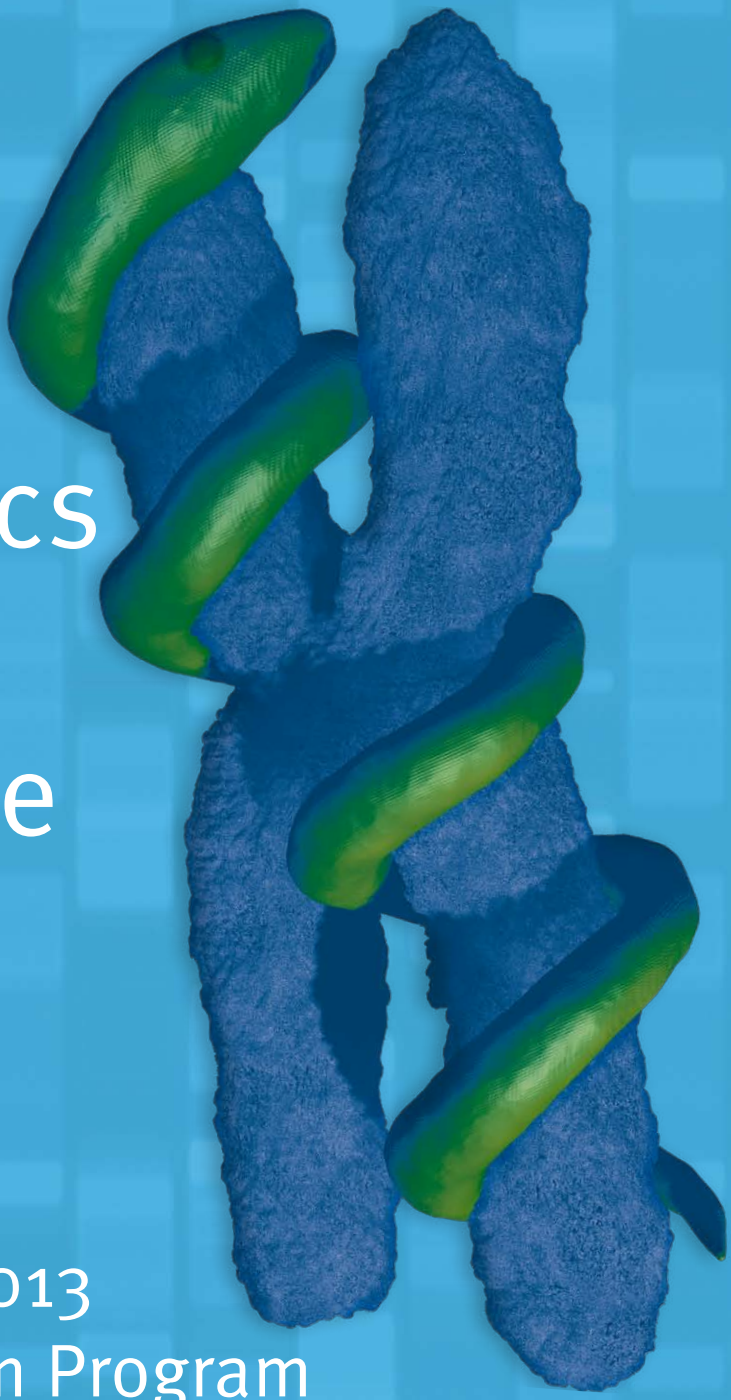
6th Student Symposium
on Molecular Medicine

ulm university universität
uulm



Genetics and Disease

April 20, 2013
Symposium Program

Symposium Program

9:15 - 9:25	Introduction	
9:30 - 10:00	Christian Kubisch, Ulm	How to identify a disease gene in monogenic and complex inherited diseases
10:00 - 10:15	Rüstem Yilmaz, Ulm	Exome sequencing revealed the role of a ubiquitin ligase in a blepharophimosis-mental retardation syndrome
10:20 - 10:50	Johannes Buheitel, Bayreuth	Cohesin: The Molecular Turnstile of DNA Cohesion
10:50 - 11:10	Coffee Break	
11:10 - 11:40	Johannes Beckers, München	Functional genomics of type 2 diabetes: Towards a better understanding of the disease
11:40 - 11:55	Barbara Fridrich, München	From genome wide association studies to gene function in mice: Potential role of Mtch2 in diabetes
12:00 - 12:30	Student representatives	Master Program and International Graduate School in Molecular Medicine
12:30 - 13:30	Lunch Break	
13:30 - 14:15	Patricia Smerdka, Konstanz	Application of next generation sequencing for non-invasive prenatal testing
14:20 - 14:50	Larissa Arning, Bochum	Genetic modifiers of Huntington disease
14:50 - 15:05	Eugen Kloster, Bochum	Association of *CNR1* gene variation with the age at onset of Huntington disease
15:05 - 15:25	Coffee Break	
15:25 - 15:55	Florian Kreppel, Ulm	Gene therapy - about options, vectors, and hurdles
15:55 - 16:10	Lea Krutzke, Ulm	Adenovirus vector delivery through the blood stream - challenges and solutions

Contact Information

Symposium Organization

www.molmed-symposium.de

Fachschaft Molekulare Medizin (c/o AStA)
Universität Ulm
89069 Ulm
+49 (0) 731 - 50 22404
organisation@molmed-symposium.de

Bachelor and Master Program in Molecular Medicine

www.uni-ulm.de/mm (left column)

Coordination Office
Stephanie Hinderberger
+49 (0) 731 - 50 33623
stephanie.hinderberger@uni-ulm.de

Student Council (Fachschaft)
www.mol-med.de
fs-molmed@uni-ulm.de

International Graduate School in Molecular Medicine

www.uni-ulm.de/mm

Coordination Office
Bettina Braun
+49 (0) 731 - 50 36290
bettina.braun@uni-ulm.de

Table of Contents

Abstracts

Abstracts

How to identify a disease gene in monogenic and complex inherited diseases

Prof. Dr. med. Christian Kubisch
Institute of Human Genetics, Ulm University

From a genetic point of view, one can distinguish between monogenic (Mendelian) and complex inherited diseases. In monogenic disorders a highly penetrant genetic alteration of a single gene is sufficient to cause the clinical phenotype, whereas in complex or multifactorial diseases the combination of a variety of genetic and environmental risk factors is involved in the modulation of disease susceptibility. This differential genetic basis of diseases is reflected by differences in the methodological approach to identify disease-associated genes and genetic variants. This lecture will give an overview about different technological approaches currently used in human genetics [like *e.g.* linkage and association studies] and will show examples for disease gene identification projects in both monogenic and complex inherited human diseases.

Curriculum Vitae

since 2010	Full Professor of Human Genetics and Head of the Institute of Human Genetics at Ulm University
2004 - 2010	Professor of Medical Genetics and Head of Genetic Counseling at the Institute of Human Genetics at the Bonn University Clinic
1999 - 2004	Research Associate at the Institute for Human Genetics at the Bonn University Clinic
1997 - 1999	Research Associate at the Center for Molecular Neurobiology and the Institute for Human Genetics at Hamburg University
1995 - 1997	Residency at the Hamburg University Neurological Clinic Additional Studies in Molecular Biology at Hamburg University
1988 - 1995	Medical Studies at Bonn University

Exome sequencing revealed the role of a ubiquitin ligase in a blepharophimosis-mental retardation syndrome

Rüstem Yilmaz, M.Sc.
Institute of Human Genetics, Ulm University

Although only about 1% of human genome codes for proteins, approximately 85% of mutations leading to monogenic disease are located in coding regions. In recent years, whole-exome sequencing has been developed as an efficient and fast tool for the detection of rare disease-causing mutations. Exome sequencing is useful in the identification of mutations causing rare genetic disorders. In the study performed in our lab, exome sequencing revealed biallelic UBE3B mutations in patients affected by an autosomal recessive blepharophimosis-ptosis–intellectual disability syndrome characterized by developmental delay, growth retardation with a small head circumference, facial dysmorphisms, and low cholesterol levels. UBE3B codes for an uncharacterized E3 ubiquitin ligase. Ubiquitination is a posttranslational protein modification that plays a crucial role in neurodevelopment as previously reported in Angelman disease. Elucidation of the role of UBE3B is essential for understanding the connection between mutation and disease. Thus, the talk will exemplify how to link identification of mutations by exome sequencing with functional studies to further understand the pathophysiology and underlying molecular mechanism of the disease.

Curriculum Vitae

since 2012	PhD Studies at the Institute of Human Genetics Genetics at Ulm University
2010 - 2012	Master Studies in Molecular Biosciences at the Ruprecht-Karls-University Heidelberg
2005 - 2010	Bachelor Studies in Molecular Biology and Genetics at the Middle East Technical University, Ankara, Turkey

Abstracts

Cohesin: The Molecular Turnstile of DNA Cohesion

Johannes Buheitel, M.Sc.
Department of Genetics, University of Bayreuth

Faithful transmission of chromosomes during eukaryotic cell division requires sister chromatids to remain paired from their generation in S phase until their separation in M phase. This so called cohesion is mediated by the cohesin complex, whose Smc1, Smc3 and Scc1 subunits form a tripartite ring that entraps both DNA double strands. At least two human diseases are known that can be associated with mutations in cohesin subunits or in proteins required for proper dynamics of the ring complex: Cornelia de Lange syndrome and Roberts syndrome. These cohesinopathies share similar symptoms ranging from embryonic lethality to craniofacial and limb deformities coupled with mental retardation and decreased life expectancy. Whereas centromeric cohesin is removed in late metaphase by Scc1 cleavage, metazoan cohesin at chromosome arms is displaced already in prophase by proteolysis-independent signaling. As a corollary to this fact, one must assume that the cohesin ring is opened at at least one of the three contact sites between Scc1, Smc1 and Smc3. Which of the three gates is triggered by the prophase pathway to open has remained enigmatic. We have shown that displacement of human cohesin from early mitotic chromosomes requires dissociation of Smc3 from Scc1 but no opening of the other two gates. In contrast, loading of human cohesin onto chromatin in telophase occurs through the Smc1-Smc3 hinge. We propose that the use of differently regulated gates for loading and release facilitates unidirectionality of DNA's entry into and exit from the cohesin ring.

Curriculum Vitae

since 2010	PhD Studies at the Department of Genetics at Bayreuth University
2008 - 2010	Master Studies in Biochemistry and Molecular Biology at Bayreuth University
2005 - 2008	Bachelor Studies in Biology at Bayreuth University

Functional genomics of type 2 diabetes: Towards a better understanding of the disease

PD Dr. rer. nat. Johannes Beckers
Institute of Experimental Genetics, Helmholtz Zentrum München

With approximately 6 million affected people, diabetes mellitus is one of the most prevalent diseases in Germany. The number of people worldwide with diabetes is expected to rise by more than 50 percent until the year 2025 – from 250 million today to approximately 380 million people. In addition, it is estimated that just as many people are unaware of their condition or are at high risk for developing the disease. The dramatically growing prevalence has made the basic understanding of diabetes and the development of new therapies one of the biggest health challenges of modern society. Epidemiological research using genome wide association studies (GWAS) has been and continues to be highly successful in the identification of genetic risk loci for metabolic diseases such as obesity and diabetes. More than 70 genetic risk loci have been identified in human patients, so far. To develop new therapies it is necessary to understand the functional role of the identified genes and the basic molecular mechanisms that underlie the disease. Mouse models are the most important tool to address this question. In addition to genetic factors, it becomes increasingly evident that the exposure to particular envirotypes (sets of environmental factors) contributes to the development of diabetes and metabolic disorders. Furthermore, novel findings in epigenetic research suggest that transgenerational inheritance of acquired traits may contribute to the epidemic dimension of diabetes. We will present some recent highlights from our research in functional genomics of type 2 diabetes and strategies that are currently followed to address the questions outlined above.

Curriculum Vitae

current position	Head of Gene Regulation Group and Deputy Director of the Institute of Experimental Genetics at the Helmholtz Zentrum München Lecturer (PD) in Genetics at the Center of Life and Food Sciences Weihenstephan of the Technical University Munich
2009 - 2010	Executive MBA Studies at the Technical University Munich
2005 - 2007	Habilitation in Genetics at the Technical University Munich
1997 - 2000	Post-Doc at the Jackson Laboratory, Bar Harbor, Maine, USA
1993 - 1997	PhD Studies at the University of Geneva, Switzerland
1988 - 1993	Studies in Biology at the Ruprecht-Karls-University, Heidelberg

From genome wide association studies to gene function in mice: Potential role of *Mtch2* in diabetes

Dipl. Ing. (FH) Barbara Fridrich

Institute of Experimental Genetics, Helmholtz Zentrum München

The Mitochondrial carrier homolog 2 (*Mtch2*) gene is located nearby one of the genetic risk loci identified in genome wide association studies (GWAS) for body mass index (BMI). The association was discovered in several independent GWAS in adult populations mostly of European descent.
The *Mtch2* gene was chosen for our analysis due to its potential importance in diabetes, because BMI is one of the major risk factors for developing the disease. The Mtch2 protein is localised in the mitochondrion and mitochondrial dysfunction is known to be closely associated with insulin resistance and might contribute to the progression of diabetes. So far, a *Mtch2* knockout mouse was only utilized to describe *Mtch2*'s role in the mitochondrial apoptosis pathway. It anchors all relevant factors to the mitochondrial membrane which are needed to build a complex to induce cytochrome C release. Its function in diabetes has not been described yet. Our strategy for describing the gene's function is to produce heterozygous *Mtch2* knockout mice, which will be challenged through the feeding of a high-fat diet. Diabetes relevant measures will be recorded. In a second step tissue specific knockout mice will be produced. Additionally, in vitro *Mtch2* knockdown assays will be established for diabetes relevant cell types and the requirement of *Mtch2* in regards to mitochondrial function will be studied.
We will share with you our current progress on the functional analysis of *Mtch2* and the next steps which will be taken.

Curriculum Vitae

since 2010	PhD Studies at the Institute of Experimental Genetics at the Helmholtz Zentrum München
2005 - 2009	Studies in Medical and Pharmaceutical Biotechnology at the IMC University of Applied Sciences, Krems, Austria

Application of next generation sequencing for non-invasive prenatal testing

Dr. Patricia Smerdka
LifeCodexx GmbH, Constance

The knowledge of circulating cell-free fetal DNA in maternal plasma and the substantial progress in next generation sequencing technologies have made massively parallel sequencing (MPS) of millions of reads from a human plasma DNA sample feasible. The application of this technique for quantifying an over-representation of fetal chromosome 21 was demonstrated by two independent groups in 2008. Since then, the technique has been further developed and applied in large-scale clinical studies to detect a broader range of fetal chromosomal aberrations.

Today, LifeCodexx, a German company located in Constance, is offering Europe's first non-invasive prenatal test for the detection of the fetal trisomies 13, 18 and 21. The development of this test from science to a marketable product will be illustrated.

Curriculum Vitae

since 2012	Medical Marketing Manager at LifeCodexx AG, Constance
2005 - 2012	Medical Advisor and Product Mangager at ALTANA Pharma GmbH, now Nycomed (part of Takeda), Constance
2002 - 2005	Scientific Sales Manager at GATC Biotech AG, Constance
1998 - 2002	PhD Studies and Post-Doc at the Tübingen Hearing Research Centre
1995 - 1998	Studies in Biology at Eberhard-Karls-University, Tübingen
1991 - 1995	Studies in Biology at Justus-Liebig-University, Gießen

Genetic modifiers of Huntington disease

Dr. rer. nat. Larissa Arning
Department of Human Genetics, Ruhr-University Bochum

Huntington disease (HD) is caused by the expansion of a CAG repeat within exon 1 of the *huntingtin* (*HTT*) gene. Although the variation in age at onset (AO) is partly explained by the lengths of the expanded repeat, the unexplained variation in AO is heritable, emphasizing the role of the so-called genetic background on disease expression. Identification of modifier genes can confirm intracellular pathways already suspected to be involved in pathophysiological processes related to HD pathogenesis, but it may also point to completely new pathways and processes that have not yet been considered. Most importantly, confirmed modifier genes provide new targets for the development of therapies. Up to now, a wide range of susceptible HD modifier genes related to different biochemical pathways has been examined. This talk provides an overview of HD modifier research.

Curriculum Vitae

currrent position	Post-Doc at the Department of Human Genetics, Ruhr-University Bochum
2002 - 2005	PhD Studies at Ruhr-University Bochum
1996 - 2002	Studies in Biology at Ruhr-Universit y Bochum

Association of *CNR1* gene variation with the age at onset of Huntington disease

Eugen Kloster, M.Sc.
International Graduate School of Neuroscience, Ruhr-University Bochum

Since down regulation of type 1 cannabinoid (CB1) receptors is a key pathogenic event in Huntington disease (HD), it has been suggested that activation of these receptors in patients may attenuate disease progression. In order to evaluate whether variations in the cannabinoid receptor 1 (*CNR1*) gene encoding the CB1 receptor have modifying effects on the age at onset (AO) of HD we performed an association study between *CNR1* polymorphisms and AO in HD patients. The $(AAT)_n$ triplet repeat and a total of nine SNPs in the *CNR1* gene were selected for genotyping in a German HD cohort of 473 patients recruited from the Huntington Center NRW in Bochum. The AO was significantly associated with alleles of the $(AAT)_n$ triplet repeat polymorphism downstream of the *CNR1* gene, as well as with one single nucleotide polymorphism (SNP) in the 3'UTR of *CNR1*. Interestingly, this SNP lies within a microRNA binding site and the minor allele leads to reduced binding to *CNR1*. These data support the idea that variation in *CNR1* may have modifying effects on the AO in HD.

Curriculum Vitae

since 2010	PhD Studies in Neuroscience at the Department of Human Genetics, Ruhr-University Bochum
2007 - 2009	Master Studies in Cell Biology at Osnabrück University
2003 - 2007	Bachelor Studies in Cell Biology at Osnabrück University

Abstracts

Gene therapy - about options, vectors, and hurdles

PD Dr. rer. nat. Florian Kreppel
Department of Gene Therapy, Ulm University

The concept of gene therapy to introduce nucleic acids into somatic cells with the aim to treat genetic diseases was proposed more than thirty years ago and it has been conceived that such introduction of new genetic material into somatic cells also holds great promise to treat or prevent cancerous and infectious diseases. Up to date more than 1700 gene therapy clinical trials have been conducted worldwide. The majority of these trials has revealed hurdles that limit the clinical efficacy of gene therapy approaches. However and importantly, in the recent past several trials have been conducted that showed clear clinical benefit for the patients. In my presentation I will give an overview over current treatment strategies, will introduce some of the successful clinical trials and discuss scientific hurdles as well as approaches to overcome these hurdles.

Curriculum Vitae

current position	Group Leader at the Department of Gene Therapy, Ulm University Lecturer (PD) at the Medical Faculty at Ulm University
2010	Habilitation in Molecular Medicine at the Medical Faculty at Ulm University
1998 - 2003	PhD Studies in Genetics at Cologne University
1992 - 1998	Studies in Biochemistry at Tübingen University

Adenovirus vector delivery through the blood stream - challenges and solutions

Lea Krutzke, M.Sc.
Department of Gene Therapy, Ulm University

The clinical use of adenovirus serotype 5 -based gene transfer vectors is limited by multiple vector-host interactions. In particular, numerous interactions with cellular and non-cellular human blood components that occur after intravenous or even local vector administration in a patient quickly lead to sequestration and inactivation or mistargeting of adenovirus vectors. Since vector administration into the blood stream is advantageous or even mandatory for various potential applications including tumor therapy, it is required to describe, understand and modulate such interactions to enable for efficient vector delivery as the basis for successful gene therapy. We have developed a combination of genetic and chemical technologies to modify adenovirus vectors in order to gain knowledge about vector interactions with human blood. Importantly, these technologies enable us to not only understand but also modulate adenovirus vector host interactions after systemic delivery into the blood stream.

The presentation will focus on the molecular basis of three major interactions: (i) the sequestration of adenovirus vector particles by human erythrocytes, (ii) the inactivation of vector particles by preexisting or natural antibodies, and (iii) the clearance of vector particles by the liver. We will introduce our technology to analyze these interactions and further demonstrate how adenovirus vectors can be generated that overcome the undesired interactions.

Curriculum Vitae

since 2012	PhD Studies in the Department of Gene Therapy, Ulm University
2010 - 2012	Master Studies in Molecular Medicine at Ulm University
2007 - 2010	Bachelor Studies in Biology at Karlsruhe Institute of Technology

International Graduate School
in Molecular Medicine Ulm

MSD

ROTH

BioRegionUlm

Gold Ochsen
SEIT 1597
ULMS FLÜSSIGES GOLD

Staib
Ihr Bäcker

Rentschler
THE BIOPHARMA MANUFACTURER

IHK Ulm

ulm university universität
uulm