



**PROJECTS FUNDED BY
MARIE CURIE EXCELLENCE GRANT
(EXT)**

AND CHAIR (EXC) ACTIONS

2004

LIFE

PATHOGENESIS AND TREATMENT OF CHRONIC AIRWAY DISEASE IN NOVEL ANIMAL MODELS

AIRWAY DISEASE

Chronic airway diseases like asthma, chronic bronchitis and cystic fibrosis belong to the most frequent chronic diseases in Europe. Progress in the understanding of the pathophysiology and development of effective treatments for these diseases has been hampered by the lack of good animal models for human disease, i.e. even "knock-out" mice for the monogenic disease cystic fibrosis lacked a lung disease phenotype. We have recently developed a novel transgenic mouse model with airway-specific overexpression of epithelial sodium channels (ENaC) and demonstrated that a dysbalance of airway ion transport causes a severe spontaneous lung disease that shares common features with human chronic airway diseases, including mucus obstruction, goblet cell metaplasia and inflammation (Mall M et al, Nat. Med. 2004). The goal of this project is to exploit and further develop this animal model for studies on the pathogenesis and the development of novel treatments for chronic airway diseases. To this end we will determine factors that influence disease severity in ENaC-overexpressing mice and test the therapeutic in vivo effects of ion channel modulators, and novel inhibitors of inflammation and mucus hypersecretion. We will evaluate the effects of these treatment modalities on airway mucus obstruction, airway remodelling, chronic inflammation and lung infection with pathogens. Our overall aim is to improve our current understanding of the in vivo pathogenesis and the development of effective therapies for chronic airway diseases in humans.



Dr. Marcus Mall

Contact Details

Host Institution: University Hospital Heidelberg
Department of Pediatrics III (Director: Prof. Dr. A. E. Kulozik, PhD)
Im Neuenheimer Feld 153, D-69120 Heidelberg, Germany

URL Host: <http://www.klinikum.uni-heidelberg.de/index.php?id=1035&L=1>

Team Leader: Dr. Marcus Mall; Email: Marcus.Mall@med.uni-heidelberg.de

URL team Leader <http://www.klinikum.uni-heidelberg.de/index.php?id=7334&L=1>

COMPARATIVE FUNCTIONAL GENOMICS OF CELLULAR SIGNALING PATHWAYS

CELLULAR SIGNALING

Cancer and other human diseases are often caused by aberrations in cellular signaling pathways. Mutations in signal transduction components have been shown to stimulate cell proliferation and migration, ultimately leading to uncontrolled growth and metastasis. Such examples include the Wnt, Hedgehog, Notch signaling pathways that are also required for development from invertebrates to mammals. Studies in model organisms such as *C. elegans*, *Drosophila* and mice have contributed significantly to our understanding of how cells transmit information in vivo. We propose to use cell-based assays and genome-wide RNAi approaches to systematically identify components of signaling pathways both in human and *Drosophila* cells. During the past years, the sequencing of the human genome and the genomes of diverse model organisms led to the annotation of many genes with unknown function. We have developed methodologies to perform rapid high-throughput RNA interference screens in cell-based assays. To identify and characterize novel signaling pathway components, we will use a comparative functional genomics approach that will allow us to use the advantages of a less complex invertebrate genome to comprehensively identify genes that may be missed in our parallel approaches in human cells. Identified pathway components will be further characterized using genetic, biochemical and molecular methods and will be analyzed for deregulation in human cancers. Identified components can constitute targets for drug discovery to interfere with inappropriate signaling pathway activation. Our main aim is to develop and apply rapid reverse genetic screens to systematically identify function on a genome-wide scale with a focus on conserved and disease-relevant signalling pathways.



Dr. Michael Boutros

Contact Details

Host Institution : Deutsches Krebsforschungszentrum
Research Group Signaling and Functional Genomics
Im Neuenheimer Feld 580
D-69120 Heidelberg
Germany

URL Host : <http://www.dkfz.de>

Team Leader : **Dr. Michael Boutros**

URL Team Leader : <http://www.dkfz.de/signaling/>

FUNCTIONAL GENOMICS OF FAMILIAL HYPERTROPHIC CARDIOMYOPATHY

FUGEN-FHC

Familial hypertrophic cardiomyopathy (FHC) is a myocardial disease with the major feature of asymmetric septal hypertrophy (ASH). It is one of the most common monogenic diseases with an estimated disease prevalence of 1:500 in young adults. It is the major cause of sudden death in the young and is associated with a significant risk of heart failure. The major objective of the present project is the elucidation of the mechanisms by which cardiac myosin-binding protein C (cMyBP-C) mutations lead to FHC. Particularly, we will investigate two new concepts, the first one emerging from our recent data: (1) Impairment by truncated cMyBP-C mutants of the ubiquitin-proteasome system (UPS) as a pathogenic factor of FHC and (2) Specific mobilization and differentiation of recently identified Isl-1 positive cardioblasts as a cause of ASH. Other objectives concern the role of cMyBP-C in sarcomere structure and its phosphorylation in regulation of cardiac contraction. The recent development of two targeted and one transgenic cMyBP-C mice by L. Carrier will allow to resolve these issues. The heterozygous cMyBP-C null mice is the first model with ASH and will therefore enable us to identify the cause of this enigmatic alteration. We recently demonstrated that truncated cMyBP-Cs are substrates and inhibitors of the UPS. Impairment of the UPS in the pathogenesis of FHC is a novel concept in cardiology, which parallels the pathogenesis of some neurodegenerative disorders. The concept will be tested in different cMyBP-C mutant mice leading to unstable mutated or truncated proteins. The material and methods used in the project will be targeted transgenesis, recombinant adenovirus, proteasome reporter mice, 3D-engineered heart tissue, echocardiography, Millar tip catheter, sarcomere length measurements and calcium handling in intact adult mouse cardiac myocytes, osmotic minipumps, confocal and electronic microscopy, transcriptome and proteome analysis.



From left to right: **Nessan Hergesell** (Medical student), **Irina Kröger** (Biochemistry student), **Lucie Carrier** (Team Leader, EU), **Lutz Pohlmann** (PhD student, EU), **Elisabeth Krämer** (Technician), **Saskia Schlossarek** (PhD student, EU), **Thomas Eschenhagen** (Host Institute Director)

Contact Details

Host Institution: University Hospital Hamburg-Eppendorf
Institute of Experimental and Clinical Pharmacology (Director Prof. Dr. Thomas Eschenhagen)
Hamburg, Germany
[http:// www.uke.uni-hamburg.de](http://www.uke.uni-hamburg.de)

Team Leader: Dr. Lucie Carrier, e-mail: l.carrier@uke.uni-hamburg.de

NEW TOOLS FOR DELIVERING THERAPEUTIC PROTEINS : APPLICATION TO HUMAN THERAPY

HUMPROTHER

There is a worldwide pent-up demand for the development of new technologies to allow rapid medical diagnostic and specific human therapy. One of the major challenge now is to develop delivery systems which are convenient and effective for tackling problems in disease treatments. We have developed two new strategies aiming at producing and delivering biotherapeutic proteins. The first one is based on the use of polypeptide transduction carriers to directly deliver therapeutic proteins into mammalian tissues and cells. We have recently isolated and characterised two new natural polypeptides transduction carriers which have the capacity with a high efficiency to directly traverse biological membranes. We anticipate that these membrane permeable proteins will represent a new class of transduction carriers and may have important functions in protein therapy for cancer and infectious diseases. The second one focused on in vitro protein synthesis technologies for producing recombinant proteins. We have recently demonstrated the effectiveness of a cell-free expression system in production of membrane proteins directly coupled to liposomes. Our technology for producing membrane proteins represents an original and powerful approach to produce immunogenic proteoliposomes for the development of new vaccines delivery systems and therapeutic proteoliposomes for human diseases. The long term objective of this proposal is to provide new vectors for biologically relevant vaccines and delivery of therapeutic proteins and also, to increase our potential in therapeutic strategies. These biological vectors will be checked for their transduction properties by testing therapeutic protein candidates on human diseases models. This original approach represents an unique system that would allow to increase the potential in therapeutic strategies for the european academic and pharmaceutical laboratories and will bring out a considerable breakthrough into the world-wide human therapy.



Team Leader: Dr. Jean-Luc Lenormand



From left to right: **Pr B. Polack** (Vaccination and Biotechnology Unit), **Pr F. Morel** (Director), **Dr B. Toussaint** (Vaccination and Biotechnology unit), and **Dr JL. Lenormand** (Team Leader)

Contact Details

Host Institution : Laboratoire Européen HumProTher, GREPI, MENRT-EA2938, Université Joseph Fourier, CHU-Grenoble, BP217, 38043, Grenoble cedex 9, France. Phone : 33(0)4 76 76 54 83 ; 33(0)4 76 76 94 14 (direct) ; Fax : 33(0)4 76 76 56 08; Email: JLLenormand@chu-grenoble.fr

url : <http://www-sante.ujf-grenoble.fr/GREPI/phoxnox/accueil.htm>

Team Leader: Dr. Jean-Luc Lenormand

CONTROL OF INSULIN SENSITIVITY THROUGH TRANSCRIPTIONAL CO-FACTORS: IMPLICATIONS FOR TYPE II DIABETES THERAPY

INSULIN RESISTANCE

According to WHO estimates, 300 million people will be diagnosed with type II diabetes in 2025 worldwide. The development of resistance against the pancreatic hormone insulin is the hallmark of diabetic pathogenesis. Importantly, insulin resistance is not only associated with the diabetic state but is intimately linked to cancer cachexia, obesity, and the adverse effects of aging, all of which become increasingly important threats to public health in European countries. Insulin resistance in skeletal muscle is the first lesion in individuals with type II diabetes susceptibility. The molecular mechanisms leading to its manifestation are still unknown, thereby, preventing the development of effective treatment strategies. To this end, the hormone-dependent activity of molecular switch proteins, so-called transcriptional co-factors, has been established by our previous studies as a critical checkpoint in the control of insulin-sensitive metabolic pathways in other tissues. Consequently, by using viral gene therapy and functional genomics/proteomics approaches, the major objective of this project is to uncover the molecular function of transcriptional co-factors in skeletal muscle and to determine their role in the development of insulin resistance in metabolic diseases. To this end, we aim to identify target gene networks in muscle and, by combining chemistry, pharmacology and bioinformatics in an interdisciplinary approach, to establish transcriptional protein complexes as novel targets for therapeutic synthetic compounds. This study aims to substantially elucidate molecular mechanisms of peripheral insulin resistance and define transcriptional co-factors as prototypic molecular targets for innovative therapy of metabolic diseases, such as type II diabetes and cancer cachexia. In this regard, the current proposal displays significant overlap with the priority of the FP6 to combat chronic diseases.



Dr. Stephan Herzig

Contact Details

Host Institution : Deutsches Krebsforschungszentrum Heidelberg
P.O. Box 101949
Im Neuenheimer Feld 280
DE-69120 Heidelberg

Url Host: <http://www.dkfz.de>

Team Leader: Dr. Stephan Herzig

Url Team Leader: http://www.dkfz.de/en/metabolic_control

MASS SPECTROMETRY-BASED MOLECULAR DIAGNOSIS OF BREAST CANCER

MS-MODIB

Cancer is the leading cause of death in people under age 85 in the Western world. Nearly half of all men and a little over one third of all women will develop cancer during their lifetimes. The sooner a cancer is found, correctly classified, and treatment begins, the better are the chances for living for many years. Breast cancer is the most prevalent form of cancer in female with one in ten women in the Western world developing breast cancer and half dying from it. A key problem of improving this situation is the correct sub-classification of the tumor. Breast cancer is not equal to breast cancer; which type is present determines the most successful strategy of treatment. The aim of the proposed work is to detect protein alterations in breast cancer cells to facilitate histological classification and to help deciphering the molecular pathology. To achieve these goals, a novel high-resolution FTICR mass spectrometer coupled to a state-of-the-art liquid chromatography system will be used for the investigation of cellular models, animal models, and patient tissue samples.



Juri Rappsilber, Alessio Maiolica, Dario Borsotti, Lau Sennels, Mogjiborahman Salek

Contact Details:

Host institution: IFOM Fondazione Istituto FIRC di Oncologia Molecolare
Via Adamello 16
I-20139 Milan
Italy
www.ifom-ieo-campus.it/

Team leader: **Juri Rappsilber**
juri.rappsilber@ifom-ieo-campus.it
www.ifom-ieo-campus.it/RESEARCH/Proteomics

THERAPEUTIC IMMUNIZATION FOR HIV/AIDS

DERMAVIR

Currently 40 million people are living with HIV/AIDS and only about 1 million of them are treated with antiretroviral therapy. The infection in Eastern Europe is more rapidly spreading than in Africa and a significant increase of new infections has been detected in Germany. Antiviral drugs have revolutionized treatment of HIV infection by delaying disease progression, but long-term management of the disease is remained difficult because treatment is associated with toxicities, resistance and high cost, whilst patients are required to stringently adhere to their drug regimens for the rest of their lives. Efforts are still underway to discover a prophylactic vaccine that is hoped to be able to contain the spread of the infection, but over 20 years have now passed since the disease was first described, and unfortunately, a vaccine that blocks HIV infection remains an elusive goal in 2005.

Prof. Julianna Lisziewicz, the beneficiary of a Marie Curie Chair (MCC) at the Semmelweis University in Budapest Hungary, has spent 16 years in the USA. She has discovered and led the development of DermaVir vaccine for the treatment of HIV/AIDS. The MCC facilitated transferring her expertise from the USA to Europe to provide scientific leadership for an interdisciplinary Vaccine Therapy research program in Central Europe and to bring DermaVir from the bench to the bedside. DermaVir applied on the skin under a patch to target the body's professional immune cells, called dendritic cells. These vaccinated dendritic cells can induce functional cytotoxic T cells that are responsible to eliminate HIV infected cells in the body(1, 2). The idea of DermaVir vaccination is originated from one of prof. Lisziewicz's early discoveries: the observation that control of HIV can be achieved by specific cytotoxic T cells after interruption of drug therapy (3, 4). The goal of DermaVir vaccination is to train the immune system of HIV infected individuals to control virus replication and live long and disease free life.



Professor Julianna Lisziewicz

Contact:
Semmelweis University Budapest
Korelettani Intezet
Nagyvarad ter 4
1089 Budapest, Hungary
<http://www.geneticimmunity.com>

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THE REACTION ENGINEERING OF PHARMACEUTICALS: EFFICIENT PRODUCTION OF COMPLEX DRUG MOLECULES

PHARMENG

Traditionally, empirical methods are used in the life-science industry to discover new drugs. Therapeutic effectiveness or bioavailability are determined mostly by trial and error - even today. However, rational discovery of drugs is beginning to revolutionize the industry. Unfortunately, the same cannot be said for the manufacturing of the final drug product - despite the fact that drugs are complex products, with a number of engineered features. Also, new drugs coming to the market are larger molecules, which are designed to be a complex, three-dimensional molecule to targets specific enzymes or cell surface receptors. This current trend is called the advent of the "large-molecule drugs". Large-molecule drugs, however, have one setback. They are difficult to make, and often it is nearly impossible to deliver them to the body. Furthermore, much of the science and technology needed to develop reliable nano-pharmaceutical products with controlled properties does not exist currently, and concerns about the safety and uniformity has delayed the systematic incorporation of nanotechnologies into therapeutic products manufacture. Thus, significant scientific know-how and expertise is required to make a drug into a product, i.e., there is a need to apply engineering and science principles to this industry.

The proposed program of the Marie Curie Chair (MCC) addresses exactly this issue, i.e., how to make a product from a newly discovered molecule. The research program of the chair is thus a unique, multi-disciplinary combination of nanotechnology, chiral catalysis, computational molecular design, and cutting-edge computer DNS simulations of multi-phase reactive flows in pharmaceutical processes. The MCC also proposes a strong educational program combined with out-reach initiatives to disseminate his work to a broad audience, and to train young researches in a relevant and new area. This initiative lies also well within the scope of the Graz University of Technology to form a Life-Science Engineering Center that includes areas such as advanced materials, bio-catalysis, reaction and bio-engineering, and nano-technology. In all activities the MCC will specifically address the need to foster women in science and engineering, as he has done in the past.



Prof. Khinast

Contact Details

Host Institution : Graz, University of Technology

Stremayrgasse 16

AT-8010 Graz

url : www.tugraz.at

Chair: Prof. Johannes G. Khinast

Url Chair : <http://sol.rutgers.edu/khinast.htm>