proteomics). Insight into DNA repair mechanisms is relevant for understanding the effect of DNA damage on vital processes as transcription, replication, recombination and cell cycle progression. Indirectly this process affects the origin of inborn defects, carcinogenesis, genome stability and ageing. Finally, a new line of research is aimed at elucidating the intriguing molecular mechanism and biological impact of the circadian clock in mammals.

Key figures

Department	SP1	SP2	SP3	SP4	SPtot	T1	T2	T3	Ttot	IS	FS	OP	Ptot
biochemistry		0	0	0	1	1							
genetics	9,05	17,23	8,25	12,11	46,64								
Total	9,05	17,23	8,25	13,11	47,64	1	2	1	4	36	2	3	45

Theses

Bruins, W. (2007, oktober 24). The role of p53.S389 phosphorylation in DNA damage response pathways and tumorigenesis. extern. Prom./coprom.: dr. H. van Steeg & A. de Vries.

Knipscheer, P.M. (2007, maart 22). Regulation of SUMO modification. EUR. Prom./coprom.: Prof.Dr. T.K. Sixma.

Repanas, K. (2007, september 20). Structural and functional studies on the LINE-1 retrotransposon endonuclease. EUR. Prom./coprom.: Prof.Dr. T.K. Sixma.

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

Apeldoorn, AA van, Boer, J. de, Steeg, H. van, Hoeijmakers, J.H.J., Otto, C. & Blitterswijk, CA van (2007). Physicochemical composition of osteoporotic bone in the trichothiodystrophy premature aging mouse determined by confocal Raman microscopy. *Journals of Gerontology Series A-Biological Sciences and Medical Sciences*, 62(1), 34-40.

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Seelig, J, Leslie, K., Renn, A, Kuhn, S, Jacobsen, V, Corput, M. van de, Wyman, C. & Sandoghdar, V (2007). Nanoparticle-induced fluorescence lifetime modification as nanoscopic ruler: Demonstration at the single molecule level. *Nano Letters*, 7(3), 685-689.

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Uematsu, N, Weterings, E.P.W.C., Yano, K., Morotomi-Yano, K, Jakob, B, Taucher-Scholz, G, Mari, P., Gent, D.C. van, Chen, BPC & Chen, DJ (2007). Autophosphorylation of DNA-PKCS regulates its dynamics at DNA double-strand breaks. *Journal of Cell Biology*, 177(2), 219-229.

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Part of book - abstract

Agarwal, S., Kanaar, R. & Essers, J. (2007). The cell biology of homologous recombination. In A. Aguilera & R. Rothstein (Eds.), *Molecular genetic of recombination* (pp. 335-362). Germany: Springer Verlag.

Bohr, V.A., Wilson III, D.M., Souza-Pinto, N.C. de, Pluijm, I. van der & Hoeijmakers, J.H.J. (2007). DNA repair and aging. In *Molecular biology of aging* (pp. 309-346). --: Cold Spring Harbor Laboratory Press.

Jaspers, N.G.J. (2007). Lang leven en jeugdig sterven? Een wetenschappelijk perspectief. In R. Custers (Ed.), *Tussen hype en hoop* (pp. 83-100). Leuven: LannooCampus.

EMC MGC-02-02-01 – Bioinformatics

Programme design in brief

In collaboration with other departments the department of Bioinformatics multidisciplinary team supports projects that generate genomics and proteomics data from basis research, forensics studies, molecular diagnostics and clinical trials. The center also runs a research program of its own, which provides the biological and technological basis of all the other activities. It concentrates on the way the genome as a whole contributes to the evolution, development, structure and function of the brain. Among others it involves analysis of gene expression in cells of the brain and combines genomics, proteomics and cytogenetic data to identify genes associated with neurological disorders. The Erasmus MC Bioinformatics department initiated a translational medicine program. This effort will assist in the critical task of moving medical research closer to commercial Ready medical technology that can be applied within and outside Erasmus University Medical Center. Moving medicine forward requires data integration from Bench to Bedside and from Patient to Population. The bioinformatics department plays a central role in linking research data onto clinical data using state of the art ICT technology and medical informatics expertise. The ultimate goal is to identify biomarkers linking genotypic data and phenotypic data to support processes such as determination of genetic risk, patient stratification, disease staging, treatment selection and evaluation of outcome to improve the quality of life of the patient. This strategy will also provide insight in environmental factors, lifestyle information, and treatment history that correlate with the natural history of the disease

Key figures

Department	SP1	SP2	SP3	SP4	S _{Ptot}	T1	T2	T3	T _{tot}	IS	FS	OP	P _{tot}
bioinformatics	1,88	0	0	0,62	2,5								
neurosciences	1	0	0	1	2								
Total	2,88	0	0	1,62	4,5	0	0	0	0	8	2	2	12

Article/Letter to the editor

Bol Raap, G., Koning, A.H.J., Scohy, T.V., Harkel, A.D.J. ten, Meijboom, F.J., Kappetein, A.P., Spek, P.J. van der & Bogers, A.J.J.C. (2007). Virtual reality 3D echocardiography in the assessment of tricuspid valve function after surgical closure of ventricular septum defect. *Cardiovascular Ultrasound*, 16(5), 8.

Cath, D, Heutink, P., Grados, M, Singer, H.S., Walkup, J.T., Illmann, C, Scharf, JM, Santangelo, S, Stewart, SE, Platko, J, Pauls, D.L., Cox, NJ, Robertson, M.M., Service, S, Keen-Kim, D, Sabatti, C, Freimer, N, Rouleau, G.A., Riviere, JB, Chouinard, S, Richer, F, Lesperance, P, Dion, Y, King, R.A., Kidd, JR, Pakstis, AJ, Leckman, J.F., Kidd, K.K., Gericke, G, Kurlan, R., Como, P, Palumbo, D., Verkerk, A., Oostra, B.A., McMahon, W, Leppert, M., Coon, H, Mathews, C, Sandor, P., Barr, C.L., Betard, C & Zelenika, D (2007). Genome scan for Tourette disorder in affected-sibling-pair and multigenerational families. *American Journal of Human Genetics*, 80(2), 265-272.

Eijken, M, Swagemakers, S., Koedam, M., Steenbergen, C, Derkx, P., Uitterlinden, A.G., Spek, P.J. van der, Visser, J.A., Jong, F.H. de, Pols, H.A.P. & Leeuwen, J.P.T.M. van (2007). The activin A-follistatin system: potent regulator of human extracellular matrix mineralization. *Faseb Journal*, 21(11), 2949-2960.

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Koning, A.H.J., Bol Raap, G., Bosch, A.E. van den, Meijboom, F.J., Bogers, A.J.J.C. & Spek, P.J. van der (2007). Virtual reality in aid of 3D echocardiography. *International Journal of Computer Assisted Radiology and Surgery*, 2(1), 123.

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Santegoets, L.A.M., Seters, M. van, Helmerhorst, T.J.M., Heijmans-Antonissen, C., Hanifi-Moghaddam, P., Ewing, PC, Ijcken, W.F.J. van, Spek, P.J. van der, Meijden, W.I. van der & Blok, L.J. (2007). HPV related VIN: Highly proliferative and diminished responsiveness to extracellular signals. *International Journal of Cancer*, 121(4), 759-766.

Tissing, W.J.E., Boer, M.L. den, Meijerink, J.P.P., Menezes, R.X. de, Swagemakers, S., Spek, P.J. van der, Sallan, S.E., Armstrong, S.A. & Pieters, R. (2007). Genomewide identification of prednisolone-responsive genes in acute lymphoblastic leukemia cells. *Blood*, 109(9), 3929-3935.

Vujkovic, M., Ocke, M.C., Spek, P.J. van der, Yazdan Panah, M., Steegers, E.A. & Steegers-Theunissen, R.P. (2007). Maternal Western dietary patterns and the risk of developing a cleft lip with or without a cleft palate. *Obstetrics and Gynecology*, 110(2), 378-384.

Part of book - abstract

Spek, P.J. van der (2007). Scaling up clinical research by expansion of electronic infrastructure. Data management in pharmaceutical research & development. In Oracle life sciences (pp. 17-19). --: --.

Stubbs, A, Yper, S.J.L. van & Spek, P.J. van der (2007). Microarray bioinformatics. In The encyclopedia of the human genome. --: Nature.

EMC MGC-02-13-02 - Gene-expression during embryonal development

Programme design in brief

Research is aimed at two main interests; the development of the hemopoietic system and the development of the brain including the neural crest. Study of the hemopoietic system is focussed on two different aspects, the control of gene expression during development and differentiation and on the processes that underlie the induction of the hematopoietic at different times of development. The control of gene expression is mainly focussed on the regulation of transcription of the globin genes and the transcription factors involved in this process. We are also very interested in B cell development, a cell type that responds to an ordered set of cell surface signals for its development resulting in the rearrangement of immunoglobulin genes. These studies are focused on one of the genes involved in signalling and the genes that are responsible for the rearrangement process. Hemopoietic induction is mainly focussed on the characterization of early stem cells that form the foetal/adult blood system. The study of the development of neural crest cells and the brain is focused on three separate areas. Firstly, we are interested in the molecular controls underlying Schwann cell development, secondly the molecular defects that underlie DiGeorge's syndrome and thirdly the relationship between cellular structure and function in the brain. Included in the last programme is the elucidation of the molecular defects in Alzheimer's disease

Key figures

Department	SP1	SP2	SP3	SP4	SPtot	T1	T2	T3	Ttot	IS	FS	OP	Ptot
cell biology	11,23	9,72	1,75	8,75	31,45								
genetics	1,85	0	0	0,15	2								
Total	13,08	9,72	1,75	8,9	33,45	4	1	0	5	36	4	0	45

Theses

Branco Madeira, F.J. (2007, september 19). Influence of protein kinases and microtubule binding proteins in cerebellar motor learning. EUR. Prom./coprom.: Prof.Dr. F.G. Grosveld, Prof.Dr. C.I. de Zeeuw & Dr. N.J. Galjart.

Carella, M. (2007, januari 31). The role of MN1-TEL, MN1 and TEL2 in leukemia. EUR (191 pag.). Prom./coprom.: Prof.Dr. F.G. Grosveld & Dr. G.C. Grosveld

Heath, H.E. (2007, december 13). CTCF: comprehending the complex functions of an 11 zinc finger transcription factor. EUR (219 pag.). Prom./coprom.: Prof.Dr. F.G. Grosveld & Dr. N.J. Galjart.

Kooren, J.A. (2007, december 19). α -Globin gene regulation and nuclear organisation. EUR (166 pag.). Prom./coprom.: Prof.Dr. F.G. Grosveld & Dr. N.J. Galjart.

Miedema, M. (2007, april 04). Cytoplasmic linker proteins keeping in shape by regulating the cytoskeleton. EUR (126 pag.). Prom./coprom.: Prof.Dr. F.G. Grosveld & Dr. N.J. Galjart.

Article/Letter to the editor

Asselin-Labat, ML, Sutherland, KD, Barker, H, Thomas, R, Shackleton, M, Forrest, NC, Hartley, L, Robb, L, Grosveld, F.G., Wees, J. van der, Lindeman, GJ & Visvader, JE (2007). Gata-3 is an essential regulator of mammary-gland morphogenesis and luminal-cell differentiation. *Nature Cell Biology*, 9(2), 201-U103.

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EMC MGC-02-13-03 - Gene-therapy

Programme design in brief

Research is centered towards some fundamental mechanisms which determine the development of disease specific gene therapies. The diseases under study are: cystic fibrosis, thalassemia, immunodeficiencies, Crigler Najjar, neoplasia and restenosis. The present and future research is focused on the development of non viral delivery vehicles with particular attention to the process of the transport of DNA into the nucleus in non dividing cells and the integration of DNA into the host genome. In addition we are developing replicating vectors based on papilloma virus replication origins. Part of this project is a joint effort with the department of Pediatrics (OR-01-54-02), Cardiology (COEUR-06-43-06) and Surgery (COEUR-04-43-04)

Key figures

Department	SP1	SP2	SP3	SP4	SPtot	T1	T2	T3	Ttot	IS	FS	OP	Ptot
cell biology	7,12	8,95	0	11,08	27,15								
Total	7,12	8,95	0	11,08	27,15	1	0	0	1	20	1	0	22

Theses

Haak, E. (2007, juni 27). The role of the embryonic microenvironment in hematopoietic cell development. EUR (153 pag.). Prom./coprom.: Prof.Dr. E.A. Dzierzak.

Article/Letter to the editor

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EMC MGC-02-21-01 - Chromatin regulation in development and disease

Programme design in brief

The goal of this research program is to understand the mechanism of gene expression control during development and disease. We are interested in how the expression of the eukaryotic genome is regulated. In particular, we focus on the role of chromatin regulation in development and disease. Over the last decade or so, it has become clear that chromatin structure forms an integral part of the mechanisms by which gene transcription is controlled in eukaryotic cells. Our studies focus on three related topics: (1) The role of SWI/SNF-class ATP-dependent chromatin remodeling complexes in transcription regulation during development and disease. (2) Transcription control by protein (de)ubiquitylation. (3) Mechanism of gene silencing by Polycomb group proteins. For many of our studies, we use *Drosophila* as a model organism because it allows an integrated combination of biochemistry, proteomics and developmental genetics. In addition, we investigate the mechanism of tumor suppression by hSNF5, a core subunit of human SWI/SNF remodeling complexes. For these studies we use human tumor cell lines and mouse models. Moreover, we investigate the role of protein (de)ubiquitylation in human cancer. Finally, we are interested in how Polycomb group silencers and chromatin remodeling factors mediate epigenetic control of the INK/ARF tumor suppression locus and its effect on human disease and (stem) cell differentiation.

Key figures

Department	SP1	SP2	SP3	SP4	SPtot	T1	T2	T3	Ttot	IS	FS	OP	Ptot
biochemistry	3,65	4	1	3,18	11,83								
cell biology	0,5	0	0	0	0,5								
Total	4,15	4	1	3,18	12,33	0	0	0	0	8	0	0	8

Article/Letter to the editor

Faber, M.J., Dalinghaus, M., Lankhuizen, I.M., Bezstarosti, K., Verhoeven, A.J.M., Duncker, D.J.G.M., Helbing, W.A. & Lamers, J.M.J. (2007). Time dependent changes in cytoplasmic proteins of the right ventricle during prolonged pressure overload. *Journal of Molecular and Cellular Cardiology*, 43, 197-209.

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Malvagias, S, Papi, L, Morrone, A, Donati, M.A., Ciani, F, Pasquini, E., Marca, G la, Scholte, H.R., Genuardi, M. & Zammarchi, E. (2007). Fatal malonyl CoA decarboxylase deficiency due to maternal uniparental isodisomy of the telomeric end of chromosome 16. *Annals of Human Genetics*, 71, 705-712.

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Sanchez, C, Sanchez, I, Demmers, J.A.A., Rodriguez, P., Strouboulis, J & Vidal, M (2007). Proteomics analysis of Ring1B/Rnf2 interactors identifies a novel complex with the Fbx10/Jhdm1B histone demethylase and the Bcl6 interacting corepressor. *Molecular & Cellular Proteomics*, 6(5), 820-834.

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EMC MGC-02-21-02 - Pathophysiology and treatment of chloride channel diseases

Programme design in brief

The transport of anions across cellular membranes is crucial for a broad range of functions, including transport of salt and water across epithelia, the regulation of cell volume, ionic homeostasis of intracellular organelles, exocytosis, pH regulation and the control of electrical excitability of muscle and nerves. This programme focuses on chloride channels involved in transepithelial ion transport (CFTR, bestrophins) and cell volume regulation (VRAC). Mutation or dysregulation of these chloride channels underlies a large spectrum of diseases including cystic fibrosis (CF), secretory diarrhea (e.g. cholera), pulmonary oedema, asthma and retinal degeneration. How mutations in the CFTR chloride channel affect the folding, processing, membrane recycling and gating of this protein and its regulation of other ion transporters such as sodium-hydrogen and chloride-bicarbonate exchangers is studied by biochemical and electrophysiological techniques at the level of cultured cells and CF mouse models. A major new research goal of the group is the *in vivo* rescue of mutant-CFTR function in CF mice by pharmacological approaches, and the *ex vivo* testing of promising candidate drugs by bioelectric assays in rectal biopsies and nasal mucosa from cystic fibrosis patients (carried out in collaboration with Drs. M. Sinaasappel and H. Tiddens from the Sophia Children's Hospital; see EMC MM-04-54-07). In addition, new approaches are explored to prevent excessive salt- and water loss in diarrheal diseases by interfering with transmembrane signaling by microbial enterotoxins or by the development of specific CFTR channel inhibitors.

Key figures

Department	SP1	SP2	SP3	SP4	SPtot	T1	T2	T3	Ttot	IS	FS	OP	Ptot
biochemistry	4,92	0	1,8	0	6,72								
Total	4,92	0	1,8	0	6,72	0	0	0	0	10	1	0	11

Article/Letter to the editor

Broere, N., Hillesheim, J, Tuo, B, Jorna, H., Houtsmuller, A.B., Shenolikar, S, Weinman, EJ, Donowitz, M, Seidler, U, Jonge, H.R. de & Hogema, B.M. (2007). Cystic fibrosis transmembrane conductance regulator activation is reduced in the small intestine of Na⁺/H⁺ exchanger 3 regulatory factor 1 (NHERF-1)-but not NHERF-2-deficient mice. *Journal of Biological Chemistry*, 282(52), 37575-37584.

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EMC MGC-02-26-01 - Forensic molecular biology

Programme design in brief

The Department of Forensic Molecular Biology is a joined initiative of the Erasmus University Medical Center (Erasmus MC), the Erasmus University and the Netherlands Forensic Institute (NFI). We are using state-of-art technologies in genetics, genomics and proteomics to answer questions in human molecular biology and human molecular genetics that are of fundamental scientific interest and in addition provide potential applications to forensic sciences. Research topics are initiated by more current issues in forensic molecular biology such as the identification of the type of tissue and the age of a sample found at the crime scene, or the identification and interpretation of a male component using Y chromosome genetic information, or the identification of the geographic ancestry of an unknown DNA sample using genetic information, but also by more future issues such as the potential use of genetic information that indirectly or directly allows prediction of externally visible characteristics of humans. In addition, we study lethal disorders and unexplained death to understand their biology and to develop biomarkers for future molecular autopsy. We are also using human genetic variation to investigate relationships, origins and migration history of human populations and are interested in footprints of local adaptation and natural selection in the human genome.

Key figures

Department	SP1	SP2	SP3	SP4	SPtot	T1	T2	T3	Ttot	IS	FS	OP	Ptot
forensic molecular biology	2,65	0	0	0	2,65								
Total	2,65	0	0	0	2,65	0	0	0	0	10	1	3	14

Article/Letter to the editor

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EMC MGC-02-52-01-A - Clinical and experimental aspects of embryogenesis and early placental development

Programme design in brief

General objectives: To study the etiology of abnormal pregnancy outcome and gene-environmental interactions in relation to abnormal embryogenesis and first trimester malplacentaion in particular. Acquired knowledge is used to develop programs of prevention of abnormal pregnancy outcome by risk selection and intervention before pregnancy (preconception) care and in early pregnancy (prenatal screening)

The following objectives are addressed:

a: the significance of 3D and 4D real-time colour Doppler ultrasound as well as the use of a Barco I-Space, a virtual reality system that allows binocular depth perception, for the study of normal and abnormal embryogenesis and placentaion in early pregnancy (in collaboration with the department of Bioinformatics)

b: genetic and immunological aspects of abnormal placental development, subsequent suboptimal fetal growth and development and maternal pregnancy complications (in collaboration with depts. Clinical Genetics, Epidemiology and Generation R)

c: psychological and medico-ethical aspects of preconception care and prenatal medicine (in collaboration with the Depts of Bioethics and Medical Psychology)

d: feasibility of hospital and community programs of preconception care and prenatal screening

Key figures

Department	SP1	SP2	SP3	SP4	SPtot	T1	T2	T3	Ttot	IS	FS	OP	Ptot
gynaecology/obstetrics	1,53	0	0	0	1,53								
Total	1,53	0	0	0	1,53	2	0	0	2	42	6	9	59

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Article/Letter to the editor

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EMC MGC-02-53-01-A - Development disorders and congenital malformations

Programme design in brief

The aim of this programme is to gain insight into the causes and effects of developmental disorders and congenital malformations. Various methods are employed. The first two subprogrammes (a, b) are based on a toxicologically-induced abnormal, or an existing and inbred phenotype, respectively, and attempt to map the genotype and associated gene products. Human material was recently included in the analyses. The third subprogramme (c) attempts to identify candidate genes, to analyse their products, and to define the process leading to the associated (abnormal) phenotype, using human material harvested during operative repair. Subprogramme (d) assesses the long-term medical, psychosocial and socially-relevant effects of the treatment of congenital malformations.

Subprogrammes:

- The role of hormones and that of the genes expressed during normal and abnormal lung development are studied in a reproducible rat model of abnormal lung development induced by Nitrofen, in transgenic mice, and in organotypic cultures of embryonic lung buds.
- Pathophysiologic and genetic characterization of the development of chronic renal insufficiency, and its possible prevention and treatment. Mainly the spontaneously hypertensive fawn-hooded (FHH) rat strain is used, which develops proteinuria and kidney damage at an early age and dies prematurely from end-stage renal failure. The susceptibility to develop renal damage is influenced by at least five genes, named Rf-1 to Rf-5. Main efforts are currently directed at pathophysiologic changes induced by the five Rf-loci and at the identification and functional characterization of Rf-1 on rat chromosome 1.
- To elucidate the phenotype-genotype relationship of derivatives of the foregut human material collected during operative repair, and combined with genomics and proteomics approaches to identify mutations. These data are combined with data from animal experiments using mutant mice evaluating the role of candidate genes during normal and abnormal phenotype expression.
- Short-term and long-term follow-up studies, somatically and psychosocially (quality of life), of congenital malformations, especially related to parental support, nutritional assessment, pain management in pediatric surgical patients in the perioperative period, and management of undescended testes.

Key figures

Department	SP1	SP2	SP3	SP4	SPtot	T1	T2	T3	Ttot	IS	FS	OP	Ptot
anesthesiology	0,5	0	0	0	0,5								
family practice	0,25	0	0	0,25	0,5								
pediatric surgery	5,09	0	0	2,67	7,76								
rehabilitation	0	0	0	0,03	0,03								
Total	5,84	0	0	2,95	8,79	4	1	0	5	30	4	5	44

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EMC MGC-02-82-01 - Reproduction and development

Programme design in brief

The research program focuses on regulation and dysregulation of development of the gonads and the genital system, sex differentiation, and gametogenesis in males and females.

The program is directly linked to sex differentiation disorders, male and female infertility, and cancers of the reproductive system. Hence it involves collaboration with the clinical disciplines Pediatric Endocrinology and Urology, Gynecological Oncology, Reproductive Medicine (including Andrology), Experimental Pathology, and Clinical Genetics.

Gametogenesis (spermatogenesis and oogenesis) includes mitotic expansion of cells, meiotic recombination of genetic information, and unfolding of dedicated gene expression programs. Molecular and cellular factors implicated in control of gametogenesis are studied in genetically modified mouse models, also using cellular imaging technology. To facilitate transfer of knowledge to the clinic, the focus is on genes and proteins that are conserved between mouse and human. We study the roles of growth and differentiation factors in (dys)regulation of testicular and ovarian cell-cell interactions and development of ovarian sexcord-stromal tumors. Furthermore, we study gametogenic and early embryonic chromatin rearrangements, X chromosome inactivation, and gene expression, since we feel that this is highly relevant in relation to evaluation of possible risk factors associated with application of assisted reproduction techniques. Collaboration with a pharmaceutical company addresses identification of molecular targets for non-hormonal contraception.

Gonadal steroid hormones play essential roles in regulation of male and female gonadal functions, sex differentiation, and development and maintenance of reproductive functions. The focus of this part of the research program is on molecular and cellular mechanisms of action of steroid hormones and analogues, involving the androgen receptor, the estrogen receptors alpha and beta, and the progesterone receptors A and B. Mechanistic and functional differences between different steroid hormone receptors, as to identity and properties of interacting proteins and receptor activities in the absence of ligand, are studied. Using mouse models and human cell lines, we aim to identify regulatory factors involved in development and regulation of the male and female reproductive systems, with special emphasis on tissue-specific actions of androgens and other steroid hormones in growth and metastasis of endometrium cancers. In collaboration with a pharmaceutical company the program includes molecular analysis of the bioactivity of several steroid hormone analogues.

Key figures

Department	SP1	SP2	SP3	SP4	SPtot	T1	T2	T3	Ttot	IS	FS	OP	Ptot
cell biology	0	0,75	0	0	0,75								
gynaecology/obstetrics	0,9	0	0	0	0,9								
reproduction and development	2,75	0,75	0	0	3,5								
Total	3,65	1,5	0	0	5,15	1	0	0	1	8	0	0	9

Theses

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EMC MGC-02-96-01 - Identification and characterisation of disease genes

Programme design in brief

Identification and characterisation of disease genes will offer the opportunity for genetic counselling of couples with an enhanced genetic risk. In this project we will develop methods to study 'single gene disorders- as well as polygenetic / multifactorial disorders in order to diagnose a (genetic) defect in patients and carriers. For several disorders the genetic and cellular defect will be studied by isolating the responsible gene (positional cloning) followed by characterizing of the cellular defect or by characterizing and purifying the protein involved and subsequent isolation of the gene. We will study the gene defects and this will allow us to study the relation between the gene mutation and the cellular defects (genotype / phenotype relation). These methods have been used successfully to elucidate the etiology and pathogenesis of the fragile X syndrome and tuberous sclerosis.

At the same time we are studying lysosomal storage disorders and genetic factors involved in neurogenetic disorders (together with the department of Neurology (NEU440201) and Epidemiology (GZZ640101). Within families with hereditary hand malformations the genetic defect will be searched for via positional cloning of the responsible gene(s). In animal models the embryonal development of the limb will be studied to gain more insight into the function of the identified genes (together with the department of Plastic Surgery (HKG500101) and Anatomy (ANA100306).

After genetic counselling it has been shown that 50-90% of parents with a high genetic risk decide not to have more children. For most parents this is a difficult decision and offering the opportunity of prenatal diagnosis (followed eventually by a termination of the pregnancy) is of great relief for the parents. The second purpose of this project is to develop fast and reliable methods for prenatal diagnosis of inborn/hereditary disorders

Key figures

Department	SP1	SP2	SP3	SP4	Sptot	T1	T2	T3	Ttot	IS	FS	OP	Ptot
cell biology	0	0	0,2	0	0,2								
clinical genetics	11,7	2,92	1,95	0	16,57								
genetics	0	0,6	0	0	0,6								
Total	11,7	3,52	2,15	0	17,37	6	0	0	6	102	7	2	117

Theses

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