

CONGRESS BROCHURE

**INTERNATIONAL CONGRESS ON RESEARCH OF
RARE AND ORPHAN DISEASES
29TH FEBRUARY–2ND MARCH, BASEL
SWITZERLAND**

RE(ACT)[®] 2012

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MILLION
PEOPLE
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FOR BETTER
RESULTS**

RE(ACT)[®] 2012
INTERNATIONAL CONGRESS ON RESEARCH OF
RARE AND ORPHAN DISEASES
FEBRUARY 2012

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WELCOME

Dear Colleagues,

Welcome to the first «International Congress on Research of Rare and Orphan Diseases», RE(ACT) 2012. It is a pleasure to host you here in Basel, in the heart of Europe. The idea behind the Novartis Campus and the Gehry Building has been that of fostering an efficient knowledge exchange between experts and to facilitate their networking – an ideal platform for our congress.

A stimulating program with a dedicated community of scientists and experts from many countries is waiting for you. Over the next three days we will discuss progress in research of rare diseases and in issues of translational medicine. We will also try to define a collaborative agenda of clinicians and of scientists from both academia and industry in order to improve therapy development for the benefit of patients in the years to come. Ideally, the research on rare diseases will also foster a better understanding of other, more common diseases.

The overall aim of this congress is not only to bring together researchers and their knowledge but also to promote research on rare and orphan diseases among the general public, industry and policy makers. New and promising therapies and treatments must be rapidly delivered to patients all around the world.

We are pleased about your active participation to the debates over the coming days and on behalf of the promoting foundations we hope you shall enjoy your time in Basel.

Olivier Menzel
BLACKSWAN Foundation

Pascale Vonmont
Gebert Rűf Stiftung



KEY FACTS

Scientific program committee and advisory board

Prof. Susan Gasser, Director Friedrich Miescher Institut, Basel

Dr. Marisa Jaconi, University of Geneva, Swiss Institute of Cell Therapy (SICT)

Dr. Olivier Menzel, BLACKSWAN Foundation

Dr. Mike Morris, University of Geneva

Prof. Juerg Schifferli, University of Basel

Dr. Pascale Vonmont, Gebert RUF Stiftung

Venue

The RE(ACT) Congress 2012 is held in the Conference Centre of the Gehry Building. Located in the district of St. Johann in Basel along the Rhine, the Novartis Campus occupies a site devoted entirely to innovation, research and knowledge.

The Gehry Building is one of the main buildings on campus Novartis. Designed by the (st) architect Frank O. Gehry (Guggenheim Museum Bilbao, Dancing House in Prague, Vitra Design Museum in Weil am Rhein), it is part of a remarkable set of buildings, works of renowned manufacturers such as Japanese or Tadao Ando Kazuyo Sejima + Nishizawa Ryue SANAA agency, the Dutchman Rem Koolhaas, Alvaro Siza, the Portuguese or the offices of Basel Diener and Diener, Herzog and de Meuron.

Congress Initiators

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Congress Organizer

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Important information for speakers

We kindly ask the speakers to submit their presentation to the “Speaker Preview Room” at least two hours before their talk.

Speakers presenting in the morning session of the day should submit their presentations the evening before so as to avoid the “mad-rush” in the early morning.

Only presentation saved on a data medium such as a USB stick or CD-ROM will be approved. Please note that is not possible to use your own laptop.

Presentation should be created in Microsoft PowerPoint, Keynote or PDF. Furthermore, please use standard fonts of Windows.

To facilitate allocation, please create a respective folder on your storage medium including your presentation (e.g. RE(ACT) 2012_Speaker’s name_Session).

To avoid missing links to video files, we kindly ask the presenters either to use the “pack for CD” function in PowerPoint or provide all clips used in the presentation in an additional folder on the CD or on the flash drive.

Important information for abstract presenters

We kindly ask all poster presenters to meet the following guidelines:

The size of your poster should not exceed DIN Format A0 Portrait - 841 mm wide and 1189 mm height. Bonding material is provided in the poster area.

- Posters may be set up on 29th February 2012 from 5pm.
- Posters should be removed on 2nd March 2012 from 6pm.
- Poster which have not been removed after this time will be discarded. Please note that the posters and others material will not be sent to you after the conference.

Continual Medical Education

The conference has been accredited by the Swiss Society of Medical Genetics for a maximum of 6 CME credits.

The certificate of attendance will be given to you at the registration counter upon request.

Posters

The poster areas are located in the level -2 (A. Gene and Cell Therapy; Stem Cells and B. Diagnostics) and in the level -3 (C. Therapeutic Applications and D. Genomic Disorders). The poster exhibition will be open during coffee breaks and lunches.

Disclaimer:

The speaker biographies and the abstracts are printed as received by the authors.

SCHEDULE AT A GLANCE

Wednesday 29th February

- 17.00 Registration Opens
- 18.00 Opening Ceremony
- 20.00 Welcome Reception

Thursday 1st March

- 08.30 Session A: Gene and Cell Therapy; Stem Cells
- 10.15 Coffee Break, Poster Viewing, Exhibition
- 10.45 Session A: Gene and Cell Therapy; Stem Cells
- 12.30 Lunch
- 14.00 Session B: Diagnostic
- 15.45 Coffee Break, Poster Viewing, Exhibition
- 16.15 Session B: Diagnostic
- 18.15 End day one

Friday 2nd March

- 08.30 Session C: Therapeutic Applications
- 09.45 Coffee Break, Poster Viewing, Exhibition
- 10.15 Session C: Therapeutic Applications
- 12.45 Lunch
- 14.15 Session D: Genomic Disorders
- 16.00 Coffee Break, Poster Viewing, Exhibition
- 16.30 Session D: Genomic Disorders
- 18.15 End of Conference

PROGRAM

Wednesday 29th February

- 17.00 Registration Opens
- 18.00 Opening Ceremony
Chairwoman: PROF. SUSAN GASSER, Director Friedrich Miescher Institut, Basel
- 18.00 Welcome
PASCAL BRENNEISEN, Novartis Switzerland
DR. GUY MORIN, President of the Executive Council, Canton of Basel-Stadt
- 18.15 Impulse
DR. SALAH-DINE CHIBOUT, Novartis
- Referrals
- 18.30 PROF. JAMES R. LUPSKI, USA
Personal Genomes Medical Genomes & Clan Genomics: A personal quest to identify the genetic underpinnings of Charcot-Marie-Tooth neuropathy
- 19.15 DR. NICK SIREAU, UK
Finding a cure to Black Bone Disease, from a patient's point of view
- 19.45 ANNE-FRANCOISE AUBERSON, SWITZERLAND
ProRaris: The Swiss National Rare Disease Alliance
- 20.00 Welcome reception

Thursday 1st March

Session A: Gene and cell therapy; Stem Cells

- 08.30 Chairwoman: DR. MARISA JACONI, University of Geneva,
Vice Director of the Swiss Institute of Cell Therapy (SICT)
- 08.45 PROF. DIDIER TRONO, SWITZERLAND
A defense against genetic invader turned into a master regulator
of mammalian homeostasis
- 09.15 PROF. ELENA CATTANEO, ITALY
Huntington from evolution to pathology via neuroepithelial stem cells
- 09.45 PROF. MICHELE DE LUCA, ITALY
Epithelial Stem Cells and Regenerative Medicine
- 10.15 Coffee Break
- 10.45 PROF. MICHAEL SINNREICH, SWITZERLAND
Proteasomal Inhibition Restores Biological Function of Mis-Sense
Mutated Dysferlin in Patient Derived Muscle Cells (Abstract n° C004_2012)
- 11.00 DR. RENATA BOCCIARDI, ITALY
Study of the ACVR1 gene expression and regulation (Abstract n° A003_2012)
- 11.15 DR. ALFRED S. LEWIN, USA
AAV Mediated Gene Therapy in Animal Models of Autosomal Dominant
and X-linked Retinitis Pigmentosa (Abstract n° A005_2012)
- 11.30 PROF. JOSÉ-ALAIN SAHEL, FRANCE
Towards a cone-directed comprehensive therapeutic strategy in retinitis
pigmentosa (Abstract n° C015_2012)
- 12.00 PROF. ETIENNE SOKAL, BELGIUM
Academic development of an advanced therapy medicinal product to address unmet
medical need and its transfer to industry to secure final access for all patients
- 12.30 Lunch

Session B: Diagnostic

- 14.00 Chairman: DR. MIKE MORRIS, University of Geneva
- 14.15 PROF. MEHDI TAFTI, SWITZERLAND
Narcolepsy: A rare autoimmune disease
- 14.45 PROF. SABINA GALLATI, SWITZERLAND
Cystic Fibrosis (CF) and CF-related disorders: From single gene testing toward array-based sequence capture and next generation sequencing
- 15.15 DR. PONTUS LUNDBERG, SWITZERLAND
Targeted next generation sequencing for clinical diagnostics of patients with myeloproliferative neoplasms (Abstract n° B009_2012)
- 15.30 DR. PERIKLIS MAKRYTHANASIS, SWITZERLAND
Consanguinity as a means to identify pathogenic recessive mutations (Abstract n° B008_2012)
- 15.45 Coffee Break
- 16.15 PROF. ANITA RAUCH, SWITZERLAND
Towards a deeper understanding of intellectual disability disorders
- 16.45 PROF. HAN G. BRUNNER, NL
Exome sequencing as a diagnostic tool in patients with unexplained intellectual disability
- 17.15 ASS. PROF. ANNE MCKINNEY, CANADA
Mitochondrial dysfunction and Purkinje cell loss in the human spastic ataxia ARSACS (Abstract n° D002_2012)
- 17.30 DR. THORSTEN HORNEMANN, SWITZERLAND
Oral L-Serine Supplementation as a Therapy in Hereditary Sensory Autonomic Neuropathy Type 1 (HSAN1) (Abstract n° C001_2012)
- 17.45 DR. DAVID B. SAVAGE, UK
Insights from extreme monogenic insulin resistance syndromes

Friday 2nd March

Special Session: Transnational research on rare diseases

- 08.30 DR. SOPHIE KOUTOUZOV, FRANCE
The ERA-Net E-RARE
- 08.45 DR. BERND WOLLNIK, GERMANY
E-RARE Granted Project coordinator - CRANIRARE
An E-RARE success story for identifying the pathogenesis of
craniofacial malformations
- 09.15 DR. MARIA MAVRIS, FRANCE
(EURORDIS) Patients and Scientists' involvement in the orphan
drug development process
- 09.45 Coffee Break

Session C: Therapeutic applications

- 10.15 Chairman: PROF. DOUG HIGGS, UK
Institute of Molecular Medicine, John Radcliffe Hospital
- 10.30 PROF. DOUGLAS HIGGS, UK
The role of the ATRX chromatin associated protein in human disease
- 11.00 PROF. ALAIN FISCHER, FRANCE
Primary immunodeficiencies: from genes to therapy
- 11.30 PROF. ECKHARD WOLF, GERMANY
Tailored pig models for rare human genetic diseases
- 12.00 PROF. MARY REILLY, UK
Inherited neuropathies 2012– bench to bedside, where are we?
- 12.30 DR. OR KAKHLON, ISRAEL
Rapamycin-mediated glycogen synthase inhibition can relieve polyglucosan
neurotoxicity in an adult polyglucosan body disease neuronal model
(Abstract n° C013_2012)
- 12.45 Lunch

Session D: Genomic disorders

- 14.15 Chairman: PROF. JÜRIG SCHIFFERLI, University of Basel
- 14.30 PROF. STYLIANOS ANTONARAKIS, SWITZERLAND
Consanguinity and Disease Gene Discovery
- 15.00 PROF. SERGEI MIRKIN, USA
Two sides of the same coin: Instability of DNA repeats and mutagenesis at a distance
- 15.30 DR. TEWIS BOUWMEESTER, SWITZERLAND
Fragile X Syndrome: from bench to bedside
- 16.00 Coffee break
- 16.30 PROF. ANDREA SUPERTI-FURGA, SWITZERLAND
The many facets of rare diseases – lessons from genetic disorders of bone
- 17.00 SHIXU YAN, SWITZERLAND
Frameshift mutations in Hyaline Fibromatosis Syndrome (HFS) reveal the significance of personalized treatment in patients (Abstract n° D001_2012)
- 17.15 DR. SEBASTIEN JACQUEMONT, SWITZERLAND
Mirror phenotypes associated with 16p11.2 rearrangements (Abstract n° D010_2012)
- 17.30 DR. PIERRE CALVEL, SWITZERLAND
Disorders of sexual development: identifying new genes and pathways involved in the sexual determination of the human gonad (Abstract n° D012_2012)
- 17.45 PROF. ARNOLD MUNNICH, FRANCE
Advances in genomics and others omics: What benefits for patients?

**SUPPORT
FASTER
DEVELOPMENT**

**CONNECT TO
A WIDER
NETWORK**

**WORK
TOGETHER
FOR BETTER
RESULTS**

**RARE
IS
COM-
MON**

**START NEW
LABORATIONS**

**ED UP
RE
EASE
ARCH**

**MEET TO
FIND NEW
PERSPECTIVES**

**NO MORE
GERMAN STATUS**

**STEP UP
DISCUSSIONS
FOR
SOLUTIONS**



SPEAKER BIOGRAPHIES

DR. SALAH-DINE CHIBOUT, SWITZERLAND

Global Head Therapeutic Areas in Preclinical Safety. Deputy Head of Translational Science in Europe (Preclinical Safety, DMPK, Translational Medicine Biomarker Development Departments). Global Head Investigative Toxicology and member of the Integrative Safety Assessment Board.

PROF. JAMES R. LUPSKI, USA

Jim Lupski is Cullen Professor and Vice Chair of Molecular and Human Genetics. Prof. Lupski received his initial scientific training at the Cold Spring Harbor Laboratory as an Undergraduate Research Participant (URP) and at New York University completing the M.D./Ph.D. program in 1985. In 1986 he moved to Houston, Texas for clinical training in pediatrics (1986-1989) and medical genetics (1989-1992) and then established his own laboratory at Baylor College of Medicine where he remains, and as of 1995, as the Cullen Professor of Molecular and Human Genetics. Through studies of Charcot-Marie-Tooth peripheral neuropathy, a common autosomal dominant trait due to a submicroscopic 1.5 Mb duplication, and Smith-Magenis syndrome, a contiguous gene deletion syndrome, his laboratory has delineated the concept of 'genomic disorders' and established the critical role of copy number variation (CNV) and gene dosage in conveying human disease phenotypes. An increasing number of human diseases are recognized to result from recurrent DNA rearrangements (recent examples include obesity and both autism and schizophrenia) involving unstable genomic regions and have thus been classified as genomic disorders. Prof. Lupski's laboratory has also used chromosome engineering to develop mouse models for genomic disorders. Recently, the laboratory's CMT studies in collaborations with Richard Gibbs and the Baylor Human Genome Sequencing Center resulted in the first personal genome sequence to identify a "disease gene" by whole genome sequencing (WGS) and demonstrated the utility of WGS for optimizing patient management. These latter investigations further elucidated the potential role of rare variants in complex traits such as carpal tunnel syndrome and fibromyalgia. For his work on human genomics and the elucidation of genomic disorders Prof. Lupski was awarded a Doctor of Science degree honoris causa in 2011 from the Watson School of Biological Science at the Cold Spring Harbor Laboratory. He has coauthored over 500 scientific publications, is a co-inventor on more than 20 patents and has delivered over 400 invited lectures in 32 countries.

DR. NICK SIREAU, UNITED KINGDOM

Dr. Nicolas Sireau is Chairman of the AKU Society, a medical charity that works to find a cure for and support patients with AKU, which affects his two sons. AKU (short for Alkaptonuria) was the first metabolic disease ever identified, in 1901 in London. It is a monogenic disease caused by a missing enzyme, leading to the accumulation of a substance called homogentisic acid at 2,000 times the normal rate. This acid binds to cartilage and bone in a process called ochronosis. AKU is called Black Bone Disease because the ochronosis turns bones black and brittle, leading to severe disability as life progresses. The AKU Society is a fast growing patient movement, with formal patient groups in the UK, France, Italy and North America, and informal patient groups across Europe. We work with AKU research and clinical centres in the UK (Liverpool and Cambridge), France (Paris), Italy (Siena), Slovakia (Bratislava and Piestany), the US (NIH and San Diego), Jordan (Mutah) as well as partners across the world. We are developing new treatments into AKU and making scientific discoveries that also have impli-

cations for osteoarthritis, of which AKU is an extreme phenotype. Dr. Sireau is also a former non-executive Director of GenSeq, a bioinformatics company. He is a fellow of the Ashoka Fellowship of Social Entrepreneurs and of the Royal Society of Arts. Dr. Sireau's previous career was in international development, where he set up SolarAid, an award-winning social enterprise bringing solar power to Africa, and wrote several books on international aid. Dr. Sireau has a PhD in Social Psychology, an MSC in Business Management, an MA in Journalism Studies, and an MA (Oxon) in History and Economics. The website of the AKU Society is www.alkaptonuria.info. Dr. Sireau also runs the AKU Guide for Rare Disease Patient Groups, an online blog: akurareddiseaseguide.wordpress.com.

PROF. DIDIER TRONO, SWITZERLAND

Dr. Didier Trono is Professor of Genetics and Virology and Dean of the School of Life Sciences at the Swiss Institutes of Technology (EPFL) in Lausanne, Switzerland. After obtaining an M.D. from the University of Geneva and completing a clinical training in pathology, internal medicine and infectious diseases in Geneva and at Massachusetts General Hospital in Boston, he worked with David Baltimore at the Whitehead Institute for Biomedical Research of MIT as a post-doctoral fellow. In 1990, he joined the faculty of the Salk Institute for Biological Studies to launch a center for AIDS research. He moved back to Europe seven years later, before taking the reins of the newly created EPFL School of Life Sciences in 2004. Didier Trono's research focuses on interactions between viral pathogens and their hosts, and on the exploration of genetics from both fundamental and therapeutic perspectives. His laboratory is particularly interested in innate defenses against retroelements such as HIV and in the role of epigenetics in the shaping of the expression of mammalian genomes.

PROF. ELENA CATTANEO, ITALY

Her research is focused on the biology of neural stem cells and their potential application, and on the study of the mechanisms underlying Huntington's disease. She has obtained the Laurea (Summa cum Laude) and the Doctorate in Biotechnology at the University of Milano. Since 2003 she is Full Professor at the same University. She has worked for three years at the Massachusetts Institute of Technology (M.I.T., Cambridge, U.S.A.) in the group of Prof. R.D.G. McKay, a pioneer in the field of neural stem cells. Back in Milano, her laboratory is active since 1994 and is part of the Department of Pharmacological Science, University of Milano. Elena Cattaneo is Director of the Center for Stem Cell Research of the University of Milan (UniStem). Since 1997 she is a Coalition Investigator of the Huntington's Disease Society of America (H.D.S.A.) and Coordinator of the Huntingtin Function Team (H.D.S.A.). In 2001 she was awarded with "Le Scienze" Prize for Medicine and with a Medal from the President of the Italian Republic, Carlo Azeglio Ciampi, for her studies on neural stem cells and Huntington's Disease. Since 2002 she is Member of the Italian Delegation for Genomics and Biotechnology at the European Union (2003-2006). In 2005 she has received the Marisa Bellisario Prize and the Chiara D'Onofrio Prize for her research activities. In 2006 she received from the President of the Italian Republic the honor of "Cavaliere Ufficiale" of the Italian Republic. In 2007 she has been member and Vice-President of the National Bioethics Committee. In 2008 she was awarded with Unamsi (<http://www.medicinaunamsi.it>) and Novartis Pharma Prize "Grande Ipocrate". Since 2009 she coordinates the European Union (FP7) funded project NeuroStemcell (www.neurostemcell.org)

PROF. MICHELE DE LUCA, ITALY

Michele De Luca is Full Professor of Biochemistry, University of Modena and Reggio Emilia, and Director of the Centre for Regenerative Medicine of the same University. He is Scientific Director of Holostem Terapie Avanzate S.r.l. Prof. De Luca was Scientific Director of the Veneto Eye Bank Foundation (2002-2007), Director of the Laboratory of Tissue Engineering at the Istituto Dermopatico dell'Immacolata, Rome (1996-2002), adjunct Professor of Cell Biology of the Medical School of Tor Vergata University, Rome (1998-2000), Deputy Head, Laboratory of Cell Differentiation, Istituto Nazionale per la Ricerca sul Cancro, Genova (1992-1995), Group Leader in the same Institute (1986-1992), Visiting Scientist at the Department of Cell Biology, Harvard Medical School, Boston (1985), Fogarty Fellow at the National Institutes of Arthritis, Diabetes, Digestive and Kidney Diseases (NIADDK), National Institutes of Health (NIH), Bethesda (1982-1985). He graduated M.D. in 1980 and obtained a Specialty in Endocrinology in 1984. He is founding member of International Ocular Surface Society, member of numerous scientific societies and member of national and international committees. He is author of more than 110 scientific publications in major international journals and author of 4 international patents. He was invited lecturer in more than 120 international meetings and symposia. He was born in Savona, Italy, May, 17, 1956.

Summary and essence of scientific activity: Prof. De Luca is internationally recognized as a leading scientist in stratified epithelial stem cell biology aimed at clinical application in regenerative medicine. Prof. De Luca played a pivotal role in epithelial stem cell-mediated cell therapy and gene therapy. Beside his pioneering work on the use of human epidermal stem cell cultures in life-saving treatment of massive full-thickness burns and in repigmentation of stable vitiligo and piebaldism, he was first in establishing human limbal stem cell culture aimed at corneal regeneration in patients with severe limbal stem cell deficiency. This treatment leads to recovery of vision in patients with poor alternative therapy. Prof. De Luca is currently coordinating the first (successful) ex-vivo epithelial stem cell-mediated gene therapy clinical trial for the gene therapy of genetic skin diseases as Junctional Epidermolysis Bullosa. Prof. De Luca is also studying molecular mechanisms regulating long term proliferative potential, clonal evolution and mitotic quiescence of epithelial stem cells.

PROF. ETIENNE SOKAL, BELGIUM

Etienne SOKAL is full professor at the Université Catholique de Louvain, and head of the pediatric GI and Liver unit at Cliniques Saint Luc, in Brussels. The unit is a tertiary referral center for pediatric liver diseases and liver based inborn errors of metabolism. More than 800 pediatric liver transplantations have been performed at St Luc since 1984. Prof. Sokal has published more than 220 peer review articles in the field of pediatric hepatology, metabolic diseases and transplantation. His current research in the field of liver regenerative medicine has allowed to launch a clinical program of liver cell transplantation, with 17 patients treated so far at Saint Luc. He owns a patent on a hepatocyte liver derived progenitor cells, that led to the creation of Promethera Biosciences, a spin off company from Université of Louvain whose aim is to bring to the market a cell based advanced therapy medicinal product to treat infants and children with life threatening liver diseases. Clinical trials are ongoing. Prof. Sokal is founder and CSO of Promethera Biosciences.

PROF. MEHDI TAFTI, SWITZERLAND

Mehdi Tafti received his PhD from the University of Montpellier in France in 1991 after completing his doctoral thesis on sleep regulation in human narcolepsy. He performed a postdoctoral fellowship and was a Research Associate at the Department of Psychiatry and Biological Sciences at Stanford University. In 1995 he moved to the Department of Psychiatry in Geneva, Switzerland where he established the first laboratory dedicated to the molecular genetics of sleep and sleep disorders. He joined the Center for Integrative Genomics at the University of Lausanne, Switzerland in 2004 as a Professor of Behavioral Genetics. Since 2006 he is also co-director of the Center for Investigation and Research in Sleep at the University-Hospital (CHUV) in Lausanne. In addition to his work on the genetics of sleep in mice, he is leading several large-scale European studies on the molecular genetics of narcolepsy. The first genes regulating normal sleep in mice have been identified by his laboratory as well as genes involved in narcolepsy and sleepwalking.

PROF. SABINA GALLATI, SWITZERLAND

Present appointment: Professor and Head of the Division of Human Genetics, Department of Paediatrics, Inselspital, University of Berne. Degrees: Diploma of Biology (1977), PhD in Human Genetics (1980), Readership (1993), Associate Professor (1997), Certification as Specialist in Medical Genetic Analysis (FAMH) (2000), since 2003 Extraordinary Professor of Human Genetics at the Medical Faculty of the University of Berne. Postdoctoral training: Hammersmith Hospital (Prof. V. Dubowitz) and St. Mary's Hospital (Prof. R. Williamson), London (UK), Inst. of Human Genetics (Prof. T. Grimm), Würzburg (D), Children's Hospital, HMS (Prof. L. Kunkel), Boston and FBI-Academy (Dr. B. Budowle), Quantico (USA). Research: Supported by the Swiss National Foundation, the EU and private Foundations. Main focus on Cystic Fibrosis (since 1989), Hereditary Haemochromatosis (HH), mitochondriopathies, epilepsy, mental retardation. Service: Genetic counseling, cytogenetic and molecular cytogenetic analyses and national as well as international service for molecular genetic testing covering more than 50 different disorders. Accreditation since 2000. Education: Lectures, seminars and practical courses for Medical students and students of Biology, supervision of diploma, MD and PhD theses. Commissions: Member of the Swiss Working group for Cystic Fibrosis (SWGCF) and the Task Force for the CF Newborn Screening, Member of the Swiss National Advisory Commission on Biomedical Ethics (2001-2008), President of the National Expert Commission on Genetic Testing in Human (since 2007), Evaluator of proposals submitted to the FP7-Health call of the European Commission, Member of the European Union Committee of Experts on Rare Diseases (EUCERD).

PROF. ANITA RAUCH, SWITZERLAND

Anita Rauch studied Medicine at the University of Erlangen-Nuremberg, Germany, where she also received her medical specialization for Human Genetics in 2000. In 2009 she was appointed to head and chair the Institute of Medical Genetics of the Medical Faculty of the University of Zurich. Her long-standing research interest systematically addresses the genetics and pathomechanisms of developmental disorders with special focus on disorders with intellectual disability or growth alterations. During recent years her research group was able to identify the underlying causes of several rare disorders such as Anauxetic dysplasia, Primordial dwarfism type MOPD II, Matthew-Wood syndrome, Short-Rib-Polydactyly syndrome type II, Pitt-Hopkins syndrome, and MEF2C-related intellectual disability, and also contributed significantly to the clinical and molecular understanding of syndromic congenital heart defects. Her group was also the first to investigate the usage of SNP arrays for molecular karyotyping in patients with developmental problems. Anita Rauch is founder and editor-in-chief of the novel Journal Molecular Syndromology, and associate editor of the European Journal of Human Genetics. Anita Rauch was awarded with the John Opitz Young investigator award in 2003, the Carl-Thiersch award of the University of Erlangen-Nuremberg in 2004, the annual scientific award of the German Society of Human Genetics in 2008, the Sir Hans Krebs award in 2008, and the Wilhelm-Vaillant award in 2009.

PROF. HAN G. BRUNNER, NETHERLANDS

Han Brunner, MD, PhD, is Professor of Human Genetics at University Hospital St Radboud in Nijmegen, the Netherlands. He obtained his medical degree from Groningen University in the Netherlands. He was board-certified in Clinical Genetics in 1988, and obtained his PhD on finding the gene for myotonic dystrophy in 1993. Prof. Brunner was appointed as head of the department of Human Genetics at Nijmegen in 1998. From 2004-2008 he was also the chairman of the Division of pediatrics, human genetics, and medical psychology of Nijmegen University Hospital. Prof. Brunner has been a member of the teams that found the genes several human malformation syndromes. His current interests are in the genetic basis of human brain development, mental retardation, and microdeletion syndromes. Han Brunner has served on the board of the Dutch Human Genetics Society. He is currently a member of the Scientific Program Committee of the International Congress of Human Genetics, and chairman of the Scientific Program Committee for the European Society of Human Genetics. He is a member of the editorial board of the Journal of Medical Genetics, Clinical Genetics, and Molecular Syndromology. He is on the Scientific Advisory Board of Telethon in Italy, and of the Dutch Neuromuscular Research Foundation.

DR. DAVID B. SAVAGE, UNITED KINGDOM

David Savage is a Wellcome Trust Senior Clinical Fellow based in the Institute of Metabolic Science at Cambridge University. The principal focus of his laboratory is to understand the molecular and physiological basis of insulin resistance in humans. He has a keen interest in rare genetic disorders characterised by extreme insulin resistance, particularly lipodystrophy in humans. In 2007, he moved to Tufts University to become a Professor and the White Family Chair in Biology. His current research concerns the role of repeat instability in human disease and the mechanisms and consequences of transcription-replication collisions.

DR. BERND WOLLNIK, GERMANY

Bernd Wollnik, MD, is head of a research group at the Center for Molecular Medicine Cologne (CMMC) and Institute of Human Genetics at the University of Cologne, Germany. After graduation as a medical doctor from the University in Bonn he was medical fellow and postdoc at Center for Molecular Neurobiology, University of Hamburg in Germany. In 1997 he received a DAAD fellowship for young scientist to continue his scientific work at the Child Health Institute at the University of Istanbul, Turkey. He got a foreign lecturer position at Istanbul University in 1999 as head of the Division of Molecular Genetics of the Child Health Institute. During his time in Turkey, Bernd Wollnik received the International Scientific Award of Istanbul University (2001) and the Young Scientist Award of the Turkish Academy of Science (2002). After returning back to Germany he established his group at the CMMC. His main research interests are to elucidate the molecular pathogenesis of craniofacial and skeletal malformation syndromes, and progeria-associated phenotypes. During the last years his group identified several disease-causing genes and the underlying molecular mechanisms. Bernd Wollnik is member of the national rare disease consortia SKELNET and FACE, an actively funded member of the Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), and co-ordinator of the ERARE network CRANIRARE.

DR. MARIA MAVRIS, FRANCE

Maria joined the Research and Therapeutic team of EURORDIS as Drug Development Programme Manager in January 2008. In this capacity she is responsible for following the development of orphan drugs as an observer on the Committee for Orphan Medicinal Products at the European Medicines Agency. She is also responsible for coordinating the group of high-level EURORDIS representatives who sit on the various scientific committees at EMA. Maria is also implicated in activities of the working parties at the EMA, namely the Scientific Advice Working Party (SAWP) where she is responsible for the identification of patients' representatives to participate in Protocol Assistance and she has a supportive role for EURORDIS representatives in the Patients' and Consumers' Working Party. In order to train and support patients' representatives in regulatory activities, she is also the organiser of the EURORDIS Summer School in clinical trials and drug development, a capacity-building project for patients' advocates in Europe.

PROF. DOUGLAS HIGGS, UNITED KINGDOM

MRC Molecular Haematology Unit, Institute of Molecular Medicine, John Radcliffe Hospital Douglas Higgs (FRS, DSc, FRCP, FMedSci) qualified in Medicine at King's College Hospital Medical School (University of London) in 1974 and trained as a haematologist. He joined the MRC Molecular Haematology Unit (Oxford) in 1977 and is currently Professor of Molecular Haematology at the University of Oxford, Director of the MRC Molecular Haematology Unit (MHU) and co-Director of the Weatherall Institute of Molecular Medicine (WIMM). The current interests of the MHU are: to understand the processes by which multi-potent blood stem cells undergo lineage commitment in haematopoiesis; to understand how genes are activated and repressed during normal haematopoiesis; and to study the inherited and

acquired human genetic diseases affecting these processes. The main interest of his own laboratory is to understand how mammalian genes are switched on and off during differentiation and development using haematopoiesis as the experimental model. The laboratory investigates a comprehensive set of transcriptional, co-transcriptional and epigenetic influences on gene expression including the role of nuclear position, chromosome conformation, the timing of replication, chromatin and DNA modification, and the potential role of non-coding RNAs. Initial studies using the well characterized globin loci are used to initiate genome-wide studies to establish the general principles underlying mammalian gene regulation. An important aim of this work, supported by strong clinical programmes, is to improve the management of patients with common blood diseases ranging from leukaemia to a variety of inherited forms of anaemia.

PROF. ALAIN FISCHER, FRANCE

Alain Fischer was born in 1949 in France. He studied medicine in Paris and specialized in pediatrics. He received his M.D. in 1979 and a PhD in immunology during the same year. After a post-doctoral stay at the University College in London, he started independent research in an INSERM unit at the Necker Hospital in Paris. In 1988, Alain Fischer became a professor in pediatric immunology. Since 1991, he directs the INSERM research unit for "Normal and pathological development of the immune system" and, since 1996, the clinical unit of Pediatric Immunology and Hematology at the Necker Hospital in Paris. He has been the President of the Immunology Committee at INSERM, Adviser for Medical Research at the Ministry of Research in France, Director of the French Program "Research on rare diseases", Member of the Initiative Committee on the reform of the French research system, and Vice-President of the board of the Pasteur Institute. His main areas of research are the development of the lymphoid system, primary immunodeficiencies, genetics of immunological disorders and gene therapy. During the course of the last fifteen years Professor Fischer and his co-workers have analyzed the mechanisms of hereditary diseases of the immune system. He is the author of about 500 scientific papers, and editor of the European Journal of Immunology, International Immunology, EMBO Journal, EMBO reports, Clinical and Experimental Immunology, Annual Reviews of Immunology, and the Science. Professor Alain Fischer has received the Halpern Prize in 1984, the Behring-Metchnikoff Prize in 1992, the Prix du Comité du Rayonnement français in 1994, the Jung Prize for Medicine (Hamburg) in 1998, the prix Pierre Royer in 2000, the NRJ Foundation – Institut de France – Award in 2000, the 2001 Louis-Jeantet Prize for Medicine (Geneva), the Novartis Prize for Clinical Immunology in 2001 and the A. Philipson Prize (Stockholm) in 2003. Alain Fischer is also a member of the European Molecular Biology Organization since 2002 and of the French Science Academy since 2002.

PROF. ECKHARD WOLF, GERMANY

Dr. Eckhard Wolf studied Veterinary Medicine at the LMU Munich, where he finished his Dr. med. vet. in 1990. In 1994 he did his Habilitation for Animal Breeding and Genetics at the University of Veterinary Sciences in Vienna, Austria. Since 1995 he holds the Chair for Molecular Animal Breeding and Biotechnology at the Gene Center, LMU Munich. Since 2003 he is also Director of the Laboratory for Functional Genome Analysis (LAFUGA) at the Gene Center. Eckhard Wolf did his veterinary specialisation in the fields of laboratory

animal science and of animal breeding and biotechnology. He is a founding diplomate of the European Colleges of Animal Reproduction (ECAR) and of Laboratory Animal Medicine (ECLAM). Eckhard Wolf is a leading specialist in the development and characterization of tailored animal models (mice and pigs) for translational biomedical research.

PROF. MARY M. REILLY, UNITED KINGDOM

MRC Centre for Neuromuscular Disease and Dept. of Molecular Neurosciences, National Hospital for Neurology and Neurosurgery and UCL Institute of Neurology, Queen Square, London WC1N 3BG, UK. Mary M. Reilly graduated from University College Dublin in 1986. She started her clinical training in Neurology in Dublin after gaining her MRCP in 1988. She moved to the National Hospital for Neurology and Neurosurgery, London in 1991 where she completed an MD thesis on Familial Amyloid Polyneuropathy under the supervision of the late Professor Anita Harding. She then completed her clinical neurological training subspecialising in peripheral nerve diseases and trained both with Professor PK Thomas and Professor Richard Hughes. Since 1998, she is head of the peripheral nerve services in the National Hospital for Neurology and Neurosurgery and has an active research programme in genetic neuropathies. She received her FRCP in 2002, her FRCPI in 2003 and has been appointed Professor of Clinical Neurology at UCL in 2010.

PROF. STYLIANOS ANTONARAKIS, SWITZERLAND

Professor Stylianos Antonarakis is the Director of the Division of Medical Genetics at the University of Geneva in Switzerland. Before moving to Geneva he was a professor at Johns Hopkins University in the USA. His lab participates in many projects involving the genetics of monogenic and polygenic disorders as well as the annotation of the human genome and particularly of human chromosome 21. He is on the editorial board of many high profile journals such as *Genome Research* and *Genomics* and has recently served as president of the European Society for Human Genetics.

PROF. SERGEI M. MIRKIN, USA

Sergei M. Mirkin received his M.S. in Genetics from the Moscow State University in 1978, followed by a Ph.D. in Molecular biology from the Institute of Molecular Genetics, Russian Academy of Sciences, in 1983. During his graduate studies under the supervision of Roman B. Khesin, he found that DNA gyrase is essential for both DNA replication and transcription in *E. coli*. He then carried out his postdoctoral studies under the supervision of Maxim D. Frank-Kamenetskii studying conformational transitions in superhelical DNA. His research resulted in the discovery of the first multi-stranded DNA structure, called H-DNA, which is an intramolecular triplex formed by homopurine-homopyrimidine mirror repeats. He was appointed a Group Leader at the Institute of Molecular Genetics in Moscow in 1988. Anticipating the demise of the Russian science, he moved to the United States in 1989, where he became an Assistant Professor at the University of Illinois, College of Medicine at Chicago in 1990. During his years at UIC, he rose in ranks to the Full Professor establishing himself as an international leader in the field of DNA structure and functioning, broadly defined. One of his major achievements was unraveling the replication mechanism of the expansion

of triplet repeats – a phenomenon responsible for more than thirty hereditary disorders in humans. In 2007, he moved to Tufts University to become a Professor and the White Family Chair in Biology. His current research concerns the role of repeat instability in human disease and the mechanisms and consequences of transcription-replication collisions.

DR. TEWIS BOUWMEESTER, SWITZERLAND

Tewis Bouwmeester, PhD. – Executive Director, Site Head DMP Basel, Novartis Institutes for Biomedical Research. Tewis Bouwmeester studied Biochemistry in Amsterdam and received his Ph.D. from the Free University of Amsterdam in 1993, having worked at the Max-Planck Institute for Molecular Genetics in Berlin. He then moved to the University of California at Los Angeles to do a post-doc stint with Prof. Eddy M. de Robertis working in the area of developmental biology. In 1997 he was recruited to the European Molecular Biology Laboratory (EMBL) in Heidelberg where he was on the faculty of the Developmental Biology Department for 4 years. In 2001, he joined Cellzome, an EMBL biotech spin-off, as Director of Molecular Biology before becoming VP Biology & Research Alliances. In May 2008 he joined Novartis where he is now the site head of the Developmental Molecular Pathways (DMP) department in Basel. His research interest spans from regenerative medicine, epigenetics and understanding the genetics of human disease.

PROF. ANDREA SUPERTI-FURGA, SWITZERLAND

Prof. Andrea Superti-Furga has obtained his medical degrees at the Universities of Genoa (Italy) in 1984 and Zurich (Switzerland) in 1989. His mentors were Professors Paolo Durand, Victor McKusick, Andrea Prader, Andreas Fanconi, Richard Gitzelmann and Beat Steinmann. He obtained board certification in Pediatrics in Italy (1988) and Switzerland (1995). Through his early internship with P. Durand in Genova he developed an interest in Inborn Metabolic Diseases, and he developed an intense laboratory research activity in Zurich and during stajes at Mount Sinai Hospital in New York, his main research themes being inborn metabolic diseases, inherited diseases of connective tissue, and skeletal dysplasias and dysostoses. After his Habilitation at the University of Zurich in 1995, he was appointed Full Professor for Molecular Pediatrics at the University of Lausanne (Switzerland) in 2002 under the direction of Prof. Sergio Fanconi; in 2004, he was appointed Chairman of the Department of Pediatrics and Director of the Children's Hospital at the University of Freiburg, Germany. Parallel to his research interest in rare diseases, he maintained strong ties to general clinical pediatrics as well as university teaching of Pediatrics, being the chief organizer of lectures and courses in Pediatrics at both the Lausanne University (2002-2005) and the Freiburg University (since 2005-2010) Schools of Medicine. In October 2010, Prof. Superti-Furga was awarded the Lee-naards Chair of Excellence in Pediatrics at the University of Lausanne, Switzerland, where he now is Director of Research of the Department of Pediatrics. A representative of science- and molecular biology-based pediatrics both in research and in clinical practice, Prof. Superti-Furga is committed to a holistic approach to pediatrics with a comprehensive perspective that includes the genetic and molecular bases of development and disease, the growth and development of healthy children as well as those with chronic disease, and the social, economical and ethical issues around disabled children with rare diseases and their families. His current research activity is centered on the clinical delineation and molecular elucidation of genetic disorders, particularly of the skeleton and connective tissue.

PROF. ARNOLD MUNNICH, FRANCE

Since 1980, Arnold Munnich has made every efforts to conciliate the clinical and molecular approaches of genetic diseases in children. His efforts have resulted in the founding of the Department of Genetics, Hôpital des Enfants-Malades, Paris, which brings together i) a Clinical Research INSERM unit, dedicated to the mapping and identification of genes causing developmental and neurogenetic diseases in children, ii) the Medical Genetic Clinic of Assistance Publique, Hôpitaux de Paris. Thanks to the improvement of the human gene map, he has mapped and/or identified twenty disease causing genes, including the genes for:

- achondroplasia (1/15,000 live births, fibroblast growth factor receptor 3),
- Hirschsprung disease (1/5,000 live births, Ret oncogene),
- spinal muscular atrophy (1/6,000 live births, survival motor neuron, SMN),
- X-linked spastic paraplegia (proteolipid protein),
- Holt-Oram syndrome (brachyury),
- multiple exostosis (EXT),
- Stargardt macular dystrophy (ABCR4),
- Leber congenital amaurosis (retinal guanylate cyclase),
- Saethre-Chotzen craniosynostosis (twist),
- Pearson's marrow pancreas syndrome (mitochondrial DNA deletion),
- the first nuclear gene for Leigh syndrome (SDH, FP),
- mental retardation (AR) : neurotrypsine,
- several nuclear genes for mitochondrial diseases (BCS1, COX10, SCO1),
- Triple A syndrome (1/50,000 live births, Aladin),
- Incontinentia pigmenti (1/5,000 live births, Nemo, with the International IP Consortium) and ectodermal dysplasia-immune deficiency (1/5,000 live births, Nemo and IkBa).

He has recently shown that Friedreich ataxia results from multiple iron-sulphur protein injury caused by iron overload in mitochondria. Based on this observation, he devised a novel therapeutic approach using short-chain quinones (Idebenone) to protect iron sulphur centers from oxidative stress. This treatment, now given to all novel cases, cures cardiomyopathy in 85% of patients. He has also identified a novel inborn error of quinone synthesis resulting in multiple respiratory chain deficiency and caused by a point mutation in a polyprenyl transferase gene. Most importantly, children are cured by oral quinone administration. Prof. Munnich has fostered several research groups and young investigators that gradually took over the leadership and seniorship of their projects. What are the benefits for the children and their families? The mapping and identification of these genes makes carrier testing, genetic counselling and prenatal diagnosis of these conditions now feasible and allow novel therapeutic approaches. The originality of his project consists in the combination of a clinical expertise and a molecular approach of medical genetics in the unique environment of a large european pediatric hospital.

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SPEAKER ABSTRACTS

PERSONAL GENOMES MEDICAL GENOMES & CLAN GENOMICS A PERSONAL QUEST TO IDENTIFY THE GENETIC UNDERPINNINGS OF CHARCOT-MARIE-TOOTH NEUROPATHY

Cullen Professor and Vice Chairman, Department of Molecular and Human Genetics and Professor of Pediatrics, Baylor College of Medicine, Houston, TX, USA

Following the “finished”, euchromatic, haploid human reference genome sequence, the rapid development of novel, faster, and cheaper sequencing technologies is making possible the era of personalized human genomics. Personal diploid human genome sequences have been generated, and each has contributed to our better understanding of variation in the human genome. We have consequently begun to appreciate the vastness of individual genetic variation from single nucleotide (SNV) to structural variants including copy number variants (CNV). Translation of genome-scale variation into medically useful information is, however, in its infancy. This talk summarizes the initial steps undertaken in clinical implementation of personal genome information, and describes the application of whole-genome and exome sequencing to identify the cause of genetic diseases and to suggest adjuvant therapies. The subject matter will focus on Charcot-Marie-Tooth neuropathy and a personal quest to understand its genetic underpinnings. Better analysis tools, particularly for determining CNV from sequence and a deeper understanding of the biology of our genome are necessary in order to decipher, interpret, and optimize clinical utility of what the variation in the human genome can teach us. Personal genome sequencing may eventually become an instrument of common medical practice, an adjuvant to the family history, providing information that assists in the formulation of a differential diagnosis. I will discuss some of the remaining challenges.

James R. Lupski

FINDING A CURE TO BLACK BONE DISEASE, FROM A PATIENT'S POINT OF VIEW

AKU Society, Cambridge, United Kingdom

AKU (short for Alkaptonuria) was the first genetic disease ever identified, in 1901 by Dr. Archibald Garrod in London. It is caused by a recessive gene that leads to a missing enzyme. This means that patients are unable to metabolise correctly an amino acid, tyrosine, and instead produce homogentisic acid (HGA) at 2,000 times the normal rate. HGA is a black pigment that binds to cartilage, destroying it and causing severe early-onset osteoarthritis. It turns bones brittle and black, which is why AKU is known as Black Bone Disease. There is no cure. Patients are often isolated, marginalised and depressed because of the rare nature of their condition. The AKU Society is a patient group set up in 2003 in the UK by AKU patients, relatives and clinicians. It exists to improve the lives of AKU patients by providing them with information and support. It also promotes research into the understanding and treatment of AKU and has built strong partnerships with more than 20 universities, hospital trusts and biotech/pharma companies across Europe, North America, the Middle East and Asia. There are now AKU Societies in the the UK, USA, Canada, France, Italy and soon in Germany, Belgium, the Netherlands and Slovakia. The AKU Society has helped set up an international consortium that is on the verge of launching a clinical trial for the first ever treatment for AKU. The AKU experience proves that a patient group can stimulate a large international movement of scientists, industry and patient organisations in order to develop new avenues for treatment.

Nicolas T. Sireau

A DEFENSE AGAINST GENETIC INVADER TURNED INTO A MASTER REGULATOR OF MAMMALIAN HOMEOSTASIS

School of Life Sciences, École Polytechnique Fédérale de Lausanne (EPFL), 1015 Lausanne, Switzerland

Close to half of the genome of higher vertebrates is derived from endogenous retroelements. These are powerful motors of evolution but they need to be tightly controlled during early embryogenesis. This is accomplished in part through the action of a large family of tetrapod-specific transcriptional repressors, the KRAB-containing zinc finger proteins (KRAB-ZFPs), which together with their universal cofactor KAP1 silence endogenized retroviruses through histone and DNA methylation. I will describe the mechanisms of this process, and how it presents striking parallels with events at play in the maintenance of imprinting marks in embryonic stem cells. I will go on to reveal how the KRAB/KAP1-mediated control of endogenous retrovirus-derived enhancers is indirectly essential to the preservation of stem cell pluripotentiality. Finally, I will illustrate how a system that was initially selected as a line of defense against retroviral invaders was co-opted to serve today as a master regulator of mammalian homeostasis.

Didier Trono

HUNTINGTIN FROM EVOLUTION TO PATHOLOGY VIA NEUROEPITHELIAL STEM CELLS

Università degli studi di Milano

Huntingtin (htt) is the ~800 million-year old protein product of the Huntington's disease (HD) gene. The gene contains a polymorphic tri-nucleotide CAG repeat that is translated into polyglutamine amino acid (polyQ) residues in the protein. When this polyQ stretch at the 18 aminoacid (aa) position of the protein expands to over 39 residues, HD occurs, a fatal, genetically dominant, neurodegenerative disease. The CAG repeats are well conserved in deuterostomes, which suggests that they are an ancestral feature retained during the evolution of the protein. Htt carries a number of specific activities in the adult brain; for instance, it promotes transcription of neuronal genes among which is the BDNF, a neurotrophin critical for the survival and activity of cortical and striatal neurons that degenerate in HD. This lecture will highlight the power of combining evolutionary and developmental approaches to the study of the biology of disease-genes and will review the more recent discovery of a function for htt in neuroepithelial stem cells.

Elena Cattaneo

HUMAN EPITHELIAL STEM CELLS AND REGENERATIVE MEDICINE

Centre for Regenerative Medicine "Stefano Ferrari", University of Modena and Reggio Emilia, Modena, Italy

Adult stem cells are cells with a high capacity for self-renewal that can produce terminally differentiated progeny. Stem cells generate an intermediate population of committed progenitors, often referred to as transit amplifying (TA) cells, that terminally differentiate after a limited number of cell divisions. Human keratinocyte stem cells are clonogenic and are known as holoclones. Human corneal stem cells are segregated in the limbus while limbal-derived TA cells form the corneal epithelium. Self-renewal, proliferation and differentiation of limbal stem cells are regulated by the $\Delta Np63$ (α , β and γ), $C/EBP\delta$ and $Bmi1$ transcription factors. Cultivated limbal stem cells generate sheets of corneal epithelium suitable for clinical application. We report long-term (up to 10 years) clinical results obtained in an homogeneous group of 112 patients presenting with corneal opacification and visual loss due to chemical burn-dependent limbal stem cell deficiency. The corneal epithelium and the visual acuity of these patients have been restored by grafts of autologous cultured limbal keratinocytes. In post hoc analyses, success was associated with the percentage of p63-bright holoclone-forming stem cells in culture. Graft failure was also associated with the type of initial ocular damage and postoperative complications. Mutations in genes encoding the basement membrane component laminin 5 (LAM5) cause junctional epidermolysis bullosa (JEB), a devastating and often fatal skin adhesion disorder. Epidermal stem cells transduced with a retroviral vector expressing the $\beta 3$ cDNA can generate genetically corrected cultured epidermal grafts able to permanently restore the skin of patients affected by LAM5- $\beta 3$ -deficient JEB. The implication of these results for the gene therapy of different genetic skin diseases will be discussed.

Michele De Luca

ACADEMIC DEVELOPMENT OF AN ADVANCED THERAPY MEDICINAL PRODUCT TO ADDRESS UNMET MEDICAL NEED AND ITS TRANSFER TO INDUSTRY TO SECURE FINAL ACCESS FOR ALL PATIENTS

Head of Pediatric Liver and Cell Therapy Unit, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, Brussels, Belgium Founder and CSO of Promethera Biosciences, Mont St Guibert, Belgium

One challenge of medicinal research is to bridge the gap allowing its final application, which applies particularly to advanced therapy medicinal products. The liver cell is a comprehensive functional metabolic unit that is able to perform hundreds of different functions, specific of the full liver itself. Liver regenerative medicine aims to restore one or more missing functions in a diseased liver: following healthy liver cells transfer, it is possible to repair the deficient liver instead of replacing it by orthotopic transplantation. The proof of concept has been shown with hepatocytes that infusing cells into the liver is able to transfer a missing function in the deficient organ. Repopulation up to 10% has been shown, and miscellaneous inborn errors of metabolism have been successfully treated on the short to medium term. However, mature hepatocytes can hardly be stored by cryopreservation, and there is a huge problem of organ shortage. Alternative cell sources are therefore needed for the development of liver targeted cell therapy, which would give unlimited access to the treatment. The challenge for these alternative cells is to acquire the same level of functionality once implanted in the target organ, and to persist and progressively replace the host's cells by donor cells. Advanced therapies are a category of new medicinal product, including in vitro engineered cells originally derived from human tissues, and produced at large scale for the purpose of regenerative medicine. Bringing such medicinal product to the market requires in vitro demonstration of the potency, safety investigations including viral and oncogenic risks, preclinical investigations, and development of GMP large scale production with stable release criteria. The human Adult Liver Derived Mesenchymal Stem Cell is a progenitor cell that is derived from the normal human liver, and able to meet these requirements. The technology has emerged from the hepatocyte transplantation program, and is currently being developed at industrial level for the treatment of children with life threatening and or severe debilitating inborn errors of metabolism. Developing a candidate cells from the patient's bed thanks to academic research and transfer to the industry is the right pathway to finalize such long term translational medicine research and ensure access to innovative therapies for all patients.

Etienne Sokal

NARCOLEPSY: A RARE AUTOIMMUNE DISEASE

CIG & CIRS, University of Lausanne & CHUV, Lausanne, Switzerland

Narcolepsy with cataplexy affects 0.02% of the general population and is characterized by excessive daytime sleepiness and emotion-triggered muscle atonia (cataplexy). Narcolepsy has the tightest HLA association ever reported, largely higher than any autoimmune disease. Nevertheless, only recently evidence strongly suggested that the condition might be autoimmune. The biological cause of narcolepsy is hypocretin deficiency. Post-mortem brain analysis indicates absence or very few hypocretin neurons in narcolepsy patients and hypocretin-1 is found undetectable in the CSF of most patients, suggesting the destruction of hypocretin neurons by a yet un-identified autoimmune attack. We have engineered a transgenic mouse model and purified mRNAs of hypocretin neurons leading to the identification of Trib2 as a target auto-antigen. Also, genome-wide association studies identified T-cell receptor alpha as the most significant gene variant associated with narcolepsy. We have also shown recently that the HLA association is causal and that a mutation in myelin oligodendrocyte glycoprotein gene causes a familial form of narcolepsy. Finally, we have introduced IVIg treatment with unexpected favorable results in patients diagnosed at early stages of the disease development. Altogether, these findings support the autoimmune hypothesis. Nevertheless, the mechanism remains unknown.

Mehdi Tafti

CYSTIC FIBROSIS (CF) AND CF-RELATED DISORDERS (CF-RD): FROM SINGLE GENE TESTING TOWARD ARRAY-BASED SEQUENCE CAPTURE AND NEXT GENERATION SEQUENCING

Division of Human Genetics, Departments of Pediatrics and Clinical Research, Inselspital, University of Berne, 3010 Berne, Switzerland

Cystic fibrosis (CF) is an autosomal recessive disorder with an incidence in the white population of 1 in 2500 live births. The disease is primarily caused by mutations in the CF transmembrane conductance regulator (CFTR) gene on chromosome 7q31.3 and encodes a protein functioning as a cAMP-dependent chloride channel. Classic CF is characterized by progressive lung disease, pancreatic insufficiency, chronic sinusitis, and male infertility. Besides the most common mutation, F508del, more than 1900 mutations and variants have been reported so far which affect the gene product through a variety of molecular mechanisms resulting in little or no functional CFTR. In principle, CFTR gene analysis contributes to CF diagnosis and allows to some extent prediction of the phenotype. However, to date it has its limitations, mainly due to the widely heterogeneous clinical course supporting the concept that even a so-called monogenic disorder is far from being caused by one single gene and requires consideration of additional genetic factors that modify outcome. Thus, CF and CFTR-related disorders (CFTR-RD) such as monosymptomatic male infertility with congenital bilateral absence of the vas deferens (CBAVD), acute recurrent or chronic pancreatitis and disseminated bronchiectasis may be modified by proteins of the CFTR interactome and/or of the inflammatory cascade, whereas pathogenic mutations within genes of these proteins may be the primary cause of CF-like diseases and may add to the development of CFTR-RD in a digenic manner raising the need for the analysis of a large number of genes. Advances in sequencing technologies such as next generation sequencing (NGS), provide rapid identification of variants on a large scale. Targeting the regions of interest, instead of resequencing the entire human genome, is a high potential strategy enabling efficient sequencing coverage and avoiding the problem of identifying variants in genes for which the analyses were not intended. Therefore, array-based and hypothesis driven sequence capture combined with NGS is thought to be a cost- and time-effective method to analyse the entire genomic sequence of the CFTR gene as well as a comprehensive number of genes involved in the manifestation of CF, CFTR-RD and the rare CF-like disorders allowing accurate diagnosis in as yet undiagnosed patients, improved prognosis and the design of individual diagnostic and therapeutic strategies in terms of a translational and personalised medicine.

Sabina Gallati

TOWARDS A DEEPER UNDERSTANDING OF INTELLECTUAL DISABILITY DISORDERS

Institute of Medical Genetics, University of Zurich, Schwerzenbach-Zurich, Switzerland

Intellectual disability (ID) is defined as a childhood onset, significant impairment of neurocognitive and adaptive function associated with an IQ below 70. With an overall prevalence of 2-3% ID is a common, but very heterogeneous trait. It occurs as an isolated feature or as part of a plethora of rare monogenic or chromosomal disorders. Albeit the identification of more than 400 genes and many chromosomal regions associated with ID, the underlying cause currently remains unclear in the majority of patients. However, recent developments of novel tools for genome-wide high-resolution chromosomal copy number and genotype profiling as well as for massive parallel sequencing now enables a quantum leap in the diagnostics and research of causes underlying ID. Small chromosomal copy number losses and gains account for about 15 % of patients with ID. Moreover, the identification of small copy number changes in key patients allows the identification of novel genes causing monogenic ID disorders. In addition, massive parallel or so called 'next generation sequencing' now enables effective mutational screening in all known exons within a single experiment. Using this so called exome sequencing within the MRNET consortium to study 50 patients with severe, unspecific ID, we identified mutations in known ID genes in one third of patients. Many more patients showed potential disease causing mutations in novel disease genes which need further investigation. In summary, these new genome-wide testing tools have the power to identify a sizable fraction of disease causing mutations in both known and novel genes and will change our diagnostic approach and understanding of ID in due course.

Anita Rauch

EXOME SEQUENCING AS A DIAGNOSTIC TOOL IN PATIENTS WITH UNEXPLAINED INTELLECTUAL DISABILITY

Radboud University Medical Center Nijmegen, Department of Human Genetics

Starting in 2011 the department of human genetics in Nijmegen has performed 500 exomes for diagnostic purposes. Of these, 50 each were dedicated to patients with blindness, deafness, metabolic disease, and movement disorders. In a series of 100 blind patients with retinal disease, we find that 45% can be given a definite genetic diagnosis by this technology. The other 300 exomes were done on DNA from 100 patients with intellectual disability and their parents. This trio design allows us to specifically look for de novo mutations as a cause of intellectual disability. All patients were sporadic, without any diagnosed dysmorphic syndrome, no consanguinity, and with normal chromosomes by array. All patients had moderate to severe intellectual disability. We have so far completed the analysis for about half of these trios (n=42). We find the following: Most newborns have 0, 1 or 2 de novo mutations. Very few have 3 or 4 de novo events. This makes analysis relatively easy. About 40% of patients have no detectable de novo mutation in their exome. About 20% of our patients with intellectual disability have de novo mutations in known ID genes (SYNGAP1, TCF4, ARHGAP9 etc). Another 20% have a de novo mutation in a new gene that very likely causes ID (e. g. DYNC1H1). A small number (5%) have inherited mutations in X-chromosomal ID genes. This means that we can make a confident diagnosis in 20-25% of our patients. These results suggest that we may rapidly identify the majority of all genetic causes of intellectual disability. The expected yield of combined array and exome analysis is at least 45% even in patients with severe intellectual disability who have no family history, and no recognized dysmorphic syndrome. Exome sequencing of all 21,000 human genes is a powerful new tool to diagnose inherited disease.

Han G. Brunner

INSIGHTS FROM EXTREME MONOGENIC INSULIN RESISTANCE SYNDROMES

Metabolic Research Laboratories, Institute of Metabolic Science, University of Cambridge, Addenbrooke's Hospital, Hills Road, Cambridge CB2 0QQ, UK

Obesity, insulin resistance and their attendant complications are among the leading causes of morbidity and premature mortality today, yet we are only in the early stages of understanding the molecular pathogenesis of these aberrant phenotypes. A powerful approach has been the study of rare patients with monogenic syndromes that manifest as extreme phenotypes. For example, there are striking similarities between the biochemical and clinical profiles of individuals with excess fat (obesity) and those with an abnormal paucity of fat (lipodystrophy), including severe insulin resistance, dyslipidaemia, hepatic steatosis and features of hyperandrogenism. Rare lipodystrophy patients therefore provide a tractable genetically-defined model for the study of a more prevalent human disease phenotype. Detailed study of these and other monogenic insulin resistance syndromes has already and continues to yield valuable insights into the molecular pathogenesis of human insulin resistance, the essential components of normal adipose tissue development, and the mechanisms by which disturbances in adipose tissue function can lead to almost all the features of the metabolic syndrome.

David B. Savage

CRANIRARE: AN E-RARE SUCCESS STORY FOR IDENTIFYING THE PATHOGENESIS OF CRANIOFACIAL MALFORMATIONS

Center for Molecular Medicine Cologne and Institute of Human Genetics University of Cologne, Cologne

Craniofacial malformations affecting head and face can result in severe functional, esthetical, and social consequences for affected individuals. Anomalies include ossification defects of facial and cranial bones, jaw deformities, malformed or missing teeth, ear anomalies, and facial asymmetries. Craniofacial anomalies – other than cleft lip and palate – occur in approximately 1 in every 2,000 newborns. A large variety of craniofacial malformations have been described in human, most of them are rare monogenic, non-syndromic or syndromic disorders. In order to improve patient care and therapeutic strategies the CRANIRARE consortium aimed to (i) further understand the fundamental and complex biological processes underlying craniofacial development, (ii) to elucidate conserved molecular pathways during development, (iii) to identify the molecular and pathogenic mechanisms of these disorders, (iv) and to translate these findings into clinical practise and use this knowledge as basis for the development of new therapies. During the first funding period, CRANIRARE ascertained and clinically characterized a substantial number of patients with various craniofacial malformations. We successfully identified 18 novel causative genes for 13 different craniofacial disorders and elucidated new conserved molecular pathways important for biological processes of craniofacial development. Moreover, we developed novel technologies for local delivery of bioactive agents to induce bone tissue regeneration. Examples of phenotypes and identified genes and mechanisms will be given. Our highly successful studies clearly demonstrate the benefit of transnational studies in rare diseases. Relying on the established CRANIRARE infrastructure, we now aim to extend our work and include 15 additional craniofacial phenotypes.

Bernd Wollnik

PATIENTS AND SCIENTISTS' INVOLVEMENT IN THE ORPHAN DRUG DEVELOPMENT PROCESS

Therapeutic Development Director EURORDIS - European Rare Diseases Organisation

Patients' representatives have an increasingly present voice in all aspects of drug development from fundamental research through regulatory processes to Health Technology Assessment. EURORDIS has conducted surveys on the involvement on Patients' Organisations in rare disease research and some results will be presented. In 2000 when the Committee for Orphan Medicinal Products was created at the European Medicines Agency, patients were included as full members. Over the last 12 years, two (and soon to be three) more scientific committees have also included patients as full members. The Orphan Drug Legislation, its criteria and incentives will be described, in particular the scientific process known as protocol assistance, where patients are often implicated.

Maria Mavris

THE ROLE OF THE ATRX CHROMATIN ASSOCIATED PROTEIN IN HUMAN DISEASE

MRC Molecular Haematology Unit, Oxford

ATRX is an X-linked gene of the SWI/SNF family, mutations in which cause syndromal mental retardation and downregulation of alpha-globin expression. We have shown that ATRX binds to tandem repeat (TR) sequences in both telomeres and pericentromeric chromosomal regions where ATRX may be targeted by recognizing specific DNA structures and/or chromatin modifications. Within euchromatin ATRX is also associated with TRs associated with a subset of genes, some of which are dysregulated when ATRX is mutated and the change in expression is determined by the size of the TR, producing skewed allelic expression. This reveals the characteristics of the affected genes, explains the variable phenotypes seen with identical ATRX mutations, and illustrates a new mechanism underlying variable penetrance in human genetic disease. Many of the TRs are G rich and predicted to form non-B DNA structures (including G-quadruplex) *in vivo*. We have shown that ATRX binds G-quadruplex structures *in vitro*, suggesting a mechanism by which ATRX may play a role in various nuclear processes (in particular transcription and DNA replication) and how this is perturbed when ATRX is mutated.

Douglas R.Higgs, David Clynes, Hsiao Voon, Clare Jelinska. R.J. Gibbons

GENE THERAPY OF PRIMARY IMMUNODEFICIENCIES

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Primary immunodeficiencies (SCID) consist in more than 200 conditions, many of them with a naturally poor prognosis. Most of PID have mendelian inheritance and many of the PID genes have today been identified leading to a substantial understanding of pathophysiology. Based on those results, it has been assumed that ex vivo gene transfer in hematopoietic stem cells could provide sustained correction of T cell immunodeficiencies such as severe combined immunodeficiencies. By using a set of retroviral vectors, several trials have been initiated since 1999. Today, evidence of sustained SCID disease correction has been demonstrated for 2 conditions, SCID-X1 and ADA deficiency, albeit, initially at the cost of insertional oncogenesis in five patients with SCID-X1. The present usage of modified vectors (so called self inactivated –SIN – γ retro – and lentiviral vectors), looks promising as potentially combining safety and efficacy and is leading to the extension of the scope of treated diseases toward several other PID and inherited bone marrow diseases as well.

Alain Fischer

TAILORED PIG MODELS FOR RARE HUMAN GENETIC DISEASES

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Animal models play crucial roles for understanding disease mechanisms and for the development and evaluation of therapeutic strategies. In biomedicine, classical rodent models are most widely used for a number of reasons, including standardization of genetics and environment, cost efficiency, and the possibility to introduce targeted genetic modifications for the generation of tailored disease models. However, due to differences in anatomical and physiological characteristics, rodent models do not always reflect the situation of human patients sufficiently well to be predictive in terms of efficacy and safety of new therapies. In this respect the pig has been discussed as “missing link” between mouse models and human patients. As a monogastric omnivore the pig shares many anatomical and physiological similarities with humans. Importantly, the techniques for genetic modification of pigs have been refined to a level allowing almost the same spectrum of alterations as in mouse models. These include the introduction of targeted genetic modifications, mimicking human hereditary diseases at the molecular level. Cystic fibrosis (CF) is the most common lethal inherited disease in Caucasians and is caused by mutations in the CFTR gene. The disease is incurable and medical treatment is limited to the amelioration of symptoms or secondary complications. A comprehensive understanding of the disease mechanisms and the development of novel treatment options require appropriate animal models. Existing CF mouse models fail to reflect important aspects of human CF. We thus generated a CF pig model by inactivating the CFTR gene in primary porcine cells by sequential targeting using modified bacterial artificial chromosome (BAC) vectors. These cells were then used to generate homozygous CFTR mutant piglets by somatic cell nuclear transfer. The homozygous CFTR mutants lack CFTR protein expression and display severe malformations in the intestine, respiratory tract, pancreas, liver, gallbladder and male reproductive tract. These phenotypic abnormalities closely resemble both the human CF pathology. Our new CF pig model underlines the value of the CFTR deficient pig for gaining new insight into the disease mechanisms of CF and for the development and evaluation of new therapeutic strategies. This model will furthermore increase the availability of CF pigs to the scientific community (publication: Klymiuk N et al., J Mol Med 2011).

Eckhard Wolf

INHERTIED NEUROPATHIES 2012: BENCH TO BEDSIDE; WHERE ARE WE?

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Charcot-Marie-Tooth disease (CMT, also called hereditary motor and sensory neuropathy, HMSN) is the commonest inherited peripheral neuropathy affecting 1 in 2,500. The related disorders hereditary sensory and autonomic neuropathy (HSAN), which mainly affects the sensory nerves and distal hereditary motor neuropathy (HMN), which predominantly affects the motor nerves, are often due to mutations in the same genes that cause CMT. Since the identification of the chromosome 17 duplication as the first genetic cause of CMT in 1991, there have been over 50 genes described for this group of disorders. Despite this, there has not been an effective therapy yet developed for CMT. This is clearly disappointing particularly for patients. The challenges in translating laboratory findings to treatment for patients are many. Firstly how are we doing at identifying the genetic causes. In a recent USA study in a large CMT clinic of over 600 patients, 67% of patients achieved a genetic diagnosis. This is similar to our experience where in a clinic of over 1,000 patients the diagnostic rate is 63% (the slightly lower rate reflects the bias in our clinic for seeing rare types of CMT). This improved diagnosis is excellent for patients allowing accurate diagnosis and prognosis and the possibility of ante natal and pre-implantation diagnosis. The access to genetic tests and the cost of these is another challenge particularly in certain parts of the world but this is a rapidly evolving field. The second and increasing challenge is whether an identified mutation is pathogenic. This not only refers to exonic mutations but especially with the developments in next generation sequencing increasingly to intronic, splice site, promoter and variations which are further afield. The issues of multiple mutations in different genes in a patient and of phenotype modifying mutations also needs to be considered. Diagnostic functional tests are generally lacking in CMT. The final and biggest challenge is performing clinical trials in this group of patients. The common form of CMT, CMT1A, is very slowly progressive and has posed real issues in terms of developing responsive outcome measures, All other forms are rare and pose equal challenges for both trial design and development of gene specific outcome measures. Despite all the challenges this is a very exciting time with the real possibility of developing therapies for some forms of CMT and the related disorders within the next decade.

Mary M. Reilly

CONSANGUINITY AND DISEASE GENE DISCOVERY

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Consanguinity and inbreeding is widely practiced in a fraction of world populations. One consequence of consanguinity is that it uncovers recessive pathogenic alleles through homozygosity and the resulting phenotypes. The technological and bioinformatics advances now permit the discovery of almost all genomic variants in people's genomes; the medical interpretation of the variants, however, is currently restricted to a fraction of the functional genomic elements, namely the exons of protein-coding genes. We have initiated a project to identify genes responsible for rare phenotypes in consanguineous families using exome sequencing, and pedigree analysis. Samples from more than 40 nuclear families with at least 2 affected (with a variety of severe phenotypes) and non-affected siblings and parents have been collected through a network of international collaborators. A combination of genotyping, array CGH and exome sequencing was performed. We will report the results of the first 12 families and the identification of the likely molecular defect in half of these.

Stylianos E. Antonarakis

TWO SIDES OF THE SAME COIN: INSTABILITY OF DNA REPEATS AND MUTAGENESIS AT A DISTANCE

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My lab is using model systems to study genetic instability of simple DNA repeats that are responsible for many hereditary diseases in humans, such as fragile X mental retardation, Friedreich's ataxia, myotonic dystrophy and others. In our yeast experimental system, we observed large-scale expansions of Friedreich's ataxia (GAA)_n repeats and established the genetic control of the expansion process. Besides expansions, we also detected repeat-dependent mutagenesis at a distance, as well as large chromosomal rearrangements originated from the repeat. Remarkably, the genetic control of all three processes appears to be similar. We are currently developing a selectable system to study repeat instability in cultured mammalian cells. Somewhat unexpectedly, we detect two simultaneous genetic events in the selected clones: a change in the repeat's length and a mutation in the body of our selectable marker. Combined our yeast and mammalian data, we hypothesize that both repeat length instability and mutagenesis at a distance could be the two sides of the same coin, which is an alteration in the replication fork as it passes through a long DNA repeat.

Sergei M. Mirkin

FRAGILE X SYNDROME – FROM BENCH TO BEDSIDE

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Fragile X syndrome (FXS) is the most common form of heritable X-linked mental retardation, with higher penetrance and expressivity in males compared to females. FXS manifests as a spectrum of characteristic physical and intellectual disability/limitations and emotional and behavioral features which range from severe to mild. FXS is a monogenic disorder, which is caused by a trinucleotide repeat expansion (>200 CGG repeats) in exon1 of the *fmr1* locus. The repeat expansion results in cis in hyper-methylation of CpG islands in the promoter and transcriptional silencing of *fmr1* and protein deficiency of FMRP in neurons. Fragile X is an interesting disease to study because: 1) of well defined genetics, the interplay between genetic alteration (trinucleotide repeat expansion) and epigenetic silencing and inheritance (DNA methylation, chromatin changes and nucleosome remodeling and silencing and 2) as a foray in understanding the molecular and cellular basis for synaptic plasticity. In *Fmr1* mutant mice, metabotropic glutamate receptor signaling-mediated LTD, a form of synaptic plasticity, is exaggerated, which may in part be due to mGluR5-mediated increase in protein synthesis. The symptoms of FXS may thus in part be due to exaggerated responses to activation of mGluR5, a mediator of communication between neurons in the brain. In my talk I will present our ongoing clinical trial activities on AFQ056, a specific and potent, allosteric mGluR5 antagonist, and I will discuss an alternative approach to reactivate *fmr1* expression utilizing iPS-derived neurons from Fragile X patients.

Tewis Bouwmeester

THE MANY FACETS OF RARE DISEASES – LESSONS FROM GENETIC DISORDERS OF BONE

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Genetic skeletal diseases (GSDs) may serve as a paradigm to illustrate many of these facets and promote a reflection on the way in which the medical system and society at large can effectively cope with rare diseases.

1. Practical aspects, sociopsychology, and stigmatization – Direct manifestations of Genetic Skeletal Diseases (GSDs) are short stature, deformity, fractures, physical inability and pain. The „visible“ changes to the gestalt can lead to stigmatization and social isolation of affected individuals, a social burden of disease that is added to the medical burden and sometimes even harder to bear.
2. Patients' organizations – Patient and families with GSDs have been among the first to unite in interest groups. These associations have had a pioneering role in promoting physician-patient partnership as well as the participation of patients in decision-making and prioritization of research goals.
3. The Nosology of individual disorders – Many of our patients have a genetic condition with no name and no diagnosis. How to deal with diagnostic uncertainty? And when does a condition become a recognized “disorder”? The delineation and characterization of diagnostic entities in the field of GSDs looks back to over 40 years.
4. The diagnostic process – A large number of patients with GSDs live with an incorrect diagnosis or no diagnosis at all. Experience with the European Skeletal Dysplasia Network (www.esdn.org) has shown that a web-based expert panel approach can be highly effective and successful in improving diagnostic efficiency.
5. Natural history and variability of individuals disorders – in most GSDs, medical decisions are based on personal experience, on individual case reports, and – in the best of cases – on literature reviews or on small case series. Efforts are needed to organize patient cohorts and learn more about the natural evolution of disorders, the type and frequency of complications and the benefits and harms of proposed interventions.
6. Basic research and diagnostics – At the diagnostic level, the ESDN model with centers of reference operating across national borders has worked well. If “next generation sequencing” and personal genome machines may facilitate molecular diagnostics significantly, it will be crucial to concentrate the databases on sequence variants and to assure a relevant interpretation of sequencing results.
7. The development of specific therapies – While it took over twenty years to develop the first lysosomal enzyme therapy, other therapies followed relatively quickly and the pipeline is promising. Enzyme replacement therapy for hypophosphatasia is proving effective. A small molecule therapy based on activation of the CNP-guanyl cyclase pathway in achondroplasia will be available for trials soon.

Andrea Superti-Furga

ADVANCES IN GENOMICS AND OTHERS OMICS: WHAT BENEFITS FOR PATIENTS?

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What are the benefits of progress in genetics for patients? The answer of the lay person will certainly be: "gene therapy and therapeutic cloning". Our contemporaries, fascinated by these futuristic prospects, tend to ignore the growth of currently available conventional treatments and the impact of symptomatic management on quality of life and life expectancy of patients with genetic diseases. This is due to a problem of oversimplification of information presented by the media, in which fashion is more important than function and the sensational more important than objective information. In this report, I have tried to establish honestly the inventory of what is already possible. In the light of several examples, let us "render under Caesar what is Caesar's" and try to establish whether replacement of a gene (the identification of which is essential for the understanding of a disease) is truly the universal panacea for the treatment of genetic diseases it is proposed to be. The first point to remember is that several genetic diseases were already treated long before the age of molecular genetics. We did not have to wait for cloning of the phenylalanine hydroxylase gene to treat phenylketonuria by a low protein diet. I would even go so far as to say that molecular genetics has had virtually no impact on the treatment of this disease. However, since the 1970s, more than 20 million French infants have been tested at birth for this disease (without knowing it) and 7000 of these, detected and treated early, have avoided mental retardation and are now healthy adults with children of their own. The same applies to many other inborn errors of metabolism, in which dietary avoidance of a toxic substrate (such as phytanic acid in Refsum disease¹) or a dietary supplement has transformed the child's expectancy and quality of life (high carbohydrate diet in glycogen storage diseases or medium chain triglycerides in fatty acid oxidation disorders²). Moreover, the dietary management of metabolic diseases is continuously improving, as illustrated by the example of protein glycosylation deficiency (CDG1b). In this case, understanding of the mechanism of the disease (impaired isomerisation of fructose into mannose) is synonymous with cure for the patient, as a dietary mannose supplement is life saving.³ The same applies to rare but not exceptional vitamin dependent forms of metabolic diseases such as biotin responsive carboxylase deficiency,⁴ pyridoxine responsive homocystinuria,⁵ cobalamin responsive organic acidurias,⁶ pseudo-Friedreich's ataxia responding to α -tocopherol⁷ and riboflavin, ⁸ or carnitine responsive lipid myopathies and cardiomyopathies.⁹ Not a year goes by without the elucidation of the mechanism of a metabolic disease resulting in a new therapeutic approach. A good example is the rare but spectacular forms of mitochondrial diseases curable by ubiquinone,¹⁰ and rare forms of mental retardation and autistic syndromes due to a deficiency of creatine synthesis and curable by oral creatine.¹¹ The real challenge at the present time is not to treat so many different diseases by a diet or the addition of cofactors, but rather to identify those affected children that can be treated, as their lives are going to be changed. We also need to remember that it was not our generation but that of our mentors which first treated hereditary kidney disease by kidney transplantation (Alport syndrome, nephronophthisis, and polycystic kidney disease), congenital biliary atresia by liver transplantation, heart malformations by heart transplantation, and immune deficiencies by bone marrow transplantation. Remember the daring innovations of the first orthopaedic surgeons and intensive care physicians who first operated on the spines of myopathic children. Remember the pioneers of visceral surgery, who treated Hirschsprung's disease, diaphragmatic hernias, and gastro-oesophageal malformations. However, our generation has also made considerable progress; for example, the fascinating results of elec-

trostimulation of the globus pallidum in torsion dystonia caused by mutation of the DYT1 gene,¹² and in Huntington's chorea and so many other dystonias. These neurosurgeons, not especially familiar with molecular genetics, have certainly done much more for these children than the whole community of geneticists combined. We must also remember that the pharmaceutical industry has transformed our knowledge into safe and effective pharmacological proteins and enzymes: insulin, growth hormone for the treatment of hereditary dwarfism, factor VIII for haemophilia, and enzyme therapy for lysosomal storage diseases (Gaucher, Hurler, Fabry and Pompe syndromes¹³). No one claims that gene and cell therapy will not, one day, have its place in the range of treatment options. However, for the patient and doctor faced with the reality of genetic disease today, these treatments are not available and we need to find other "tricks" to use until this breakthrough really takes place. Such tricks include inducing re expression of the foetal haemoglobin (HbF) gene by hydroxyurea, avoiding the need for transfusion of children with thalassaemia and sickle cell anaemia.¹⁴ Another consists of chelating a toxin by means of drugs, such as cysteamine for the treatment of cystinosis,¹⁵ or blocking a metabolic pathway that leads to accumulation of a toxic substance. For example, blocking the catabolism of tyrosine by NTBC transforms the severe tyrosinaemia type 1 into tyrosinaemia type 2, which is almost benign: 16 90% of affected children are cured. Even more recently, rapamycin has been shown to be potentially active in the treatment of Bourneville's tuberous sclerosis,¹⁷ as it replaces the inhibitory effect of tuberin and hamartin proteins in the mTOR pathway, activation of which is responsible for the disease; a promising clinical trial is underway. Another treatment was the somewhat incidental discovery that colchicine transforms (although we do not know why or how) the prognosis of familial Mediterranean fever.¹⁸ Yet another involves enhancing residual enzyme activity by a drug, such as fibrates in fatty acid oxidation disorders,¹⁹ or inhibiting a normal function if this function worsens the course of the disease. For example, by inhibiting osteoclastic activity, bisphosphonates limit bone resorption and reduce the consequences of collagen type 1 mutations in osteogenesis imperfecta; the mutation is still there, but multiple fractures and bone pain are considerably reduced.²⁰ Finally, it is possible to use a drug to protect a threatened function, such as short chain quinones (idebenone) that protect the iron sulphur centres of the respiratory chain against oxidative stress caused by the absence of frataxin in Friedreich's ataxia;²¹ cardiomyopathy is controlled by idebenone in 85% of these children. We clearly did not wait until genes and their mutations were identified before starting to treat genetic diseases. Our patients do not suffer from their mutations but from their functional consequences. So let us target the real enemy; accumulating evidence supports the view that understanding and properly addressing the mechanism of a genetic disease is tactically more useful to circumvent the problem than replacement of the mutant gene, which is technically very complex. Understanding the exact mechanism of disease is the information that we really need in order to devise the new treatments that will change our patients' lives. Although precise identification of mutations may appear to be useless for treatment, it could soon become vitally important for the development of tailor-made molecular therapy strategies, as shown by the correction of stop codon CFTR mutations by gentamycin in cystic fibrosis.²² Nevertheless, discoveries are not made on command and they take time. We must therefore avoid dogmatism and let ourselves dream, giving free rein to the wildest ideas and paying full attention to incidental observations, as they could prove to be very promising and lead to real breakthrough. The treatment of genetic diseases is much too serious to be the subject of passing fads, so let us not put all of our eggs in one basket.

Arnold Munnich

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ABSTRACTS

EFFECT OF TETRAHYDROBIOPTERIN AND PHARMACOLOGICAL CHAPERONES ON TYROSINE HYDROXYLASE: CORRECTION OF NEUROTRANSMITTER DEFICIENCIES

ABSTRACT N° A001_2012 / GENE AND CELL THERAPY; STEM CELLS

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Tyrosine hydroxylase (TH) is the rate-limiting enzyme in the synthesis of dopamine, noradrenaline and adrenaline. Primary inherited defects in TH have been associated with L-DOPA responsive dystonia (DRD) and infantile parkinsonism. We have shown that both, tetrahydrobiopterin (BH4) and a pharmacological chaperone (compound III; a small compound that rescues misfolded proteins), stabilize in vitro human TH as well as mutants associated to DRD [Calvo et al (2010) *J Neurochem* 114, 8531]. Supplementation of mice with either BH4 or compound III increases total TH activity and protein in mouse brain. This increase was not accompanied by changes of steady-state brain levels of dopamine and monoamine neurotransmitter metabolites DOPAC and HVA. The failure to observe an increase in dopamine, despite a higher total TH activity, might reflect the strict enzyme regulation in vivo. Nevertheless, we anticipated that increased TH activity will lead to increased dopamine synthesis in certain conditions, including pathological states. We have investigated this possibility using mice models of phenylketonuria (PKU) where synthesis of neurotransmitters is compromised due to high concentration of L-Phe in brain ([Phe] is 5-fold higher in ENU1/2 than in normal C57BL/6 mice). Supplementation with either BH4 (50 mg/kg/day) or compound III (8 mg/kg/day) for 10 days increases TH activity and protein in brain of ENU1/2 mice on normal diet, and we also found a trend towards elevated content of dopamine in mice treated with compound III. These treatments might be promising as therapy for disorders associated with TH misfolding and other deficiencies in dopaminergic neurotransmission.

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RESTORATION OF ANTI-ASPERGILLUS DEFENSE BY NETS IN HUMAN CGD AFTER GENE THERAPY IS CALPROTECTIN-DEPENDENT

ABSTRACT N° A002_2012 / GENE AND CELL THERAPY; STEM CELLS

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Introduction Infection by *Aspergillus* spp is a potentially lethal disease in patients with neutropenia or impaired neutrophil function. We showed previously that *Aspergillus nidulans* hyphae which are too large for neutrophil phagocytosis are growth inhibited by reactive oxygen species-dependent formation of neutrophil extracellular traps (NETs). NETs are composed of chromatin (DNA and histones) and intracellular antimicrobial substances, liberated by activated neutrophils for trapping of microbes and concentrated antimicrobial defense. This process is defective in a genetic phagocyte defect, chronic granulomatous disease (CGD) due to impaired phagocyte nicotinamide adenine dinucleotide phosphate (NADPH) oxidase function. The antifungal agent responsible for *A. nidulans* growth inhibition within NETs has not been characterized. **Methods** Antifungal activity of free and NET-released calprotectin (S100A8/A9) was assessed by incubation of *A. nidulans* with purified calprotectin, induced NETs from control and FACS (gp91phox) sorted CGD neutrophils after gene therapy (GT) in presence or absence of Zn²⁺ or -S100A9 antibody, and with induced NETs from wild type or S100A9^{-/-} mouse neutrophils. **Results** We identified the host zinc-chelator calprotectin as neutrophil-associated antifungal agent expressed within newly formed NETs after reconstitution of NADPH oxidase function by GT for human CGD. Calprotectin prevents *A. nidulans* growth reversibly at low concentration, and leads to irreversible fungal starvation at higher concentration. Reconstituted NET-formation was associated with rapid cure of pre-existing therapy refractory invasive pulmonary aspergillosis in vivo. **Conclusion** These results demonstrate the critical role of NET-associated calprotectin in human innate immune defense to combat invasive *Aspergillus* infection.

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STUDY OF THE ACVR1 GENE EXPRESSION AND REGULATION

ABSTRACT N° A003_2012 / GENE AND CELL THERAPY; STEM CELLS

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ACVR1 encodes a BMP type I receptor mutated in Fibrodysplasia Ossificans Progressiva, a rare and severe autosomal dominant form of heterotopic ossification. Elements such as the promoting region, transcriptional and post-transcriptional mechanisms regulating ACVR1 expression are still unknown and are the object of our studies. According to data available in GenBank, ACVR1 has two main transcripts differing for their 5'UTR end. Our bioinformatic analysis of the genomic region containing the gene reveals the presence of several ESTs, predicting the existence of multiple transcripts in which different 5'UTR exons are combined to a common coding sequence. The 3'UTR region is common to all transcripts and contains AU-rich elements and putative, well-conserved binding sites for miRNAs. Following the above prediction, we found transcripts with different exon composition at the 5'UTR and show their expression profile in different tissues. These data suggest complex regulation, with different transcription start sites (TSS) and promoter regions and possible elements controlling transcript stability or translation. Our work has allowed the identification of a TSS common to some of these alternative mRNAs and has allowed the identification and functional characterization of a promoter region upstream of it. ACVR1 transcript, assessed by quantitative PCR after treatment with inhibitors of transcription, appeared unstable. Functional analysis of the 3'UTR region of the ACVR1 gene by Luciferase reporter assays revealed a negative role in regulating its expression. As our *in silico* analysis suggested that several putative binding sites for miRNA were present in the ACVR1 3'UTR region, we selected three of those, mir148b, mir365 and mir26a, for our experimental work. Here, we show experiments that demonstrate negative regulation of ACVR1 expression by mir148b and mir365, as assessed by RT-qPCR on the endogenous mRNA and by transfection of Pre-miR miRNA precursor Molecules in combination with the ACVR1-3'UTR reporter construct. With the same experimental procedures we found that mir26a could upregulate ACVR1 expression, probably by interfering with the function of an ARE module adjacent to the mir26a binding site. Taken together, our results highlight the complexity of transcriptional and post transcriptional regulation of ACVR1 gene expression.

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AAV MEDIATED GENE THERAPY IN ANIMAL MODELS OF AUTOSOMAL DOMINANT AND X-LINKED RETINITIS PIGMENTOSA

ABSTRACT N° A005_2012 / GENE AND CELL THERAPY; STEM CELLS

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Background: Retinitis pigmentosa (RP) is a blinding disease affecting approximately 1 in 4000 people. We focused on developing gene based therapy for dominantly inherited and for X-linked retinitis pigmentosa. Mutations in 18 genes cause autosomal dominant retinitis pigmentosa (ADRP), though mutations RHO, the gene for rhodopsin, are responsible for about 30% of cases. While delivery of a wild-type copy gene is often sufficient for therapy of a recessive disease, treatment of dominantly inherited disorders may require silencing of the mutant allele in addition to gene augmentation. Methods: For the study of ADRP we used rat and mouse models containing mutant rhodopsin (RHO) transgene. For X-linked retinitis pigmentosa (XLRP), we employed two canine models with mutations in the RPGR-ORF15 gene, associated with the most common form of human XLRP. We used Adeno-associated virus (AAV) for gene delivery by subretinal injections. Electoretinography (ERG) and optical coherence tomography (OCT) were used to assess retinal function and structure in living animals, and microscopy was used to assess retinal preservation in fixed tissues. Results: We tested a combination of siRNA and resistant RHO cDNA in a mouse model of ADRP and observed significant protection of the retina for at least 9 months, as demonstrated by preservation of ERG response and of photoreceptor cells. In addition to this RNA replacement approach, we determined that suppression of the unfolded protein response (UPR) by gene delivery of the molecular chaperone Grp78 significantly retards retinal degeneration in a rat model of ADRP. In the canine models of X-linked retinitis pigmentosa (XLRP), AAV-delivery of human RPGR-ORF15 cDNA, preserved rod and cone photoreceptors in the region of the retina transduced by the virus. ERG amplitudes were increased in treated eyes compared to control eyes. Conclusions: There is currently no effective treatment for retinitis pigmentosa. The siRNAs and ribozymes we tested for ADRP also target human RHO, so that the RNA replacement vectors might be useful for human gene therapy. Since mutations in RPGR-ORF15 typically lead to early onset blindness, developing gene therapy for children with XLRP is compelling.

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DEVELOPMENT OF MINICIRCLE-DNA VECTORS AS NON-VIRAL LIVER-DIRECTED GENE THERAPY FOR HEPATIC DISEASES

ABSTRACT N° A006_2012 / GENE AND CELL THERAPY; STEM CELLS

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The liver is a potential target for transgene delivery and expression for gene therapy of hepatic and various metabolic diseases, including amino acid metabolism or urea cycle disorders. We have previously reported long-term correction of hyperphenylalaninemia in the PKU mouse model, C57Bl/6-Pahenu2, after liver-directed gene transfer with recombinant adeno-associated viral (AAV) vectors (Ding et al 2006, Ding et al 2008, Rebuffat et al 2010). However, questions of expression stability, treatment toxicity, potential for insertional mutagenesis, and safety required for targeting newborn and paediatric patients for potential life-long treatment remain a risk for virus-dependent approaches. Currently, we are developing and evaluating highly efficient non-viral gene transfer method by targeting the murine liver as a potential alternative gene-therapeutic approach. Here, we report the use of the minicircle (MC) technology for the gene therapy of PKU mouse model. Our MC-DNA vectors contain a liver-specific promoter, various mouse phenylalanine hydroxylase (mPah) transgene expression cassettes and bovine growth hormone polyA. Delivery was mediated by hydrodynamic tail vein (HTV) injection as a liver-targeted approach, and our data showed that vectors were exclusively delivered to the liver. Subsequently, blood phenylalanine (Phe) levels normalized in PKU treated mice injected with MC-DNA containing codon-optimized mPah in a dose dependent manner for several weeks compared to the mice injected with MC-DNA containing non-codon-optimized mPah (on-going experiment). Upon sacrificing the PKU treated mice, PAH enzyme activity was found to be elevated in liver. In Summary, MC gene delivery for maximizing safety and sustained gene expression is a potential new approach for PKU treatment.

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SELF-INACTIVATING LENTIVIRAL VECTORS FOR CORRECTION OF RAG1 SEVERE COMBINED IMMUNODEFICIENCY

ABSTRACT N° A007_2012 / GENE AND CELL THERAPY; STEM CELLS

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Severe combined immunodeficiency (SCID) patients with an inactivating mutation in recombination activation gene 1 (RAG1) lack B- and T lymphocytes due to the inability to rearrange immunoglobulin (Ig) and T-cell receptor (TCR) genes. Our purpose is to develop gene therapy for RAG1-SCID patients lacking a suitable bone marrow donor. As a preclinical model for RAG1-SCID, we used Rag1^{-/-} mice and lentiviral SIN vectors harboring different internal (promoter) elements, namely, EF1 alpha, short form (EFS), SFFV or enhancer-less ubiquitous chromatin opening element (UCOE), to deliver native or codon-optimized human RAG1 (coRAG1) sequences. Treatment with UCOE.coRAG1 and SFFV.coRAG1 resulted in the appearance of B- and T cells in peripheral blood and developing B- and T cells were detected in central lymphoid organs. Serum Ig levels and Ig and TCR V β gene-segment usage was comparable to wild-type controls, indicating that RAG-mediated rearrangement took place. Remarkably, relatively low frequencies of B cells produced wild-type levels of serum Ig in treated Rag1^{-/-} mice, whereas T-cell numbers often came close to WT levels. Upon stimulation of the TCR, corrected spleen cells proliferated and produced IL-2 and IFN γ . In vivo challenge with TNP-KLH resulted in production of TNP-specific antibodies, confirming correct cooperation of B and T cells. Toxicity related to ectopic RAG1 expression was not observed. Comparing the native and codon-optimized RAG1-vectors in vivo, the vector copy number (VCN) found in BM 19 weeks after transduction is 3 to 13-fold higher in animals that received cells transduced with the native RAG1 vector. In contrast, the RAG1 expression in these SFFV.RAG1-treated mice was 2.5-fold lower than the SFFV.coRAG1-treated mice. On a per-copy basis, this resulted in an 18-fold higher transgene expression. Evaluating transgene expression per vector copy in bone marrow, thymus and spleen cells, 20 weeks after transplantation, the UCOE.coRAG1 gave a 5 to 20-fold higher expression per integrated vector than SFFV.coRAG1. These properties allowed for correction of the Rag1^{-/-} phenotype, while limiting the VCN. In that respect, the use of the UCOE.coRAG1 SIN lentiviral vector is promising for clinical application. To conclude, fine-tuning the use of promoters or promoter-like elements in combination with the codon-optimization of the RAG1 coding sequence has brought us closer to clinical application of lentivirus-based gene therapy for RAG-SCID patients.

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PROGRESS TOWARD THE CLINICAL APPLICATION OF AUTOLOGOUS INDUCED PLURIPOTENT STEM CELLS AND GENE REPAIR THERAPY FOR TREATMENT OF FAMILIAL HYPERCHOLESTEROLEMIA

ABSTRACT N° A009_2012 / GENE AND CELL THERAPY; STEM CELLS

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Stem cell transplantation has been proposed as an attractive alternative approach to restore liver mass and function. Recent progress has been reported on the generation of induced pluripotent stem (iPS) cells from somatic cells. The production of autologous cell therapies would avoid immune rejection and enable correction of gene defects prior to cell transplantation. Here we show for the first time, reprogramming of diseased human hepatocytes-derived cells (Familial Hypercholesterolemia, FH) to pluripotency. Moreover, differentiation into mature hepatocytes is more efficient than with iPS cells derived from fibroblasts. These results will have implications for the treatment of human liver diseases, via auto-transplantation of genetically modified hepatocytes, avoiding LT and lifelong immunosuppression. FH hepatocytes were reprogrammed using a single lentiviral vector expressing the four transcription factors, Oct4, Klf4, Sox2, and cMyc, from a single multicistronic and excisable lentiviral vector. LDL uptake was restored by the transduction of a lentiviral vector encoding for the human LDL receptor. We established a differentiation protocol under well-defined culture conditions alternating between normal and hypoxic O₂ concentrations with a cocktail of hepatocytes-specific growth factors. Hepatocyte-derived iPS cells appear indistinguishable from hES cells with respect to colony morphology, growth properties, expression of pluripotency-associated transcription factors and surface markers, and in their differentiation potential in embryoid body formation and teratoma assays. These cells are able to directly differentiate into definitive endoderm, hepatic progenitors, and mature hepatocytes, and we were able to restore the missing metabolic function by transgenic methods. Karyotype analysis of these cells did not show any gross genomic differences between original and reprogrammed cells. Examination of the methylome showed that iPS cells exhibited a methylation pattern similar to the cells they were reprogrammed from. The protocol to develop disease affected hepatocyte-derived human iPS cell lines will provide a foundation for studying the safety, efficacy and clinical potential of differentially derived human iPS cells for cell therapy. For the study of liver disease pathogenesis, this technology also provides a potentially unlimited reservoir of cells generating genetically corrected liver-specific iPS cells.

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TISSUE ENGINEERING STRATEGY FOR THE REPAIR OF CONGENITAL DIAPHRAGMATIC HERNIA

ABSTRACT N° A014_2012 / GENE AND CELL THERAPY; STEM CELLS

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Congenital diaphragmatic hernia (CDH) is a severe congenital diaphragm malformation where abdominal content ascends into the thorax and compromises lung development in utero. By antenatal temporary positioning of a balloon in the fetal trachea respiratory failures are reduced resulting in improved survival of severely affected patients. However, their clinical outcome will rely on successful postnatal repair or reconstruction of the diaphragm. Today, large defects are treated by placing acellular biological prosthetic or synthetic materials which are either too fragile or unable to adapt in size and often need to be replaced. Amniocentesis-derived and thus ethically unproblematic mesenchymal amniocytes have been studied for the repair of diaphragmatic defects in an ovine model. The lacking vascular supply in the middle of the graft causing extensive cell death limits such an approach. Here, we present strategies to form mechanically preconditioned and vascularized tissue-engineered diaphragmic constructs from patients' own stem cells. Biomimetic materials, fibroblasts, muscle cells, endothelial cells, or amniotic fluid derived stem cells (AFCS) will be assembled by recently established layer-by-layer deposition. Such prevascularized constructs will be mechanically stretched and thus preconditioned on a cell culture adapted custom made biaxial loading device. We will present data on 3D-positioning of cells in growth factor presenting biomaterials, which is required for the assembly of initial vascular structures. In order to allow site specific stimulation of cells, growth factor immobilization strategies based on affinity interactions or covalent tethering will be shown. Additionally, initial data on the isolation, culture and phenotypic characterization of amniotic fluid cells as well as the design of our biaxial loading device are presented. Next, by rigorous phenotypic and functional characterization of individual AFCS, we will explore their potential to generate muscle, tendon or blood vessels. Well-defined subpopulations will be coaxed in engineered biomaterials and directed towards tendon, muscle, or vessel tissue. Mechanical preconditioning with cyclic loading regimen will be performed on muscle or tendon constructs. Finally, tissue-engineered diaphragms will be assembled and preconditioned to form tailor-made constructs that can be transplanted, are readily integrated and can bear up to 1MPa of load.

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LYSOGB3 AND S1P IN FABRY DISEASE IS THERE A COMMON STORY?

ABSTRACT N° B001_2012 / DIAGNOSTICS

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Cardiovascular Fabry disease patients manifest left ventricular hypertrophy and increased intima-media thickness. The left ventricular hypertrophy correlates with common carotid intima-media thickness. The major substrate of alpha-galactosidase A is globotriaosylceramide (Gb3), which accumulates within the tissues and organs of Fabry patients. Recently we have identified and proposed sphingosine-1 phosphate (S1P) as a growth promoting factor at the origin of cardiac and vascular abnormalities in this disease. In order to provide evidence for possible relation between S1P and Gb3, we have performed cellular immuno-labeling of both S1P and Gb3 in Fabry patient and control healthy subject fibroblasts. The labeling intensities showed that both S1P and Gb3 were elevated in Fabry fibroblasts. When the labeling intensities were normalized to cell surface area, only Gb3 preserves high level labeling in Fabry patient fibroblasts. This indicates a different cellular dynamic release behavior between Gb3 and S1P. Moreover, globosphingosine (LysoGb3) was proposed as a factor involved in cardiovascular hypertrophy, which similarly to S1P induced vascular smooth muscle cells (VSMC) proliferation. Based on the common structural features between S1P and LysoGb3, we hypothesized that S1P is generated from LysoGb3 that subsequently induces VSMC proliferation. Gb3 has no effect on VSMC proliferation in contrast LysoGb3 and S1P induced VSMC proliferation with optimum at 500 nanoM and 1 microM concentrations. When using S1P1 receptor antagonist W146 at 10 microM the induced VSMC proliferation was inhibited in both cases. Our data highly suggest that S1P comparatively to Gb3 is rapidly released to extracellular milieu, Gb3 somehow generates LysoGb3 which in turn generates S1P that induces VSMC proliferation.

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EUROPEAN REGISTRY AND NETWORK FOR INTOXICATION TYPE METABOLIC DISEASES (E-IMD)

ABSTRACT N° B002_2012 / DIAGNOSTICS

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Background: Patients with organic acidurias (OADs) and urea cycle defects (UCDs) have an enormous need for improved medical awareness, optimization of the diagnostic process and therapy, and improved networking between healthcare professionals and patients. Methods: An initiative called the “European registry and network for Intoxication type Metabolic Diseases (E-IMD)” funded by the European Commission through DG Sanco started in January 2011. E-IMD aims to promote health for patients with OADs and UCDs. Results: E-IMD already has 49 partners from 20 countries linking healthcare professionals, patient representatives, industry and government authorities within Europe, Canada, the US, and Australia. E-IMD will continue to expand its network by inviting new members. The registry (<https://www.eimd-registry>) was launched in August 2011. Since then more than 130 patients have been registered. It is expected to collect data on at least 600 individuals with an OAD or UCD over the next 3 years. A website (www.e-imd.org) providing information brochures for patients, their families, and healthcare professionals in their own language was launched in August 2011. Evidence-based diagnostic and management protocols which are developed by the E-IMD consortium will also be disseminated via this website. Conclusion: The new network will improve access to rapid diagnosis and care for patients, will improve the knowledge base of OADs and UCDs, and will empower patients and patient organisations by providing a network and better access to expert advice and knowledge.

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MUTATIONAL SPECTRUM OF SMITH-LEMLI-OPITZ SYNDROME PATIENTS IN HUNGARY

ABSTRACT N° B003_2012 / DIAGNOSTICS

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Introduction. Smith-Lemli-Opitz (SLO) syndrome is a severe monogenic autosomal recessive syndrome associated with mental retardation and multiple congenital anomalies. SLO is caused by mutations in the 7-sterol reductase (DHCR7) gene. DHCR7 mutations are usually small-scale and show a large inter-ethnic variability. Our goal was to set up a diagnostic scheme that includes both biochemical and molecular genetic methodology to diagnose SLO and to detect mutations responsible for SLO in Hungarian patients. **Patients and methods.** Eleven Hungarian patients were analyzed. 7-dehydrocholesterol (7-DHC) and cholesterol levels in the serum were measured using an UV spectrophotometry method and using an enzymatic colorimetric method, respectively. For mutation detection, the entire coding region of DHCR7 gene was amplified and sequenced, and in one case the promoter, the non-coding exons and 3' regions were also analyzed. **Results.** All patients had elevated 7-DHC level (reference range <0.15 mg/L), ranging from 71.4 to 300.0 mg/L. Cholesterol levels were generally low (between 0.3 and 2.7 mmol/L). The cholesterol/7DHC ratio was abnormal in all cases. Altogether, 10 different mutations were found, one splicing, one nonsense and 8 missense mutations. The detected alterations are known to be causative, except the previously unidentified c.374A>G (p.Y125C) which was inherited in trans with a known mutation. c.374A>G (p.Y125C) mutation is located in a phylogenetically conservative position. The closest known pathogenic mutations affect amino acid positions 119 and 138. Nine patients were compound heterozygous for two causative mutations, while one patient was homozygous for a null allele. In one patient, only one of the causative mutations could be identified. **Conclusions.** Using biochemical and molecular genetic methods, the molecular background of ten Hungarian SLO patients could be established. Identification of mutations on 21 of 22 DHCR7 mutant alleles was successful. In addition to the known missense, nonsense and splicing mutations, a novel, most likely pathogenic mutation was identified.

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SANGER SEQUENCING AND MLPA APPLIED TO ORPHAN-DISEASE-ASSOCIATED GENES

ABSTRACT N° B005_2012 / DIAGNOSTICS

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Introduction: Meaningful diagnosis of orphan diseases requires knowledge of the underlying molecular lesion. This will not only support the clinical diagnosis (and thus the treatment), but also help parents in taking decisions regarding future off-spring. In the current study, we retrospectively evaluated the results of our genes-on-demand Sanger sequencing and MLPA service for orphan disease genes. **Methods:** Primers amplifying the exons and the adjacent intronic sequences of each gene were designed with ExonPrimer and Primer 3 and checked for specificity and polymorphisms with SNPCheck. PCR conditions were established with wildtype DNA and then applied to patient DNA, followed by Sanger sequencing. Sequences were analyzed with SeqScape or SeqPatient, and positive results were confirmed by an independent PCR. In case a gene-specific probe-kit was available, MLPA was performed, with identified deletions being confirmed by GAP-PCR. The current survey is based on written reports of these screenings; it does not include thalassemia and BRCA1 / BRCA2 screenings as well as mutation-specific analyses. **Results:** Over the last 2 years, we analyzed 43 different genes in 59 patients. In 6 of these 59 patients, more than one gene was analyzed (e.g. COL1A1 and COL1A2). The most commonly requested analysis was screening of MECP2 (associated with RETT syndrome, 7 cases), followed by CFTR (cystic fibrosis, 4 cases), and MEFV (familial mediterranean fever, 4 cases). 23 analyses had been requested only once by December 2011. In 19 patients, disease-causing mutations could be identified, giving an overall mutation detection rate of 32%. Of the 26 mutations identified, 15 (58%) were missense mutations, 8 (31%) nonsense, and 2 (8%) splice mutations. The only deletion identified was detected by PCR failure of the X-chromosomal XK gene, while no deletion was detected by MLPA. **Discussion:** We identified disease-causing mutations in a substantial number of patients, demonstrating that Sanger sequencing can be highly supportive in the diagnosis of orphan diseases.

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STRUCTURAL ANALYSIS OF SACCHARIDE-LIPID DEPOSITS USING CHROMATOGRAPHIC METHODS IN CELL LINES FROM PATIENTS WITH MUCOPOLYSACCHARIDOSES

ABSTRACT N° B006_2012 / DIAGNOSTICS

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Mucopolysaccharidoses (MPSs) are rare hereditary metabolic diseases belonging to the group of lysosomal storage diseases. They are caused by a defect in a specific enzyme involved in degradation of glycosaminoglycans (GAGs). Deficiency or lack of enzyme activity leads to accumulation within the lysosomes of compounds that are substrates for this enzyme, and consequently to a gradual damage of cells, tissues and organs. Research in improving the life of patients suffering from MPS is ongoing on various therapeutic approaches. Therefore, it is important to implement an appropriate method to control the changes in the level of individual GAGs, as well as to monitor the effectiveness of the therapy, for both patients and basic knowledge, as most research on treatment begins with *in vitro* studies on cell cultures. Determination of the individual glycosaminoglycans and monitoring of their level in cells exposed to GAG synthesis reducers or their degradation factors using high pressure liquid chromatography (HPLC) is the topic of our work. Such analysis has an application in evaluating the effects of experimentally induced changes in expression levels of biosynthetic enzymes or other specific regulatory factors. A simple procedure, requiring only standard HPLC instrumentation, involving isolation, purification and precipitation of GAGs, followed by a separation by reverse-phase HPLC that is sensitive to as little as ~100pg of an individual disaccharide, thereby allowing analyses of >10 ng of total glycosaminoglycan is handled. As for GAG isolation methods protocol optimization was carried out by using papain and proteinase K treatment of fibroblasts for GAG purification on SPE columns with DEAE Sepharose bed, followed by their precipitation on PD-10 column was taken to provide total GAG preparation for disaccharide analysis with HPLC. Disaccharide analysis of particular sulphated glycosaminoglycans, instead of their entire content in the sample, is a qualitative approach to quantify individual GAGs in MPS and HDFa fibroblasts in contrast to untreated cultures. So far, as a result of the experiments we determined the suitability of the application of HPLC to monitor the effectiveness of therapeutic agents used in *in vitro* studies.

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DORA (DOENÇAS RARAS) PROJECT: A PROPOSAL FOR AN INTEGRATED MANAGEMENT OF RARE DISEASES IN THE STATE OF SAO PAULO, BRAZIL

ABSTRACT Nº B007_2012 / DIAGNOSTICS

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The State of Sao Paulo (Brazil) has a population of 41 million inhabitants with 600,000 live births/year. It has been experiencing significant advances in the control of diseases related to malnutrition-infection binomial but the infant mortality rates are still high (11.9 / 1,000 live births in 2010), 21% of these deaths being due to congenital malformations and rare diseases, which now emerge as major focus of attention within the context of the State's public health system. The purpose of the present communication is to introduce the DORA project, a joint effort between the Children's Hospital (University of Sao Paulo Medical School) and the Sao Paulo Secretary of State for Health in order to organize early diagnosis and integrated care of congenital malformations and rare diseases in the State of Sao Paulo. The following actions are currently under way: 1. Creation of a network of the university hospitals and outpatient clinics for early diagnosis and protocol based treatment 2. Establishment of a "warning signs" list and protocol based clinical management (as a basis for future cohort studies) for 1-2 diseases in each one of the following areas of interest: metabolic diseases, neuromuscular diseases, growth and sexual differentiation diseases, primary immunodeficiency, kidney and urinary tract disorders, ophthalmology, orthopedics, pulmonology, HEENT, hematology, chromosomal anomalies and complex malformations and cardiac malformations. 3. Creation of an integrated computer system with the following interfaces: A. non health professional homepage with an A-Z list of topics on rare diseases, a list of available services for diagnosis and follow up, a list of patient advocacy organizations B. a homepage for health professionals with an A-Z list of topics on rare diseases, a list of available services for diagnosis and patient follow up; links to educational videos presenting the warning signs for each group of clinical conditions , a link to consult with a specialist before referring a difficult case and a link for the University hospitals network participants to be used for cohort studies data management. It is our estimate that DORA project will be launched in the second semester of 2012 after completion of the integrated computer system which will enable dissemination of concepts of the warning signs for primary care doctors and cohort related data management by the network participants.

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CONSANGUINITY AS A MEANS TO IDENTIFY PATHOGENIC RECESSIVE MUTATIONS

ABSTRACT N° B008_2012 / DIAGNOSTICS

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Statement of purpose: To define a strategy for the identification of pathogenic variants in patients of consanguineous families. Methods and experimental strategy: We have initiated a project to collect samples from families with seemingly recessive phenotypes in consanguineous families. Any phenotype and family history compatible with autosomal recessive disorder is a candidate for participation in the study, which has been approved by the local ethics committee and all participants or their legal representatives have signed an appropriate consent form. 42 families of different ethnic background (mainly from countries where consanguineous marriages are common) are already participating in the study. From each family, DNA from the patient(s), all their unaffected siblings, and the parents is extracted from blood samples. First samples from one or more of the affected individuals per family are examined by aCGH 244K chips for the identification of homozygous deletions and/or pathogenic heterozygote deletions/insertions. Then the samples of all the family members are genotyped with a dense SNP array (720K) in order to identify the Runs of Homozygosity (ROH), allowing the definition of chromosomal regions likely to contain the responsible genes and finally exome sequencing (96% of CCDS, Consensus Coding Sequences) is performed in one of the affected individuals. Variants are called genome wide and filtered according to polymorphic SNVs deposited in public databases; variants' pathogenicity is also scored using several publicly available software. A step-wise approach has been selected in order to diminish the total number of probable variants. ROH found only in the patients and no other family member are screened first, followed by different comparisons of ROH between the affected individuals and the other family members. 12 families have been screened using this approach so far. Preliminary Results: This approach has allowed the identification of the molecular defects in some families. For example, causative variations of known genes have been identified two families (in the VLDLDR gene, causing disequilibrium syndrome, and the FKTN gene causing Fukuyama muscular dystrophy). In other families, variations in unknown candidate genes are being investigated. Consanguineous families provide an opportunity to identify genes responsible for recessive phenotypes and rapidly fill in the space of genotype phenotype links.

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TARGETED NEXT GENERATION SEQUENCING FOR CLINICAL DIAGNOSTICS OF PATIENTS WITH MYELOPROLIFERATIVE NEOPLASMS

ABSTRACT N° B009_2012 / DIAGNOSTICS

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Statement of purpose Myeloproliferative neoplasms (MPNs) are a group of diseases characterized by aberrant proliferation of the myeloid, erythroid and/or megakaryocytic lineages. A number of gene mutations have been described that can initiate or advance MPN when acquired as a somatic event in hematopoietic stem cells (e.g. mutations in the genes JAK2, MPL, or TET2). However, as the list of mutations grows larger there is a need for improved diagnostic methods in order to genotype a patient for diagnostic, prognostic and treatment purposes. Here we describe a clinically applicable method for mutation screening using multiplexed enrichment of desired genes followed by next generation sequencing (NGS). Methods DNA from 48 MPN patients was individually fragmented and barcoded using indexed adapters. The DNAs were pooled and enriched using an Agilent SureSelect custom design. The custom design covers all genes where mutations have been reported in MPN, as well as 100 additional genes involved in hematopoietic signaling. After enrichment, samples were sequenced using Illumina HiSeq2000. All patients were analyzed in duplicates using separate PCR reactions and enrichments to reduce false positive results. Results The average read coverage of the regions of interest was 474x and 411x for the duplicate runs of the first 48 patients, respectively. The amount of exons covered by >20 reads was 95.9% and 95.6% and >100 reads 90.5% and 89.5%, respectively. Previously observed mutations in these 48 patients were used to validate the mutations generated by NGS of which 33/34 JAK2-V617F mutations, 3/3 JAK2 exon 12 deletions and 4/4 TET2 alterations were detected. The JAK2-V617F mutation not detected using NGS could only be found in one of the two duplicate reads, however this mutation was present in <1% of the cells as determined using allele specific PCR. In addition, 1 novel JAK2 mutation, 12 additional mutations in TET2 (9 missense and 3 nonsense), 6 DNMT3A (3 R882H, 2 other missense and 1 nonsense) and 2 IDH1 (R132H) mutations were discovered. Also, 90 mutations in genes with no previous reported involvement in MPN were found. Analysis of the somatic nature of these mutations is currently underway. Conclusion Multiplexed enrichment and NGS was found to be a cost efficient and reliable tool for a cohort based screening of MPN patients. The method can be applied to any disorder where multiple genes are to be screened for diagnostic purposes with high sensitivity.

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FBN1, TGFBR1, TGFBR2, AND SLC2A10 MUTATION ANALYSES IN PATIENTS WITH SUSPECTED MARFAN SYNDROME: A SWISS STUDY

ABSTRACT N° B010_2012 / DIAGNOSTICS

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Marfan syndrome (MFS) is caused by FBN1 mutations in the majority of cases. Many of the features of MFS show overlap with related aortic disorders, such as Loeys-Dietz syndrome (LDS), familial thoracic aortic aneurysms and dissections (TAAD), and arterial tortuosity syndrome (ATS). In patients with suspected MFS, FBN1 genetic testing detects only ~80% of mutations. This may be due to technical limitations of currently used PCR-based screening methods and/or because the disease-causing mutation occurs in a different gene. We have investigated the impact of these possibilities. In a cohort of unrelated individuals with suspected MFS in whom previous analysis of FBN1 revealed no mutation, we have sequenced the genes TGFBR1, TGFBR2, and SLC2A10. We have also screened for large deletions/duplications by multiplex ligation-dependent probe amplification (MLPA). The pathogenic impact of novel sequence variants was assessed by *in silico* predictions and/or RT-PCR, and segregation analyses. The breakpoints of large deletions identified by MLPA were narrowed down by using microarrays. In patients with suspected MFS who finally could be diagnosed with LDS and TAAD, we identified heterozygous TGFBR1 or TGFBR2 nucleotide substitutions and in one ATS patient a homozygous SLC2A10 nonsense mutation. The deleterious alleles occurred *de novo* or segregated with the disease in the families, indicating a causative association between the sequence variants and clinical phenotypes. Neither a TGFBR1- nor a TGFBR2-specific phenotype could be detected. In two patients, MLPA revealed large genomic rearrangements affecting FBN1. Our data demonstrate that TGFBR1 mutations are associated not only with LDS but also with TAAD, and that true FBN1 haploinsufficiency is sufficient to cause MFS.

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EVALUATION OF EXOME SEQUENCING WITH DIFFERENT TYPES OF SEQUENCE VARIATIONS IN GENES ASSOCIATED WITH AORTIC DISEASES

ABSTRACT N° B011_2012 / DIAGNOSTICS

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Whole-exome sequencing is a combination of ultra-high-throughput next-generation sequencing and the state-of-the-art enrichment of all known human protein-coding exons and flanking canonical splice sites. In addition to qualitative analyses, which can detect point mutations and small insertions/deletions, whole-exome sequencing data can also be used for quantitative sequence analysis in order to detect large insertions and deletions (copy number variations). In this study, we have evaluated the qualitative and quantitative properties (i.e. mutation detection rate) of exome sequencing for different mutation types and genes. These genes are associated with syndromic forms of rare aortic diseases, such as Marfan syndrome (FBN1), Loeys-Dietz syndrome (TGFBR1 and TGFBR2), and Ehlers-Danlos syndrome vascular type (COL3A1) or with non-syndromic forms such as familial thoracic aortic aneurysms (ACTA2, MYH11, and MYLK). For this evaluation, DNA samples with known point mutations and small deletions/duplications detected by Sanger sequencing as well as large deletions/duplications detected by MLPA were used as template in exome sequencing. In a first step, we applied Agilent's in solution sequence capturing of all coding exons and flanking intronic sequences and performed next generation sequencing using a SOLiD4 platform. Exome sequencing data visualised by the Integrative Genomics Viewer (IGV) revealed that the mutation detection rate of the used exome sequencing method was lower than that of Sanger sequencing and MLPA, varying between mutation types and genes. Whereas point mutations were successfully detected in enriched exons with sufficient read-coverage depth, the used exome sequencing protocol needs to be improved for the detection of small deletions and duplications/insertions as well as for the more balanced capturing (enrichment) of exons.

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HEMIZYGOUS DELETION LEADING TO TRUE HAPLOINSUFFICIENCY OF COL3A1 CAUSES AORTIC DISSECTION

ABSTRACT N° B012_2012 / DIAGNOSTICS

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Aortic dilatation/dissection (AD) can occur spontaneously, non-syndromic or in association with genetic syndromes, such as Marfan syndrome (MFS) caused by FBN1 mutations, Loey-Dietz syndrome caused by TGFBR1 or TGFBR2 mutations, and vascular Ehlers-Danlos syndrome (EDS IV) caused by COL3A1 mutations. Although mutations in FBN1, TGFBR1, and TGFBR2 account for the majority of AD cases referred to us, we have encountered negative genetic testing results in a large group of patients, suggesting the involvement of other genes, e.g. COL3A1, ACTA2 or MYH11. In this study, we have assessed the impact of COL3A1 mutations in patients with suspected MFS in whom mutation screening in FBN1, TGFBR1 and TGFBR2 revealed no disease-causing sequence variation. MLPA analysis of 100 unrelated patients identified hemizygous deletion of the entire COL3A1 gene in one patient with abdominal AD. Subsequent microarray analyses and sequencing of breakpoints revealed the deletion size of 3,408,306bp. Furthermore, gDNA sequencing revealed COL3A1 sequence variants in some of our patients. Our data not only emphasize the importance of screening for COL3A1 mutations in comprehensive genetic testing of AD patients with suspected MFS not fulfilling the Ghent criteria, but also extend the molecular etiology of EDS IV by providing evidence for true haploinsufficiency of COL3A1.

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BONE MARROW ALTERATION IN PATIENTS WITH TYPE 1 GAUCHER DISEASE ON ENZYME REPLACEMENT THERAPY

ABSTRACT N° B013_2012 / DIAGNOSTICS

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Purpose: To analyze changes in the bone marrow in patients with Type 1 Gaucher disease and correlate the results with genotype and laboratory findings. **Materials and Methods:** MRI of the lower extremities performed between 1996 and 2009 to evaluate the effect of enzyme replacement therapy (ERT) on bone marrow infiltration by Gaucher disease were reviewed. Signal changes were recorded before initiating ERT and followed annually or bi-annually. The marrow changes were classified as: decreased, scattered or confluent, signal on T1 weighted imaging (WI); increased or unchanged on STIR imaging. The extent of the marrow involvement was also evaluated. The patient's genotype was recorded. The changes were correlated with laboratory findings. **Results:** 221 patients' MRIs were examined. 52 patients on ERT showed improvement in the marrow infiltration over the study period. These patients have a variety of genotypes but the majority, 30/52 (58%), have the milder N370S/N370S genotype. In general, bone marrow improvement is a slow process that does not manifest immediately with ERT but occurs over the course of several years. **Conclusion:** Bone marrow infiltration in patients with Type 1 Gaucher disease does respond to ERT but generally takes many years to manifest on MRI. Although those that responded were of several different genotypes, the majority had the more benign N370S/N370S. Surveillance MRI is essential for clinical decision making concerning ERT and dosing.

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PREVALENCE OF GALLSTONES IN PATIENTS WITH TYPE I GAUCHER DISEASE

ABSTRACT N° B014_2012 / DIAGNOSTICS

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Purpose: To compare the prevalence of gallstones in patients with Type I Gaucher disease with that of the general population. **Material and Methods:** The Comprehensive Gaucher Disease Treatment Center at our institution follows approximately 300 patients with Type I Gaucher Disease. Each patient is followed with abdominal MRI or CT scans to evaluate visceral manifestations of Gaucher disease. These imaging studies from 1994 to present were reviewed to determine if each patient had gallstones or had undergone cholecystectomy. The patient's sex and age at the time of the first imaging study that demonstrated gallstones or gallbladder surgery were recorded. Comparison was made to the generally accepted 10% prevalence of gallstones in the general population. **Results:** 271 patients had studies to evaluate; 131 males and 140 females, age range 7 to 96 years. 54 patients had gallstones or cholecystectomy yielding a prevalence of 20% (54/271). 40 patients (19 male, 21 female) had gallstones. Of these patients 15 (5.5%) also had undergone splenectomy. 14 patients (5 male, 9 female) had undergone cholecystectomy. Of these patients 7 (2.6%) also had undergone splenectomy. The age group most affected in males was 61-70 years followed by 51-60 years; in females the most common age group was 51-60 years followed by 31-40 years. **Conclusion:** The prevalence of gallstones in Type I Gaucher patients is significantly higher than that of the general population. Females are more commonly affected than males and appear to manifest signs or symptoms at a younger age. The high prevalence of gallstones is likely due to the abnormal biliary lipid secretion that can be a manifestation of Gaucher disease. **Clinical Relevance:** Gallstone disease has increased prevalence in Type 1 Gaucher Disease patients but splenectomy does not appear to be a significant risk factor.

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MOLECULAR ANALYSIS OF POLISH PATIENTS WITH EPIDERMOLYSIS BULLOSA SIMPLEX

ABSTRACT N° B015_2012 / DIAGNOSTICS

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Epidermolysis bullosa (EB) is a group of genodermatoses characterized by spontaneous or mechanically induced blisters formation. Depending of the level of epidermis-dermis separation during bullae formation, four EB types can be distinguished: simplex (SEB), junctional (JEB), dystrophic (DEB) and Kindler syndrome (KS). Clinical symptoms varies between those types and about 30 subtypes have been described in EB. SEB is recognized when blisters form in basal or suprabasal layers of epidermis. There are about 12 subtypes in SEB, of which three the commonest: localized SEB (previously known as Weber-Cockayne), Dowling-Meara SEB and other generalized SEB (Koebner previously) are autosomal dominant and caused by mutations in KRT5 and KRT14 genes. However, mutations in KRT14 are also found in rare autosomal recessive SEB subtype and KRT5 in some other sporadic variants. The aim of the study was to investigate the spectrum of mutations in Polish simplex epidermolysis bullosa patients. The 34 probands (10 - localized SEB; 2 - Dowling-Meara SEB; 5 - other generalized SEB, 17 - undefined) diagnosed on the basis of clinical symptoms or immunofluorescence mapping were enrolled to the study. DNA was isolated from leukocytes and analyzed by direct sequencing of coding regions of KRT5 and KRT14. In this group of patients, we found 9 distinct variants in KRT5 and 7 in KRT14, including overall 7 changes unreported before. In 17/34 (50%) cases full genotype was established; in 5 cases mutations in KRT5 and KRT14 genes haven't been identified. In case of remaining 12 patients molecular analysis has not been completed yet. Mutations p.Val186Met and p.Glu170Lys in KRT5 were found in at least two distinct families each. In one patient with mild SEB and her affected brother, two variants in KRT5 gene: p.Val143Ala and p.Glu170Lys were identified. Both parents of these patients are carriers and seemed to be unaffected. According to our knowledge only few patients with compound heterozygosity in KRT5 gene have been reported previously. In conclusion, our preliminary results broaden the knowledge about pathogenesis and epidemiology of SEB and also have practical impact on preparing the polish population-specific molecular diagnostics scheme.

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THE RATIO OF URINARY PYRIDINOLINE TO DEOXYPYRIDINOLINE CROSSLINKS – A PROMISING DIAGNOSTIC TOOL IN OSTEOGENESIS IMPERFECTA

ABSTRACT N° B017_2012 / DIAGNOSTICS

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Urinary pyridinoline crosslinks, hydroxylslyl-pyridinoline (HP, or pyridinoline PYD) and lysyl-pyridinoline (LP, or deoxypyridinoline DPD) are well characterized markers for bone resorption and collagen degradation, and proven diagnostic tools for genetic disorders of collagen metabolism such as EDS VIA, SCD-EDS and Bruck syndrome. Osteogenesis imperfecta (OI) is a heterogeneous genetic disorder characterized by increased susceptibility to fractures. The majority of OI is inherited as an autosomal dominant trait caused by mutations in COL1A1 and COL1A2. A small proportion of OI is inherited in an autosomal-recessive manner due to mutations in eight different genes encoding proteins of the prolyl 3-hydroxylation complex (CRTAP, LEPRE1, PPIB); collagen chaperones (SERPINH1, FKBP10); a proteinase (BMP1/mTLD) involved in processing of the procollagen I C-terminal propeptide; a transcription factor (SP7/OSX) assumed to regulate the differentiation of preosteoblasts to osteoblasts; and SERPINF1, a secreted glycoprotein of the serpin superfamily. The aim of this study was to evaluate the ratio of total urinary pyridinolines LP/HP (or: DPD/PYD) as a non-invasive, reliable and cost effective screening tool in individual OI patients, prior to collagen biochemical and/or molecular genetic analyses. We analyzed spot urines of controls and OI patients of known genetic background, with defects in LEPRE1, CRTAP, SP7/OSX and SERPINF1, as well as heterozygous carriers and 20 patients with dominant mutations in COL1A1 or COL1A2. Compared to controls (0.20 ± 0.03 , $n=325$), we found markedly decreased LP/HP ratios in OI caused by mutations in LEPRE1 (mean: 0.078, $n=3$), CRTAP (mean: 0.105, $n=3$) and SP7/OSX (0.086), and slightly decreased LP/HP ratios in heterozygous carriers for mutations in CRTAP (mean: 0.172, $n=2$) and SP7/OSX (mean: 0.128, $n=2$). We found normal LP/HP ratios for mutations in COL1A1/COL1A2 (mean: 0.20; $n=20$), and SERPINF1 (mean: 0.195, $n=2$), and in the heterozygous carriers for a LEPRE1 defect (mean: 0.2, $n=2$). Thus, LP/HP ratios have the potential to detect recessive forms of OI caused by mutations in the genes LEPRE1, CRTAP and SP7/OSX, thereby improving the diagnostic efficacy and reducing the costs of molecular genetic investigations. Similarly, we expect decreased LP/HP ratios in OI cases caused by mutations in PPIB. With this report, we hope to attract more cases of OI with a known genetic defect in order to statistically validate this preliminary study.

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ORAL L-SERINE SUPPLEMENTATION AS A THERAPY IN HEREDITARY SENSORY AUTONOMIC NEUROPATHY TYPE 1 (HSAN1)

ABSTRACT N° C001_2012 / THERAPEUTIC APPLICATIONS

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Background: Sphingolipids are commonly formed from the precursors L-serine and palmitoyl-CoA - a reaction which is catalyzed by the serine-palmitoyltransferase (SPT). Several SPT missense mutations are associated with the inherited sensory neuropathy HSAN1 – a rare axonal neuropathy which typically presents with decreased pain and temperature sensation accompanied with painless blisters and ulcers. Results: SPT is not strictly depending on serine but metabolizes also alanine and glycine to a certain extent. This results in the formation of 1-deoxy-sphingolipids (dSL) which lack the C1 hydroxyl group of normal sphingolipids. They are therefore not converted into complex sphingolipids nor degraded by the normal catabolic pathway. This promiscuous activity is greatly increased in HSAN1. Significantly elevated dSL levels were found in plasma from HSAN1 patients but also in plasma and PNS tissue of transgenic HSAN1 mice. Deoxy-sphingolipids were shown to be neurotoxic and to induce neurite retraction in cultured primary neurons. Interestingly, dSL formation is suppressed at elevated L-serine levels. HSAN1 mice which received an L-serine enriched diet showed significantly reduced plasma dSL levels. On long term supplementation the mice were protected and did not develop neurological symptoms. In contrast, alanine fed mice developed severe neurological deficits already at the early age of three months. The positive effects of an L-serine supplementation were further corroborated in a human pilot study with 14 HSAN1 patients. The patients received an oral serine treatment (200 or 400mg/kg/day) for 10 weeks. Within 6 weeks dSL levels decreased to normal values in both groups and increased again after the end of the trial. Despite the short duration of this study some patients reported an increase in sensation (hand tingling, increased menstrual cramps) and significant improvements in skin robustness and body hair growth. Conclusions: Our results showed that an elevated dSL generation is the pathological cause for HSAN1. An oral supplementation with the amino acid L-serine suppressed dSL formation and might therefore be a potential therapy in HSAN1. Initial results of a short term intervention study were positive and are currently re-evaluated in a more comprehensive clinical trial. If successful this would be the first available therapy in HSAN1 but also the first rational treatment option for an inherited peripheral neuropathy in general.

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FROM RATIONING TO RATIONALITY: AN N-OF-ONE TRIAL SERVICE FOR OFF-LABEL MEDICINES FOR RARE DISEASES

ABSTRACT N° C002_2012 / THERAPEUTIC APPLICATIONS

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Background In the Netherlands, some medicines are not reimbursed for off-label use without sufficient evidence of efficacy. Patients with rare (including genetic) diseases are disadvantaged because the burden of proof is difficult to meet. There are obstacles both for industry and academia to performing large-scale randomized, controlled trials for rare diseases. Reimbursement rules also discourage doctors from prescribing medicines off-label, even to small groups of patients. Controlled n-of-one (single-patient) trials with internal randomisation (e.g. AB-BA-BA) could generate evidence on efficacy for rare, chronic conditions where the aim of treatment is symptom control. **Objective** This project aims to initiate development of an n-of-one trial service, embedded in the Dutch health care system, for research on efficacy and safety of certain medicines with no marketing authorisation for the rare diseases for which they are prescribed. **Methods and preliminary results** Reimbursement problems with off-label medicines for rare neuromuscular diseases were inventoried among neuromuscular specialists and patients with neuromuscular disease in the Netherlands. A multidisciplinary expert meeting was organized to define legal, ethical and scientific preconditions for formalizing and sustaining an n-of-one trial service. The problem was widely acknowledged by stakeholders. Willingness was expressed to consider new forms of evidence for efficacy and safety of medicines for rare diseases and personalized therapies. Recommendations and preconditions for carrying out n-of-one research in a scientifically sound and socially robust manner were given. **Implications** Regulatory authorities and insurers may accept evidence from n-of-one trials, provided that data can be aggregated and that benefit/risk ratio is considered. An n-of-one trial service can facilitate this process.

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FEASIBILITY OF NONSENSE MUTATIONS READTHROUGH AS A NOVEL THERAPEUTICAL APPROACH IN PROPIONIC ACIDEMIA

ABSTRACT N° C003_2012 / THERAPEUTIC APPLICATIONS

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Aminoglycosides and other compounds can promote premature termination codon (PTC) readthrough constituting a potential therapy for patients with nonsense mutations. In a cohort of 190 propionic acidemia patients, we have identified 12 different nonsense mutations, six of them novel, accounting for 10% of the mutant alleles. Using an in vitro system we establish the proof-of-principle that nonsense mutations in the PCCA and PCCB genes encoding both subunits of the propionylCoA carboxylase (PCC) enzyme can be partially suppressed by aminoglycosides, with different efficiencies depending on the sequence context. To correct the metabolic defect, the amino acid incorporated at the PTC, usually Gln or Trp, should support protein function and this has been evaluated in silico and by in vitro expression analysis of the predicted missense changes, most of which retain partial activity confirming the feasibility of the approach. In patients' fibroblasts cultured with readthrough drugs we observe a 4-50 fold increase in PCC activity, reaching up to 10-15% levels of treated control cells. The ability to partially correct nonsense PCCA and PCCB alleles represents a potential therapy or supplementary treatment for a number of propionic acidemia patients encouraging further clinical trials with readthrough drugs without toxic effects such as PTC124 or other newly developed compounds.

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PROTEASOMAL INHIBITION RESTORES BIOLOGICAL FUNCTION OF MIS-SENSE MUTATED DYSFERLIN IN PATIENT DERIVED MUSCLE CELLS

ABSTRACT N° C004_2012 / THERAPEUTIC APPLICATIONS

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BACKGROUND: Dysferlin is a transmembrane-protein implicated in surface-membrane repair of muscle cells. Mutations in dysferlin cause the progressive muscular dystrophies Miyoshi-Myopathy, Limb-Girdle-Muscular-Dystrophy 2B, and distal-anterior-compartment-myopathy. Dysferlinopathies are inherited in an autosomal recessive manner, and many patients with this disease harbor mis-sense mutations in at least one of their two pathogenic DYSF alleles. These patients have significantly reduced or absent dysferlin levels in skeletal muscle, suggesting that dysferlin encoded by mis-sense alleles is rapidly degraded by the cell's quality-control system. We reasoned that mis-sense mutated dysferlin, if salvaged from degradation, might be biologically functional. **METHODS:** We used a dysferlin-deficient human myoblast culture harboring the common Arg555Trp mis-sense allele and a DYSF null allele, as well as control human myoblast cultures harboring either two wild-type or two null alleles. We measured dysferlin protein and mRNA levels, resealing kinetics of laser-induced plasmalemmal wounds, myotube formation, and cellular viability after treatment of the human myoblast cultures with the proteasome inhibitors Lactacystin or Bortezomib (Velcade). **RESULTS:** We show that endogenous Arg555Trp mis-sense mutated dysferlin is degraded by the proteasomal system. Inhibition of the proteasome by Lactacystin or Velcade increases the levels of Arg555Trp mis-sense mutated dysferlin. This salvaged protein is functional as it restores plasma membrane resealing in patient-derived myoblasts, and reverses their deficit in myotube formation. Bortezomib and Lactacystin did not cause cellular toxicity at the regimen used. **CONCLUSION:** Our results raise the possibility that inhibition of the degradation pathway of mis-sense mutated dysferlin could be used as a therapeutic strategy for patients harboring certain dysferlin mis-sense mutations.

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REGULATORY EXPERIENCE WITH PROPOSED TREATMENTS FOR MENDELIAN DISORDERS IN THE UNITED STATES

ABSTRACT N° C005_2012 / THERAPEUTIC APPLICATIONS

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Purpose: Identification of features underlying success or failure of applications for FDA approval of proposed treatments for Mendelian disorders. **Methods:** Exhaustive review of publicly available FDA Orphan Designations and Summary Bases of Approval for Mendelian disorders, as well as our anonymized experience with an extensive but nonrandom sample of regulatory dossiers that have failed to achieve approval. **Summary:** As of 29 November 2011, there are 448 FDA designations of Orphan Status for proposed treatments of Mendelian disorders, with a skewed distribution among 121 disorders, 8 with more than 10 designations each. In descending order, designations were awarded to medium to small cap biotechnology firms (298), large pharmaceutical houses (113), unaffiliated individuals (21), academic institutions (9), disease-related charities (6), and a governmental agency. The overall rate of marketing approval for Mendelians has been 16.5%, nearly identical to the 15.6% approval rate for all 2520 designated orphans, the majority for oncology. However, the approval rate for Mendelians varies significantly with therapeutic class [small molecule (9.9%) or biologics (24.2%)] and the nature of the sponsor. Among the biologics designated for Mendelian disorders (215), all approvals have been for proteins (52), none for advanced therapeutics (cells, genes, inhibitory RNAs) even though the latter have received 55 Mendelian designations, one advanced therapeutic having been approved in 2010 for oncology. Mendelian orphans sponsored by large pharmaceutical companies achieved an overall approval of 34.5% vs 11.4% for biotechs. The approval advantage of integrated pharmaceutical companies over other sponsors spanned therapeutic classes: proteins 46.3% vs 22.6%, small molecules 23.1% vs 7.2%. This disparity accords with our observations of difficulties in demonstrating consistent manufacture and safety, as well as our corroboration of findings published by Heemstra: failures resulting from “clinical trial design, the level of experience of the sponsor and the level of interaction with the FDA.” **Conclusions:** Although the focus of nonpharmaceutical sponsors is frequently centered on proof of concept, equal attention needs to be afforded to CMC (chemistry, manufacturing, control) safety, dose selection, and design of pivotal trials, the four predominant causes of failure for Mendelians, as for other indications when resource constraints preclude thorough investigation.

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LESSONS FROM AN ULTRA-RARE DISORDER: A NEW INSIGHT INTO GLUTAMINE SYNTHETASE DEFICIENCY

ABSTRACT N° C006_2012 / THERAPEUTIC APPLICATIONS

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Background: A defect in glutamine synthetase (GS) leads to systemic glutamine deficiency and is an ultra-rare disorder described so far in only three patients with severe epileptic encephalopathy. This rareness possibly points towards the indispensable role of GS in particular since glutamine is the unique amino moiety donor for many substances including nicotinamide adenine dinucleotide (NAD⁺). Thus, deficiency of glutamine in itself is a major factor of this disease but still the entire pathophysiology of GS deficiency has not been fully understood. **Materials and Methods:** Building up on the recent description of the natural course of GS deficiency in a 3 years old patient we performed functional studies in different cell types (in vitro in fibroblasts and lymphoblasts, in vivo in leukocytes) obtained from this single living patient affected by GS deficiency and hereby focussed on NAD⁺ metabolism. In detail, we studied the basal NAD⁺ concentrations in these cells and compared them with levels after substitution of glutamine or nicotinamide. **Results:** Both in vitro and in vivo, untreated cells revealed a severe lack of NAD⁺. However, substitution of either glutamine or nicotinamide allowed to correct the deficiency of this abundantly needed energy metabolite. **Conclusion:** Albeit being an ultra-rare disorder with only one known living patient, studies presented here underline the absolute requirement of glutamine for NAD⁺ metabolism. This study highlights the potential of rare disorders to help elucidating basic biological processes and opening the window for novel therapeutic approaches.

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BENEFICIAL EFFECTS OF EARLY CHILDHOOD HELICOBACTER PYLORI INFECTION ON THE DEVELOPMENT OF ALLERGIC AND CHRONIC INFLAMMATORY DISORDERS

ABSTRACT N° C007_2012 / THERAPEUTIC APPLICATIONS

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Helicobacter pylori infection affects 50% of the world's population and is associated with chronic gastritis in all infected individuals which can lead to gastric and duodenal ulcers, MALT-lymphoma and adenocarcinoma. Recently, our lab reported that neonatal infection of mice with *H. pylori* protects from development of gastric pathology by induction of tolerance to the bacterium. This is accomplished by the capacity of *H. pylori* to induce semi-mature dendritic cells, which activate T regulatory cells. Furthermore, we were able to confirm epidemiological data demonstrating an inverse correlation between *H. pylori* infection and asthma development by showing that the T regulatory cells induced by neonatal *H. pylori* infection can protect from ovalbumin-induced asthma. Our recent experiments show that the oral administration of *H. pylori* sonicate also efficiently suppresses asthma development. Epidemiological studies have also demonstrated an inverse correlation between *H. pylori* infection and inflammatory bowel disease, major forms of which are Crohn's disease and ulcerative colitis. In a DSS-induced mouse model of colitis, mice infected in the neonatal period showed less pathology and less secretion of pro-inflammatory cytokines. Interestingly, a strategy of "tolerizing vaccination" with *H. pylori* sonicate is almost fully protective in our mouse model of inflammatory bowel disease. We will now investigate the Treg involvement of sonicate protection by adoptive transfer experiments and will try to elucidate the bacterial factor as well as the host molecular mechanism that induces the protective effect. Our overall goal is to define preventive and therapeutic treatment strategies for asthma and inflammatory bowel disease.

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NEONATALLY ACQUIRED IMMUNOLOGICAL TOLERANCE TO HELICOBACTER PYLORI INFECTION PREVENTS GASTRIC IMMUNOPATHOLOGY AND PROTECTS AGAINST ASTHMA AND CHRONIC COLITIS

ABSTRACT N° C008_2012 / THERAPEUTIC APPLICATIONS

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Persistent infection with the gastric bacterial pathogen *Helicobacter pylori* causes gastritis and predisposes carriers to a high gastric cancer risk, but has also been linked to protection from allergic, chronic inflammatory and autoimmune diseases. The beneficial consequences of chronic *H. pylori* infection have been proposed to result from the pathogen's immunomodulatory properties. We have utilized mouse models of allergic airway disease induced by ovalbumin or house dust mite allergen to experimentally examine a possible inverse correlation between *H. pylori* and asthma, a chronic T-cell driven disease of the airways. *H. pylori* infection efficiently protected mice from the airway hyper-responsiveness, tissue inflammation and goblet cell metaplasia that are hallmarks of asthma, and prevented the allergen-induced pulmonary and bronchoalveolar infiltration of eosinophils, Th2 and Th17 cells. Protection against asthma was abrogated by antibiotic eradication of *H. pylori* and was most robust in neonatally infected mice, which develop peripheral tolerance to *H. pylori*. Asthma protection was further associated with impaired maturation of lung-infiltrating dendritic cells, and accumulation of highly suppressive regulatory T-cells in the lungs. Systemic Treg depletion abolished asthma protection; conversely, the adoptive transfer of purified Treg populations was sufficient to transfer protection from infected donors to uninfected recipients. Our results thus provide experimental evidence for a beneficial effect of *H. pylori* colonization on the development of allergen-induced asthma. We have further investigated the involvement of dendritic cells (DCs) in tolerance induction to *H. pylori*. Infection of DCs with *H. pylori* reprograms the cells towards a tolerance-promoting, semi-mature state. The experimental depletion of DCs breaks *H. pylori*-specific, neonatally acquired tolerance and results in improved control of the infection, but also in more severe immunopathology. Interestingly, "tolerizing" vaccination with *Helicobacter* sonicate is as efficient at preventing asthma as live infection. Similarly, vaccination or live infection efficiently prevents chronic colitis in experimental models of the disease. Overall, our results suggest that *H. pylori* reprograms DCs in favor of tolerance over immunity to maintain persistence, and that this systemic immunomodulation protects against asthma and other chronic T-cell driven immunopathologies.

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COMPARING R&D INCENTIVES FOR NEGLECTED DISEASES

ABSTRACT N° C009_2012 / THERAPEUTIC APPLICATIONS

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Neglected diseases are typically characterised as those for which adequate drug treatment is lacking, and the potential for return on investment in research and development (R&D) to produce new therapies is too small to stimulate companies to invest significant resources in the field. Examples include infectious diseases that predominantly affect the developing world, such as African trypanosomiasis and schistosomiasis. Various incentive mechanisms have been associated with such initiatives. Broadly speaking, these can be classified either as 'push' or 'pull' programmes. Push programmes have a direct impact on R&D expenditures, supporting drug discovery, and often take the form of upfront research grants, from public institutions or charities to pharmaceutical firms. Pull incentives instead stimulate research effort indirectly, by enhancing the revenue potential and/or lowering delivery costs. Examples include differential pricing, advanced market commitments (AMC) and prize mechanism proposals. Hybrid options that include push and pull incentives have also become increasingly popular in recent years. Supporters and critics of these various incentive schemes have argued in favour of their relative merits and limitations, although the view that no mechanism is a perfect fit for all situations appears to be widely held. For this reason, the debate on the advantages and disadvantages of different approaches has been important for policy decisions, but is dispersed in a variety of sources. With this in mind, the aim of this paper is to contribute to the understanding of the economic determinants behind R&D investments for neglected diseases through the presentation of economic models of various incentive schemes. The analysis confirms that incentive schemes based on constant sums appear to be much less effective at inducing R&D investment by companies, and/or more expensive for the sponsor, than simple linear incentive functions such as $F(C) = bC$. Finally, the work suggests that co-funded "push" schemes with linear incentives $F(C) = bC$ are more effective than "pull" schemes in inducing R&D effort by firms. Moreover, whenever intermediate goals are contractible "pay-as-you-go" incentives, that is when funding is provided sequentially upon reaching the agreed upon intermediate goals, could be even more preferable than "push" schemes.

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APPLICATIONS AND DELIVERY OPTIONS FOR ANTISENSE THERAPY IN CELLULAR MODELS OF INHERITED METABOLIC DISEASES

ABSTRACT N° C010_2012 / THERAPEUTIC APPLICATIONS

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The use of antisense genetic therapy for RNA mis-splicing diseases has gained increased attention as the splicing changes account for up to 15% of all mutations and with massive parallel genomic sequencing of individual patients the number of splicing mutations will be increased. Although the number of patients who can be potentially treated is low for each IMD, it represents an excellent therapeutical option representing a type of personalized molecular medicine which is especially relevant for diseases for which there is to date no efficient treatment. In this work we summarize the splicing modulations explored to date especially targeted to deep intronic changes and the potential use to reprogram the splicing process using antisense therapy against intronic and exonic new or cryptic splice sites. In addition, we present our recent data in the investigation of new transporter structures that are thought to provide effective in vivo delivery. We are working on an octa-guanidine dendrimer covalently linked to specific morpholinos and also a new approach using locked nucleic acids monomers (LNA) bound to carbosilane dendrimers. We have successfully recovered the splicing process in PMM2, MUT, PTPS, PCCA, PCCB and ALDH7A1 disease cellular models suggesting that we are closer to applying the antisense therapy in animal models.

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THE BENEFITS OF MULTIDISCIPLINARY PHENOTYPING: EXPERIENCES FROM THE DUTCH CHARGE OUTPATIENT CLINIC

ABSTRACT N° C011_2012 / THERAPEUTIC APPLICATIONS

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Purpose: Multidisciplinary expert clinics on rare disorders can be a powerful tool for patient-driven research or translational research, and can even lead to key concepts for fundamental research. We present the research outcomes from our national CHARGE clinic and show how, through international collaboration, these expert clinics can make a big difference to our knowledge on patients with rare disorders and to their care. **Methods:** The Dutch CHARGE clinic was started in 2005 and currently has 70 patients with proven CHARGE syndrome in follow-up. All patients are seen every 1-2 years by a paediatric endocrinologist, ENT specialist and clinical geneticist. Other specialists are involved, depending on the patient's problems and questions, for example, a psychiatrist, speech therapist, gynaecologist, cardiologist, or occupational therapist. All clinical data are stored in a dedicated database and research questions are extracted from the experiences of the team members, who include several PhD students. **Results:** Our approach has led to a series of clinical and translational papers on CHARGE syndrome. The main achievements so far have been an online locus-specific database that contains all the identified CHD7 mutations, a classification system for CHD7 missense variants, insights into the pathogenesis of anosmia and pubertal delay along with recommendations for the surveillance of pubertal development in CHARGE syndrome, a guideline for CHD7 analysis in CHARGE and Kallmann syndromes, an extensive inventory of heart defects due to CHD7 mutations, and a further exploration of the phenotypical and aetiological overlap between 22q11 deletion syndrome and CHARGE syndrome. Recently, several other CHARGE clinics have been set up based on the Dutch model, including in the United Kingdom, United States, Denmark and Australia. These clinics have equally high standards of phenotyping and are facilitating international research collaborations; they have already resulted in a broad international study on immunodeficiency in CHARGE syndrome. **Conclusion:** Multidisciplinary expert clinics not only improve patient care by concentrating experience of the syndrome and its problems, but can also initiate and greatly facilitate clinical and translational research, thereby further advancing patient care through the development of evidence-based guidelines and recommendations.

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A CELL-BASED DRUG DISCOVERY PLATFORM TO IDENTIFY NOVEL THERAPIES FOR FRIEDREICH'S ATAXIA

ABSTRACT N° C012_2012 / THERAPEUTIC APPLICATIONS

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Friedreich's ataxia (FRDA) is a degenerative disease caused by deficiency of the protein frataxin. To date, neither regulation of the native frataxin gene (FXN) promoter nor the precise mechanism of frataxin gene silencing is well understood. Importantly, the mutation causing FRDA is an expansion of GAA•TTC triplets in the first intron of the FXN gene that does not alter the protein coding sequence but rather affects RNA polymerase II dependent transcriptional elongation (Punga & Bühler 2010). Therefore, gene reactivation could provide therapeutic benefit to FRDA patients and we thus aim at elucidating the regulatory mechanisms of frataxin gene expression. To enable high-throughput screening approaches, we developed reporter cell lines for simple detection of endogenous human FXN gene expression in its natural genomic context by exploiting a ZFN-mediated genome editing approach. In order to study frataxin gene expression in the disease-relevant cell types, we are also working towards reprogramming our reporter cell lines into the cell types that are mainly affected in FRDA. First results from a pilot RNAi screen using this system will be presented.

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RAPAMYCIN-MEDIATED GLYCOGEN SYNTHASE INHIBITION CAN RELIEVE POLYGLUCOSAN NEUROTOXICITY IN AN ADULT POLYGLUCOSAN BODY DISEASE NEURONAL MODEL

ABSTRACT N° C013_2012 / THERAPEUTIC APPLICATIONS

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Background and purpose: Adult Polyglucosan Body Disease (APBD) is a rare neurometabolic disorder caused by mutations in Glycogen Branching Enzyme 1 (GBE1), which enables glycogen branching, thus preventing the formation of insoluble polyglucosan in cells. While loss of function of GBE1 can evoke lethal childhood disorders such as Glycogen Storage Disease type 4 (GSD-IV), other mutations, such as Y329S still allow residual GBE1 activity and cause the late onset, slowly progressing APBD. The link between the accumulation of polyglucosans and APBD pathogenesis is unknown and its treatment is so far symptomatic. We attempted to relieve the burden of polyglucosan accumulation in neurons using the autophagy inducer rapamycin. Methods: GBE1 expression in rat embryo cortical neurons was suppressed by transduction with lentiviruses whose RNA genome encodes for shRNA sequences against GBE1. GBE1, the autophagy marker LC3 and glycogen levels were assessed by immunoblotting and indirect immunofluorescence using confocal microscopy. GBE1 and glycogen synthase (GS) activities were assessed by ¹⁴C-glucose incorporation into glycogen. Apoptosis was assessed by flow cytometry, and intracellular morphology by transmission electron microscopy. Results: GBE1 knocked down neurons were apoptotic and showed glycogen accumulation, similarly observed in APBD patient-derived cells. Induction of autophagy by rapamycin was able to clear glycogen aggregates and rescue the GBE1 knocked down neurons from apoptotic death. Nevertheless, autophagic maturation was dispensable for the corrective effects of rapamycin, apparently mediated by inhibition of glycogen synthase activity. Conclusions: Our data show that while rapamycin is a classical inducer of autophagy, its actual mode of action in clearing glycogen in this APBD model is through GS inhibition. Our results suggest a strategy for treating APBD based on down-modulation of the ratio between glycogen synthesis and branching, which would reduce the levels of neurotoxic polyglucosan. This approach might also be applied to reversing the polyglucosan accumulation observed in other neurological disorders, such as Alzheimer's.

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PATIENT ADVOCACY NEEDS GREATER FOCUS ON PATIENT NEEDS

ABSTRACT N° C014_2012 / THERAPEUTIC APPLICATIONS

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Acromegaly is a rare pituitary adenoma that most patients have never heard of when they are diagnosed. Medical and pharmaceutical industries are spending a tremendous amount of their time and energies in researching new treatments and surgeries to deal with rare diseases such as Acromegaly without working to provide 3-dimensional care for their patients. While this dedication to research and development is essential to the physical survival of patients, it does nothing to help with the emotional survival of the patient and the family unit. This is where the use of third party patient advocates provides that key third dimension of patient support. The goal of this presentation is to demonstrate the value of third party patient advocacy groups, and practical demonstration of how such services are best employed by the medical professional. Frequently, patients are sent out of the doctor's office with a prescription, and maybe a well-meaning comment of optimism. There are no local support groups, few inspirational books, and seemingly no one to talk with about their fears. This is further complicated with restrictions related to HIPPA. Even if a medical professional wanted to team up patients and loved ones with more seasoned patients and loved ones, the process is slow and cumbersome. While pharmaceutical companies have not adequately addressed the emotional needs of patients, they have begun to recognize the importance of working with third party specialists who focus solely on patient care and advocacy. One of the greatest services a medical or pharmaceutical company can do to support their patients is to strengthen third party advocacy groups led by patients, former patients, and people who have traveled the patient path, and are willing to be a community leader. Patients are eager to have their voices heard, when the audience is genuinely interested in what they are saying. When genuine partnerships of support are built with patient advocates, patient needs and desires are communicated straight from the patient. When a patient receives a diagnosis they may have been anticipating for months, years, or even decades, they need support. While there is a sense of relief when diagnosed with a long-suffering condition, there is an emotional cascade to follow. How those emotions are supported will have a significant impact on how the patient lives with their medical condition.

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TOWARDS A CONE-DIRECTED COMPREHENSIVE THERAPEUTIC STRATEGY IN RETINITIS PIGMENTOSA

ABSTRACT N° C015_2012 / THERAPEUTIC APPLICATIONS

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In retinitis pigmentosa, the loss of light-adapted visual responses is the key event leading to blindness. We shall describe the potential strategies to protect or restore cone function, our clinical experience in high resolution imaging of these cells, and methods to assess reliably and enhance the impact of such innovative therapies in daily life. We demonstrated that cone cell function loss might result from the loss of expression of Rod-derived Cone Viability Factor (RdCVF) consecutive to the degeneration of rod photoreceptor cells directly affected by causative mutations. Administration of RdCVF, irrespective of the gene defect, induced in relevant animal models a strong preservation of cone cell function related to the maintenance of rod outer segments (Leveillard and Sahel, 2010). Recently, work conducted by Botond Roska with our group showed that in advanced cases, cone cell bodies of dormant cones can be reactivated by vectorization of halorhodopsins, i.e. chloride-pumps activated by light, thus restoring cone function through adequate stimulation (Busskamp et al, 2010). These experiments bring strong emphasis on the assessment of the status of cone photoreceptors during the course of the disease. We have followed longitudinally over the past years a cohort of over 3000 patients and studied the morphology and function of cone photoreceptors, using novel high resolution imaging technologies and functional testing such as adaptive optics and segmentation of spectral-domain optical coherence tomography images. We show that cone outer segment degeneration during the course of the disease can be documented and that patients suitable for clinical trials testing neuroprotection or optogenetics can be selected on the basis of the presence of cone cell bodies and, respectively, the shortening or lack of cone outer segments. A comprehensive personalized set of therapeutic strategies can be tailored on this basis. In order to evaluate and document functional outcomes, we have developed novel tools for assessing reproducibly visual impairment and restoration, as well as palliative aids and associated training protocols. These include the development of virtual simulators, the construction of versatile environments reproducing daily life situations (e.g. apartment, street, shop, obstacles...) and the implementation of monitoring tools (captors, cameras, multiparametric modelling).

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PORPHYRIAS

ABSTRACT N° C017_2012 / THERAPEUTIC APPLICATIONS

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Introduction and aims The porphyrias are clinical expressions and metabolic defects caused by enzymatic activities responsible for biosynthesis of heme. In hepatic porphyria, the acute attacks are typified by a triad of symptoms: abdominal pain, neurological and psychiatric disorders and in severe cases it can come up to respiratory paralysis and coma. The PCT, chronic hepatic porphyria, occurs with skin lesions especially on sun-exposed areas. The renal involvement in acute hepatic porphyria is represented by hyponatremia, urinary retention, renal tubular interstitial, hypertension and chronic kidney disease. Most of our patients had a pain similar to renal colic ache with a propagation forward and down till the genitals associated with pallor, nausea, vomiting, fever and acute retention of urine with the emission of dark urine which sometimes turn dark red. **Methods** Our case study consists of 50 patients: 31 with Intermittent Acute Porphyria, 10 with Hereditary Coproporphyrinuria, 6 with Porphyria Cutanea Tarda and 3 with Erythropoietic Protoporphyrinuria. **Results** 7 patients with AIP and 3 with HCP are treated with hemin i.v. (Normosang®), life-saving drug for them, at a dose of 3 mg/kg/24h with resolution of clinical symptoms and resumption of normal daily activities. It is also used maltodextrin (Polycose®), which gives an addiction to a normocaloric and hyperperglycaemic diet therapy. **Conclusions** At the present time, porphyria mortality has been reduced since it first reached 20-25% in the first 5 years after the first attack. The most important thing is prevention. It doesn't have to be administered drugs that can induce the disease, as well as common treatments medications, tonics and herbal remedies. It has to be prescribed a high carbohydrate diet in addition to maltodextrin. This therapy makes us see a ray of great hope for the survival of patients with porphyria, providing them with a therapeutic element of high compliance, low-cost, without the collateral effects of drugs and indisputable clinical results with the future possibility of increasing once more the percentage of carbohydrate in diet.

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THERAPY INDUCED LATE TOXICITY IN CHILDREN WITH RARE DISEASES: LONG-TERM FOLLOW-UP IS NEEDED BUT GETS DISRUPTED IN ADOLESCENCE. A STUDY IN PEDIATRIC ONCOLOGY FROM THE SWISS CHILDHOOD CANCER REGISTRY

ABSTRACT N° C018_2012 / THERAPEUTIC APPLICATIONS

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Background As with patients of other rare diseases, intensive therapy may alter cellular structure and organ function in childhood cancer patients (approx. 200 new cases/year in Switzerland). Even decades after diagnosis, 3 out of 5 former patients suffer from chemo- and radiotherapy-associated late effects including second cancers and late mortality. Therefore, lifelong follow-up is needed for the majority of patients. However, during adolescence many patients stop adhering to recommendations putting themselves at risk for undetected and advanced late effects. **Aims** We thus aimed to determine 1) the proportion of former patients still attending follow-up care at the time of study in adulthood. In those no longer attending: 2) the age at last follow-up attended, 3) whether they had attended a follow-up program specially focused on the phase of transition from pediatric to adult care in adolescence, and 4) whether they had been informed about the importance of continuing follow-up. **Methods** In 2010 and 2011, we sent a questionnaire to 449 former patients registered from the Swiss Childhood Cancer Registry, diagnosed 1990-2006, >5 years after diagnosis and aged ≥ 18 years. The questionnaire included several questions on follow-up care. **Results** By 2012, 204 former childhood cancer patients replied (response rate 45%; mean age at survey= 21 years; mean age at diagnosis=8 years). Overall, 41% (n=86) reported to attend follow-up care. This did not differ by initial cancer diagnosis. Their median age at last attended follow-up was 18 years (minimum: 3, maximum: 27, interquartile range: 15-20 years). Only 7 (6%) had attended a special follow-up program during adolescence. Forty-five per cent (n=53) had been told about the importance of continued follow-up care. **Conclusion** In adolescence, a relevant number of former childhood cancer patients gets lost to follow-up. Research to discover underlying causes and setting up follow up structures within the health care system is needed. This may also be the case in other clinical disciplines with life-threatening rare diseases and aggressive therapy. Funded by MD/PhD grant SNF-323630-133897, KFS-02606-06-2010, and Ambizione grant SNF-PZ00P3_121682/1.

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CORNEAL CYSTINOSIS IN THE CYSTINOSIN KNOCKOUT MOUSE: DEVELOPMENT OF A QUANTITATIVE MODEL TO EVALUATE NOVEL THERAPIE

ABSTRACT N° C021_2012 / THERAPEUTIC APPLICATIONS

Corneal Cystinosis in the Cystinosis Knockout Mouse: Development of a Quantitative Model to Evaluate Novel Therapies

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Purpose: 1) To characterize the time course of corneal cystine crystal development in the cystinosis (ctns $-/-$) knockout mouse model of cystinosis 2) To assess quantitatively the effects of topical cysteamine therapy using in vivo confocal microscopy (CM). Methods: 1) 2 Ctns $-/-$ mice and one C57Bl/6 mouse were examined using in vivo CM at each of the following time points: 2,3,5,7,10,12 and 14 months of age. Animals were then sacrificed and cornea blocks evaluated for cell morphology using phalloidin and for lymphocyte infiltration using CD45 antibodies. Corneal cystine crystal content was measured by calculating the pixel intensity of the crystals divided by the stromal volume. 2) Next, the CVI of one eye receiving topical cysteamine eyedrops (0.55%) for 4 weeks was compared to the contralateral eye in five Ctns $-/-$ mice. Results: 1) Corneal crystals were identified in Ctns $-/-$ eyes beginning at 3 months of age, increasing in density from 7–12 months (when animals begin to succumb to the disease and corneas become scarred and neovascularized). Ctns $-/-$ mice (7 months and older) demonstrated cell infiltrates that stain positively for CD45, which is associated with progressive keratocyte disruption. At 12 months of age, decreased cell density and endothelial distortion were also detected. 2) Eyes treated with cysteamine drops for 4 weeks beginning at 5 months of age showed significantly less crystal accumulation compared to control eyes ($p < 0.001$) with only a 15% increase in treated eyes ($p = ns$) compared to 173% increase ($p < 0.04$) for untreated eyes. Conclusions: 1) CM identified corneal crystals starting at 3 months in Ctns $-/-$ eyes, which subsequently demonstrate findings that are consistent with observations in human cystinosis. 2) Topical cysteamine inhibits crystal volume progression in the Ctns $-/-$ mouse, again analogous to clinical observations in cystinosis patients. Taken together, these data support the use of CVI and the Ctns $-/-$ mouse model as a promising tool for novel therapeutic development.

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FRAMESHIFT MUTATIONS IN HYALINE FIBROMATOSIS SYNDROME (HFS) REVEAL THE SIGNIFICANCE OF PERSONALIZED TREATMENT IN PATIENTS

ABSTRACT N° D001_2012 / GENOMIC DISORDERS

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Hyaline Fibromatosis Syndrome (HFS) is a rare autosomal recessive disease, which is caused by mutations in capillary morphogenesis gene 2 (*cmg2*). This gene encodes a type I transmembrane protein, the physiological function of which is not clearly understood while its role as the main anthrax toxin receptor in mammals is well established. Mutations were identified throughout the gene. Among them, exon 13, which is one of the exons encoding the cytosolic tail of the protein, has shown to be a hot spot for frameshift mutations. Here we focused on the 3 sequenced frameshift mutations in this exon due to single or double base insertions or deletions. The 3 frameshift mutations all led to a decrease in messenger RNA in patient cells presumably due to targeting to the NMD pathway (nonsense mediated mRNA degradation). We next analyzed the consequences of the mutation at the protein level in both transfected Hela cells and fibroblasts from patients. One base insertion led to a protein with a shorter cytosolic tail, which was properly targeted to the plasma membrane and we are analyzing the functional effects of the mutation. Two bases insertion or one base deletion in the same codon also led to a truncated cytosolic tail with only one amino acid difference in sequence between them. Interestingly however, these mutant proteins did not exit the ER, underwent polyubiquitination and were rapidly targeted to the ER associated degradation pathway. And transplantation of this truncated tail to other transmembrane or cytosolic proteins also led to a similar degradation. While the native CMG2 tail is intrinsically unstructured and highly polar, the mutant tail was predicted to have a high helical content and significantly hydrophobic. Thus, ironically, changing the cytosolic tail from a sequence that should not fold to a sequence that has structure but cannot fold properly, renders it a substrate for ER quality control, the identity of which remains to be identified. Therefore, even if saving the mRNA by inhibiting NMD pathway in patients, the proteins with these mutations would still get recognized and degraded. And treating patients with proteasome inhibitor like Bortezomib, as shown in previous studies on point mutations mapping to exons encoding CMG2 ectodomain, would not help the accumulated proteins get out of ER to reach the plasma membrane in this case. The implications in these findings highlighted the importance of personalized treatment of HFS patients.

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MITOCHONDRIAL DYSFUNCTION AND PURKINJE CELL LOSS IN THE HUMAN SPASTIC ATAXIA ARSACS

ABSTRACT N° D002_2012 / GENOMIC DISORDERS

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Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) (OMIM: 270550) is a childhood-onset neurological disease resulting from mutations in the SACS gene encoding saccin, a massive 4579 amino acid protein of unknown function. Originally identified as a founder disease in Quebec, ARSACS is now recognized worldwide. Prominent features include pyramidal spasticity, peripheral neuropathy and cerebellar ataxia but the underlying pathology and pathophysiological mechanisms are unknown. We have now generated saccin knock out mice that display age-dependent neurodegeneration of Purkinje cells and modified mitochondrial function. Mitochondrial dysfunction is a common pathophysiological feature of major neurodegenerative diseases including Huntington's, Parkinson's, and Alzheimer's. We show that saccin localizes to mitochondria in neurons and nonneuronal cells and that it interacts and co-localizes with dynamin-related protein 1, which participates in mitochondrial fission. Disruption of saccin function leads to an overly interconnected and functionally impaired mitochondrial network. Mitochondria accumulate in the soma and proximal dendrites of neurons and there are striking alterations in the organization of dendritic fields and the morphology of dendritic spines that precede neuronal cell death. Our data reveals mitochondrial dysfunction/mislocalization as the likely cellular basis for ARSACS.

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LAMIN B1 OVEREXPRESSION IS ASSOCIATED WITH INCREASED STIFFNESS OF NUCLEI ISOLATED FROM HUMAN SKIN FIBROBLASTS OF PATIENTS WITH AUTOSOMAL DOMINANT LEUKODYSTROPHY

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Autosomal dominant leukodystrophy (ADLD) is a rare, progressive and fatal genetic disease affecting patients in their late 40s. Duplication of a region of chromosome 5 encompassing the gene encoding for lamin B1 (LMNB1) protein has been causally linked to ADLD in nine pedigrees of different ethnic origin. In such kindreds, the duplication of the gene leads to overexpression of the LMNB1 protein. LMNB1 is one of the major components of the nuclear lamina, a filamentous meshwork underneath the inner nuclear membrane. LMNB1 forms a stable structure in the nuclear lamina and, together with other lamins (e.g., lamin A/C), contributes to determine nuclear mechanical stability. Consistent evidence indicates that lamin A (LMNA) mutations or absence significantly alter nuclear shape and elasticity. Here, we evaluated whether LMNB1 upregulation linked to ADLD could also alter nuclear morphology and mechanical properties. To this purpose, we have established primary cultures of human skin fibroblasts from 3 ADLD patients with LMNB1 duplication and 6 age-matched healthy volunteers. LMNB1 protein levels were significantly increased in fibroblasts from ADLD affected patients, while levels of the cognate LMNA and LMNC proteins were apparently unchanged. LMNB1 upregulation was associated with altered nuclear morphology as shown by the reduced circularity index and presence of nuclear blebs. The elasticity of isolated nuclei was probed by atomic force microscopy (AFM) using spherical polystyrene beads mounted on silicon tipples cantilevers TL1 as indenters. Force maps covering a 16µm² area were acquired on each nucleus. AFM analysis on nuclei isolated from control fibroblasts revealed that nuclear elasticity varied with the proliferating status of the cells, but not with aging in vitro. Therefore, to avoid confounding effects due to cell proliferation, we performed AFM analysis on nuclei isolated from ADLD and control fibroblasts synchronized by serum deprivation for 24h. Notably, nuclei from ADLD fibroblasts were on average significantly stiffer than control nuclei, suggesting that LMNB1 upregulation impacts on nuclear mechanical properties. We are currently dissecting the specific contribution of LMNB1 to nuclear stiffness using mouse embryonic fibroblasts from LMNB1-deficient and wild type mice or cells with controlled overexpression of LMNB1. Further studies are warranted to evaluate the impact of nuclear abnormalities on gene expression and pathogenic mechanisms.

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DOGS PROVIDE CLINICALLY AND GENETICALLY RELEVANT MODELS FOR RARE HUMAN DISORDERS

ABSTRACT N° D004_2012 / GENOMIC DISORDERS

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Inherited disorders are common in humans and dogs, and the clinical signs in dogs often closely mimic human diseases. For an increasing number of canine diseases the molecular cause is known and often mutations are reported in the orthologues of the corresponding human diseases. However, canine genetic studies have also potential to identify new candidate genes for human diseases. For example, we identified SERPINH1 as a new osteogenesis imperfect (OI) gene in Dachshunds, and a recent independent study showed that coding mutations of the SERPINH1 gene are also responsible for the recessive forms of human OI. Besides being useful for revealing specific disease genes, canine genetic studies even have the potential to reveal entirely new pathways. An example is that of ectodermal dysplasia (ED) in the Chinese Crested dog, which is caused by a 7-bp duplication in the coding region of FOXI3. This study indicated for the first time an essential role for a forkhead box (FOX) class transcription factor in hair and tooth development. There are still many human ED patients without causative mutation and FOX class transcription factors and genes in the related pathway are good functional candidates. In a current study we aim to identify the causative mutation for recessive inherited craniomandibular osteopathy (CMO) in certain Terrier breeds. CMO is characterized by a non-neoplastic proliferation of bone on the ramus of the mandible and/or the tympanic bulla. The disease in various respects resembles Paget's disease and infantile cortical hyperostosis (Caffey's disease) of humans. We mapped CMO to a 1.8 Mb region on dog chromosome 5 by a GWAS. The mapped region contains no obvious functional candidate gene and therefore offers a chance to identify a new candidate gene for canine and human CMO. The identification of canine disease genes establishes clinically important animal models and offers unique opportunities to test new therapies. Dog is a large animal and physiologically and clinically closer to human than rodent models. Canine disorders resemble better human condition, which is useful in pre-clinical trials of new treatments. Thus, testing the feasibility and efficacy of new therapies in these genetically characterized large animal models may facilitate translation of curative treatments for rare human genetic diseases.

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MUTATIONS IN THE PLEKHG5 GENE CAUSE PERIPHERAL NEUROPATHY

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Inherited peripheral neuropathy (also called Charcot-Marie-Tooth disease) includes a clinically and genetically heterogeneous group of neuromuscular disorders characterized by progressive distal muscle weakness and atrophy, foot deformities, and distal sensory loss. Using a homozygosity mapping approach in a consanguineous Moroccan family with a late-onset, recessive, and predominantly demyelinating form of hereditary neuropathy, we identified a 7-bp homozygous duplication (c.1143_1149dup17 - TGAAGAC) in the PLEKHG5 gene on chromosome 1p36 in all affected members of this pedigree. This DNA change introduces a premature stop (E384X) in the reading frame and is predicted to result in a null allele. Our expression analysis of the mouse *Plekhg5* gene in developing and adult central and peripheral neural systems revealed its temporally regulated endoneurial expression, indicating a role in Schwann cell myelination. Interestingly, it was previously reported that a homozygous missense change (c.1940T>C) in PLEKHG5 leads to an autosomal recessive form of lower motor neuron disease with childhood onset (Maystadt et al., 2007. *AJHG* 81:67-76). Together with our results, these data indicate that different mutations in PLEKHG5 lead to clinically diverse outcomes, perhaps related to a reduced activity versus the complete absence of the protein. Regardless of the molecular mechanisms of action, intact PLEKHG5 function seems to be necessary for normal function of both peripheral neural system glia and neurons.

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DEVELOPMENT OF PATHOPHYSIOLOGICALLY BASED BIOCHEMICAL ASSAYS TO IDENTIFY SMALL MOLECULAR WEIGHT COMPOUNDS FOR THE TREATMENT OF MYOTONIC DYSTOPHY TYPE I

ABSTRACT N° D006_2012 / GENOMIC DISORDERS

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Myotonic Dystrophy type I (DM1) is a disabling, genetic disease affecting multiple organ systems, including skeletal and cardiac muscle, central nervous system, gastrointestinal tract, endocrine glands and eye, with no causal treatment available. This disease is caused by expanded CTG triplet repeats in the 3'UTR of the Myotonic Dystrophy Protein Kinase (DMPK) gene. Disease severity is correlated to the repeat expansion size: Normal subjects harbor less than 37 CTG repeats, whereas in subjects with congenital forms the repeat length can exceed 2000 triplets. On the RNA level such expanded CUG repeats (CUGexp) form hairpin structures, which lead to ribonuclear inclusions. More specifically, the RNA with expanded CUG repeats sequesters the splice-factor muscleblind-like 1 (MBNL1), which is involved in alternative splicing. Lack of available MBNL1 leads to mis-regulated alternative splicing of many different genes, explaining thus the multisystemic defects in DM1. We wish to identify small molecular weight compounds that liberate sequestered MBNL1 from CUGexp-RNAs in affected organs. In order to identify such small molecular weight compounds for the treatment of Myotonic Dystrophy type I, we developed different pathophysiologically based biochemical assays. Beside an improved gel-shift assay, and ELISA-based assay, we also developed an assay based on Differential Scanning Fluorometry. Each of the different assays has its specific advantages as well as disadvantages. These assays could be applied to drug screenings for other rare RNA-mediated diseases like Myotonic Dystrophy type II, Fragile-X Tremor Ataxia Syndrome and different types of Spinocerebellar Ataxias.

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ANALYSIS OF SUPEROXIDE DISMUTASE GENE FAMILY IN PATIENTS WITH AUTISTIC SPECTRUM DISORDER IN SLOVENIAN POPULATION

ABSTRACT N° D007_2012 / GENOMIC DISORDERS

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Autistic spectrum disorder (ASD) is a group of neurodevelopmental disorders with common impairments in social interaction, language development and communication, with rather unknown aetiology. The ASD has prevalence of ~4/1000, with 3:1 male to female ratio. The prevalence of ASD for siblings of ASD patients is much higher (2%-6%), indicating significant genetic background of the syndrome. Several studies indicate that levels of oxidative stress markers are significantly higher in ASD patients compared to group of healthy individuals. Superoxide dismutases (SOD1, SOD2 and SOD3) catalyse superoxide radical into oxygen and hydrogen peroxide. Thus they are important in regulating homeostasis of reactive oxygen species (ROS) and reduce levels of oxidative stress. The aim of this study was to analyse 5'UTR and coding regions of genes of superoxide dismutase (SOD) family in 96 individuals diagnosed with ASD and compare the results with results from healthy unrelated controls to establish correlation between genetic variation of SOD genes and susceptibility for ASD. In our group, 70 individuals were diagnosed with classical autism, while 26 were diagnosed with Asperger syndrome. All individuals or their parents signed informed consent and volunteered for participation in this research. Whole blood samples were taken from each individual and DNA isolation was performed according to established laboratory protocols. We performed screening for genetic variations of SOD gene family by high resolution melting (HRM) analysis. All detected genetic variants were confirmed by DNA sequencing. Results were statistically evaluated by comparison to the healthy control subjects from Slovenian population. We identified 56 different genetic variants. None of the genetic variants analysed so far had any statistically significant correlation with ASD or any specific ASD subgroup. Therefore, these preliminary results are suggesting that SOD gene family variations might not be correlated with ASD aetiology.

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CYSTIC FIBROSIS PHYSIOTHERAPY TREATMENT IN DAILY ROUTINE OF NEW-BORN BABIES AND TODDLERS

ABSTRACT N° D009_2012 / GENOMIC DISORDERS

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This study is aiming to enhance the quality of life in CF children, integrating, with the help of parents, the treatment in daily routine and promoting the joy of movement in a safety environment. Methods This study was conducted in the Romanian National Cystic Fibrosis Centre in 2010-2011, and the study lot was represented by a number of 20 patients, aged between 6 months and 3 years. The initial and final assessment was made with the help of parents who chosen the 6 most important items for them from Quality of life scale in CF: quality of sleep, fatigue during play activities, nutritional status, coughing, clinical status, number of hospitalizations. The chosen therapeutic techniques were: modified postural drainage, contact breathing, vibrations, therapeutic and facilitation postures, massage, games for blowing incentive games and stretching and strengthening exercises. Results: We noticed improvements regarding all items in the study group: deep sleep quality increased with 20% and this had an positive effect on weight gain(increased on average with 30% from varying degrees of growth bankruptcy to normoponderal). Fatigue during play activities decreased due to secretion mobilization, infections reduction, improvement of sleep quality and muscles strength growth. The number of hospitalisations also decreased from 60% to 40%. Conclusions: Combining airway clearance techniques and physical activities could optimize quality of life in toddlers with cystic fibrosis. Physiotherapy must be included in the daily program of any patient with cystic fibrosis and must be conducted by parents not only by physiotherapists. Funding acknowledgement: This study was financially supported by the research grant CNCSIS RO, TE/cod 36.

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MIRROR PHENOTYPES ASSOCIATED WITH 16P11.2 REARRANGEMENTS

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Recent extensive GWAS identified numerous loci associated with obesity, but they only account for a small fraction of the heritability of this trait. We previously reported a highly penetrant form of obesity resulting from a heterozygous deletion of 600 kilobases at the 16p11.2 locus. Deletions identified from GWAS data in 16053 individuals from 8 European cohorts were absent from healthy non-obese controls and accounted for 0.7% of our morbidly obese cases (body mass index, BMI ≥ 40 kg.m⁻² p = 6.4x10⁻⁸, OR = 43.0) In contrast to obesity, few genetic variants underlying clinical conditions associated with being underweight (BMI <18.5) have been reported. We identified 138 carriers of the reciprocal duplication from individuals clinically referred for developmental or intellectual disabilities (DD/ID) or psychiatric disorders, or recruited from population-based cohorts. These carriers show significantly reduced postnatal weight and BMI. Half of the boys under five years of age are underweight with a probable diagnosis of failure to thrive; whereas adult duplication carriers have an 8.3-fold increased risk of being clinically underweight. Gene dosage correlates with changes in transcript levels for genes mapping within the duplication, but not in flanking regions. The reciprocal impact of these 16p11.2 copy-number variants indicates that severe obesity and being underweight could have mirror etiologies, possibly through contrasting effects on energy balance. We are conducting a systematic characterization of associated clinical symptoms focusing on mirror eating behaviors and psychiatric disorders, including autism and psychotic symptoms. Structural and functional imaging is also being performed. Progress in these studies will be reported. This study highlights a promising strategy for identifying missing heritability in complex traits.

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NOONAN-LIKE SYNDROME WITH LOOSE ANAGEN HAIR IS CAUSED BY DIFFERENT MUTATIONS IN SHOC2

ABSTRACT N° D011_2012 / GENOMIC DISORDERS

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Noonan-like syndrome with loose anagen hair (NS/LAH; MIM #607721) is a clinically distinct entity in the spectrum of neuro-cardio-facial-cutaneous disorders, mainly characterized by typical facial features, growth deficiency (frequently with growth hormone deficiency), easy pluckable, sparse, slow-growing hair, darkly pigmented skin and developmental delay. In 2009, Cordeddu et al. identified a germline mutation in SHOC2 (c.4A>G, p.Ser2Gly) present in all patients published so far. Because of its particular functional mechanism (creation of a recognition site for N-terminal myristoylation), this has been supposed to be the only causative SHOC2 mutation. We report on a 4 ½ year-old girl, born to healthy non-consanguineous German parents after an uneventful pregnancy at 37+3 weeks of gestation with normal birth measurements [3300g weight (75th perc.), 50cm length (50th perc.) and 33cm OFC (25th perc.)]. Her psychomotor development was mildly delayed. Hand X-rays at age 15 months and 25 months showed a significantly delayed bone age of 6 and 9 months, respectively. At age 2 7/12 years, she was first presented because of short stature with relative macrocephaly, delayed closure of large fontanel, short, sparse, brittle blond hair and a greyish complexion. Measurements were 82.3cm length (3cm <3rd perc.), 11.1kg weight (10th perc.) and 49cm OFC (50th perc.). Endocrinological evaluation revealed a neuro-endocrine dysfunction and growth hormone therapy was start at age 3 8/12 years. Re-evaluation at age 4 7/12 years showed a length of 97.7cm (almost 3rd percentile), a weight of 15.8kg (25th-50th percentile), and an OFC of 52cm (90th percentile). Echocardiography, hair microscopy, copper and caeruloplasmin levels, array analysis and c7orf11 sequencing were all normal. The DYSCERNE experts suggested SHOC2 mutation analysis. The typical mutation c.4A>G was excluded, but a novel previously undescribed mutation in exon 2 (c.517A>G, p.M173V) of initially unknown significance was identified and confirmed in a second tissue (saliva sample). Analysis of both parents indicated de novo occurrence. The de novo occurrence of this SHOC2 mutation combined with the typical clinical phenotype suggested the mutation to be pathogenic –thus being the first mutation different from the single mutation described in all earlier published patients. Therefore, extended sequence analysis should be performed in absence of the c.4A>G mutation in patients with typical SHOC2 phenotype.

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DISORDERS OF SEXUAL DEVELOPMENT: IDENTIFYING NEW GENES AND PATHWAYS INVOLVED IN THE SEXUAL DETERMINATION OF THE HUMAN GONAD

ABSTRACT N° D012_2012 / GENOMIC DISORDERS

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Disorders of sexual development (DSD) are rare pathologies affecting one baby in every 3000 births. In such pathologies, the distribution of sexual chromosomes (chromosomal sex), the differentiation of the embryonic gonads (gonadal sex) or the action of sexual hormones (hormonal sex) can be affected. In the case of gonadal dysgenesis (GD), where the determination of the gonadal sex is altered, the genetic etiology remains unknown for almost half of the cases, even though several causative genes such as SOX9, FOXL2, SF1, DAX1 or WNT4 have been identified in past genetic studies. The recent burst into the development of high-throughput methods for the genetic testing of individuals now give us new tools to investigate unresolved cases of disorders of sexual development with the final goal to identify new factors involved in the sexual development of the human gonad. For this purpose, we gathered a large cohort of 46,XX and 46,XY GD and researched within each cases copy number variations (CNVs) by CGH arrays and single nucleotide variants (SNVs) using deep exome sequencing. Patients who have a normal karyotype, complete clinical data and unknown genetic etiology for their pathology were selected for analysis. The genomic DNA from 38 cases of 46,XY DSD and 18 cases of 46,XX DSD have been collected and are currently analyzed by CGH array and deep exome sequencing. Up to now, we identified and validated 2 causative (CNVs) in 46,XY GD patients, including a duplication of the WNT-pathway regulator DAAM2 as well as a deletion of HMGCS2, an important gene for sexual dimorphism in mouse. Parallel to that, one putative causative SNV have been identified in a case of 46,XX GD and remain to be validated. Globally, our strategy appears efficient in bringing new perspectives in the genetic analysis of gonadal dysgenesis. This work is currently ongoing, and by proposing an optimized protocol for the characterization of each case clinic and by prioritizing the analysis of complete families, we should be able to provide new insights into the genetics of human sexual determination.

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HYALINE FIBROMATOSIS SYNDROME INDUCING MUTATIONS IN THE ECTODOMAIN OF ANTHRAX TOXIN RECEPTOR 2 CAN BE RESCUED BY PROTEASOME INHIBITORS

ABSTRACT N° D014_2012 / GENOMIC DISORDERS

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Hyaline Fibromatosis Syndrome (HFS) is a human genetic disease caused by mutations in the anthrax toxin receptor 2 (or *cmg2*) gene, which encodes a membrane protein thought to be involved in the homeostasis of the extracellular matrix. Little is known about the structure and function of the protein and the genotype-phenotype relationship of the disease. Through the analysis of 4 patients, we identify 3 novel mutants and determine their effects at the cellular level. Altogether, we show that missense mutations that map to the extracellular von Willebrand domain or the here characterized Ig-like domain lead to folding defects and thereby to retention of the mutated protein in the endoplasmic reticulum. Mutations in the Ig-like domain prevent proper disulfide bond formation and are more efficiently targeted to ER associated degradation. Finally we show that CMG2 can be rescued in fibroblasts of some patients by treatment with proteasomes inhibitors and that CMG2 is then properly transported to the plasma membrane and functional, identifying the ER folding and degradation pathway components as promising drug targets for HFS.

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HOST- AND PATHOGEN-DERIVED FACTORS IN CHRONIC MUCOCUTANEOUS CANDIDIASIS

ABSTRACT N° D016_2012 / GENOMIC DISORDERS

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Chronic mucocutaneous candidiasis (CMC) is a rare but severe disease characterized by persistent or recurrent infection of the nails, skin or oral mucosa caused by fungi of the genus *Candida*, mainly *Candida albicans*. The lesions are clinically heterogeneous and respond poorly to anti-fungal treatment. Only lately the first genetic etiologies of this rare disease have been described, including an autosomal dominant (AD) mutation in the gene encoding IL-17F resulting in a deficiency of this cytokine and an autosomal recessive (AR) mutation in the gene encoding the IL-17 receptor A (IL-17RA), resulting in a deficiency of the receptor for IL-17 cytokines. However, additional parameters may predispose for disease. In particular, the pathogenicity traits of the fungus may impact greatly on disease progression versus resolution. *C. albicans* is an opportunistic pathogen that lives as commensal in healthy individuals and only causes disease when host defenses are breached. It is believed that the host immune system alone determines the balance between commensalism and pathogenicity. However, the genetic traits of different clinical isolates may have a strong impact on their pathogenicity and on the consequence for the host, namely colonization versus invasion and disease. A detailed understanding of the molecular and cellular mechanisms that lead to the development of disease symptoms, combined to detailed knowledge of antifungal immune mechanisms, is indispensable for an integrated understanding of the disease. This project will use an integrated approach to evaluate the relative importance of host- and pathogen-derived factors in the development of a rare infectious disease. Applying an original, innovative and interdisciplinary approach that shall combine in vivo and in vitro studies using immunologic, genomic and proteomic techniques we propose to identify new host- and pathogen-derived factors that contribute to the development and control of CMC. This project shall help to better understand the molecular pathogenesis of CMC with the aim to identify novel therapeutic targets and diagnostic markers, and to promote the development of novel antifungal strategies.

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A MUSCULAR DYSTROPHY-CAUSING LAMIN MUTATION INTERFERES WITH DIFFERENTIATION SPECIFIC RELOCATION OF A MUSCLE-SPECIFIC PROMOTER

ABSTRACT N° D017_2012 / GENOMIC DISORDERS

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Chromatin is non-randomly organized in the interphase nucleus with heterochromatin often being found adjacent to the nuclear lamina. To see if gene position facilitates heritable repression states during cell differentiation, we have visualized developmentally controlled promoters in *C. elegans*. The position of low-copy integrated transgenes containing developmentally regulated promoters (*myo-3::mCherry* or *pha-4::mCherry-H2B*) and arrays of LacO sites, were examined during development. In early embryos, inactive tissue-specific promoters were randomly distributed throughout the nuclear volume. During cellular differentiation, transgene position depended strictly on transcriptional status. In four different tissues repressed transgenes were shunted to the nuclear periphery, while active promoters were sequestered internally. In contrast, large heterochromatic arrays were sequestered at the nuclear envelope even in embryonic nuclei. To examine the role of lamin in heterochromatin anchoring, we performed RNAi of the unique worm lamin gene, and tested a point mutated lamin that causes Emery Dreifuss Muscular Dystrophy in humans. Loss of lamin derepresses and delocalizes heterochromatic arrays, whereas the EDMD point mutation interfered with the release of active muscle-specific promoter arrays, uniquely in muscle cells. The mutation reduces expression from the array-borne *myo-3* promoter and led to morphological disruption of actin fibers and sarcomeres. The worms lose muscular coordination as in human EDMD. We have thus reconstituted a human disease in *C. elegans* and find that a point mutated lamin can lead to tissue-specific defects in chromatin position and tissue structure. The effects of the disease causing mutation in lamin are unlike the effects of lamin deletion, and therefore shows that this EDMD-linked mutation acts in a dominant fashion to provoke muscle-specific defects in nuclear organization and tissue function.

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HIGH THROUGHPUT SEQUENCING OF THE 22Q11.2 DELETION IN VELOCARDIOFACIAL SYNDROME TO STUDY SIGNIFICANT VARIANTS FOR SCHIZOPHRENIA

ABSTRACT N° D018_2012 / GENOMIC DISORDERS

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Velocardiofacial syndrome is a microdeletion in 22q11.2 ranging between 1.5 and 3 Mb, containing about 60 genes, with an incidence of 1 in 4,000 live births. One third of VCFS patients develop schizophrenia during early adulthood. The incidence of schizophrenia in patients with VCFS is thirty times higher than in the general population; thus making VCFS an important risk factor for schizophrenia and suggesting a strong correlation between it and the 22q11.2 microdeletion. Based on the high incidence of schizophrenia in these individuals, we hypothesized that some patients with VCFS develop schizophrenia due to hemizygoty of one or more critical regions in the 22q11.2 portion of the genome. Paired-end libraries were prepared from 38 VCFS patients, half with schizophrenia or schizo-affective disorder, and half without. Agilent's target enrichment capture was performed for a 3 Mb region spanning the 22q11.2 area. The enriched regions from the healthy chromosomes were then sequenced on an Illumina GAlIx. The reads were then aligned and mapped, obtaining at least 8x coverage in 98% of the region. On average, 16 non synonymous variants were found per sample. After preliminary analysis a trend was identified among patients with a clear and confirmed schizophrenic phenotype (8 out of 16). Fisher association test reports a signal of at least one intergenic SNP ($p < 0.05$ in 8 out of 16 affected and none of the 16 non-affected). Therefore, a larger cohort of patients with a clear schizophrenic phenotype is needed to confirm the findings of this preliminary study.

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SEDLIN AND PROSTAGLANDIN E2 DEHYDROGENASE – INTERACTIONS AND IMPLICATIONS FOR SPONDYLOEPIPHYSEAL DYSPLASIA TARDA

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Spondyloepiphyseal dysplasia tarda (SEDT) is a rare X-linked, late-onset skeletal disease. Affected individuals develop phenotypes in their early childhood, displaying barrel-shaped chests, vertebral bodies malformation, flattened disc spaces and premature osteoarthritis in weight-bearing joints. The disease was found linked to the gene *SEDL* coding for the protein *sedlin*. *Sedlin* is one of the subunits of the TRAPP (Transport Protein Particle) complex, which is responsible for vesicle tethering during endoplasmic reticulum-to-golgi transport. Although *sedlin* is known to function in intracellular trafficking, the reason why mutations in a trafficking protein lead to a skeletal disease remains unknown. To address this, four missense mutations (D47Y, S73L, F83S and V130D) of *sedlin* observed in SEDT patients were studied. Except D47Y, the other three mutations cause proteosomal degradation of *sedlin* in cultured cells, whereas the D47Y mutation had a minor effect on Bet3 binding to *sedlin*. Pull-down assay was performed to identify novel *sedlin* interacting partners. 15-hydroxyprostaglandin dehydrogenase (PGDH) was pulled down and the interaction was confirmed in cell culture system. *Sedlin* activates PGDH activity *in vitro*. By confocal microscopy, *sedlin* was also found to colocalize with PGDH in the cytosol. PGDH catalyzes the degradation of prostaglandin E₂, which affects cartilage and bone growth. Further investigation is ongoing to understand the function of *sedlin* and the mechanism of disease for SEDT. This work was supported by Research Grants Council of Hong Kong Administrative region (AoE/M-04/04).

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BLACKSWAN FOUNDATION

Rare diseases are also known as “orphan” diseases precisely because of their singular nature. Rare diseases are not seen as a field for priority action by the medical community. In fact, poor characterisation of the pathologies and low numbers of cases make diagnosis difficult, often resulting in a real ordeal for patients and their families, who find themselves on a seemingly endless trek from one consultant to another... Rare diseases offer sufferers little hope of survival – and even less chance of leading a normal life. These diseases go hand in hand with discrimination, isolation and incomprehension in others. And, paradoxically, the problem is aggravated by administrative and bureaucratic obstacles, as standards and norms cause these cases to fall through the safety net. Dr. Menzel, who has dedicated his life to studying rare diseases, is focusing attention on the lack of public funding made available for research in this sector, especially in Switzerland. A problem which he now wants to solve through the BLACKSWAN Foundation.

The idea is to support active advanced research into rare diseases by means of a non-profit structure in order to fill the gap, where possible, caused by the chronic lack of public and private funds in this area. The goal is to find a solution to this very important public health problem. In fact, there are already 8,000 rare diseases listed in the scientific literature and 5 new diseases are added each week. In other words, this means that some 6 to 8% of the world population suffer from rare diseases: 470 million around the world and 500,000 in Switzerland.

The BLACKSWAN Foundation puts all donations towards pre-clinical and clinical research into rare diseases. A committee of recognised international experts is responsible for deciding which projects the foundation finances.

The mission

- To collect funds to finance research into rare diseases and specific pathologies
- To promote and fund therapeutic application of new scientific protocols in order to find effective cures
- To inform and make the public more aware of the problem of rare diseases

The fight against rare diseases merits a special effort to ensure they are no longer orphans: we are counting on your help.

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GEBERT RÜF STIFTUNG

The charter of Gebert Rüt Stiftung, founded in 1997, states the purpose as «promoting Switzerland as a place to live and do business». The foundation has an annual grant budget of around 10 million Swiss francs. The mission statement provides support for new approaches and selected junior scientists in the so-called valley of death. In line with the support criteria, a project must be impact-oriented and of a high quality if it is to be eligible. Gebert Rüt Stiftung is not an operating foundation that exclusively maintains its own projects, but is a grant-making foundation actively shaping and enabling. On the one hand, Gebert Rüt Stiftung supports externally proposed high-quality innovative projects which satisfy the support criteria especially closely. At the same time, it initiates and interlinks projects with the aim of continually developing new, time-limited areas of activity within the overall scheme of its grant-making activities.

Time-limited areas of activity

With its limited funds Gebert Rüt Stiftung seeks to create impetus by bundling its operations into areas of activity. It does not establish clearly drawn, consolidated programme lines, but periodically redefines its focal points. The fact that the areas of activity are time-limited means that capacity is repeatedly freed up for the development of new and bigger initiatives.

Current grant-making strategy

Gebert Rüt Stiftung's five active areas of activity place its programme focal points in the domains of scientific entrepreneurship (venture kick), the transformation of universities of applied science (BREF), biomedicine (Rare Diseases), grants for Eastern Europe (ASCN) and support for pilot activities (pilot projects).

Rare Diseases – New Approaches

The initiative «Rare Diseases – New Approaches» wants to improve the diagnosis and treatment of rare genetic diseases. The programme aims at bridging the worlds of basic and clinical research: projects with new approaches or technologies will be supported that focus on a clinical or diagnostic application. The project results should lead to a better understanding of the genetic, molecular and biochemical processes underlying these diseases and pave the way towards new diagnostics and new forms of treatment. The ideal project scenario would show concrete compounds and diagnostic tests from which patients suffering from a rare disease could benefit. The focus must be on innovation, feasibility and effectiveness, while attaining high scientific and technological standards. The call is aimed at researchers developing and implementing innovative approaches or technologies to address currently unresolved needs. The programme has been established in 2009 as a five-year area of activity.

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