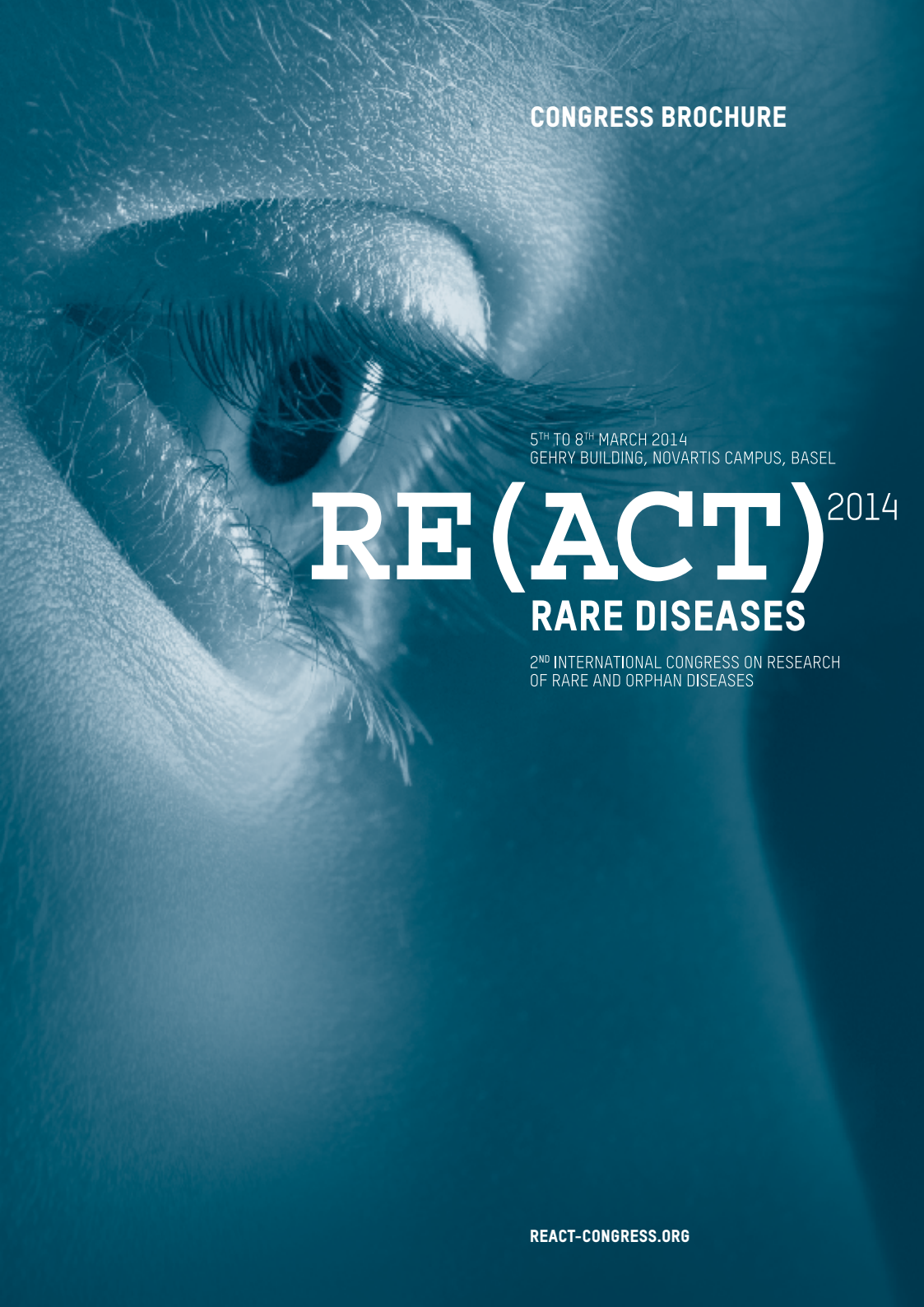


CONGRESS BROCHURE

5TH TO 8TH MARCH 2014
GEHRY BUILDING, NOVARTIS CAMPUS, BASEL

RE(ACT) 2014
RARE DISEASES

2ND INTERNATIONAL CONGRESS ON RESEARCH
OF RARE AND ORPHAN DISEASES

REACT-CONGRESS.ORG

CONTENTS

WELCOME MESSAGE

Dear Colleagues,

Welcome to the second "International Congress on Research of Rare and Orphan Diseases", RE(ACT) Congress 2014. 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 days we will discuss progress in research of rare diseases and in issues of translational medicine. We will define a collaborative agenda of patient organization representatives, clinicians and scientists from both academia and industry in order to improve therapy development for the benefit of patients. 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. To assure a continuous exchange we are happy to announce the launch of the online RE(ACT) Community (react-community.org). The RE(ACT) Community is a unique world-wide platform to collaborate on research projects, to identify and finance new research proposals and to optimize synergies between scientists and patients advocating together with policy makers and companies.

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
President and Founder
BLACKSWAN FOUNDATION

Pascale Vonmont
Deputy Director
GEBERT RÜF STIFTUNG

KEY FACTS & CONTACT

PROGRAM COMMITTEE AND SCIENTIFIC ADVISORY COMMITTEE

- **Prof. Dr. Susan Gasser**, Friedrich Miescher Institut, Switzerland
- **Dr. Emmanuelle Lecomte-Brisset**, Shire, Switzerland
- **Dr. Olivier Menzel**, BLACKSWAN Foundation, Switzerland
- **Dr. Michael Morris**, Synlab Lausanne, Switzerland
- **Prof. Dr. Jürg Schifferli**, University of Basel, Switzerland
- **Prof. Dr. Andrea Superti-Furga**, University of Lausanne, Switzerland
- **Prof. Dr. Joris Veltman**, Genomic Disorder Nijmegen, Netherlands
- **Dr. Pascale Vonmont**, Gebert Rüf Stiftung, Switzerland

CONGRESS INITIATORS

BLACKSWAN Foundation
Chemin de la Riaz 11, CH -1418 Vuarrens
+41 76 378 17 77; blackswanfoundation.ch

Gebert Rüf Stiftung
Bäumleingasse 22, CH - 4051 Basel
+41 61 270 88 22; grstiftung.ch

CONGRESS SECRETARIAT

Amiconi Consulting
Via Al Forte 10 CH-6900 Lugano
+41 91 921 38 12; amiconiconsulting.ch

EXHIBITION/SPONSORSHIP AND REGISTRATION

Stéphane Talboom
sponsorship@react-congress.org
contact@react-congress.org

CONTINUAL MEDICAL EDUCATION

The congress has been accredited by the Swiss Society of Medical Genetics for a maximum of 18 CME credits.

CONGRESS INTRODUCTION

In its first edition in 2012, the RE(ACT) Congress brought together almost 300 people to discuss research into rare diseases and the development of active substances to treat them. What made the congress unique was the interdisciplinary collaboration. Scientists from different disciplines – stem cell researchers, geneticists, biochemists, clinicians and pharmacists – exchanged information with patient organizations.

CONGRESS GOALS

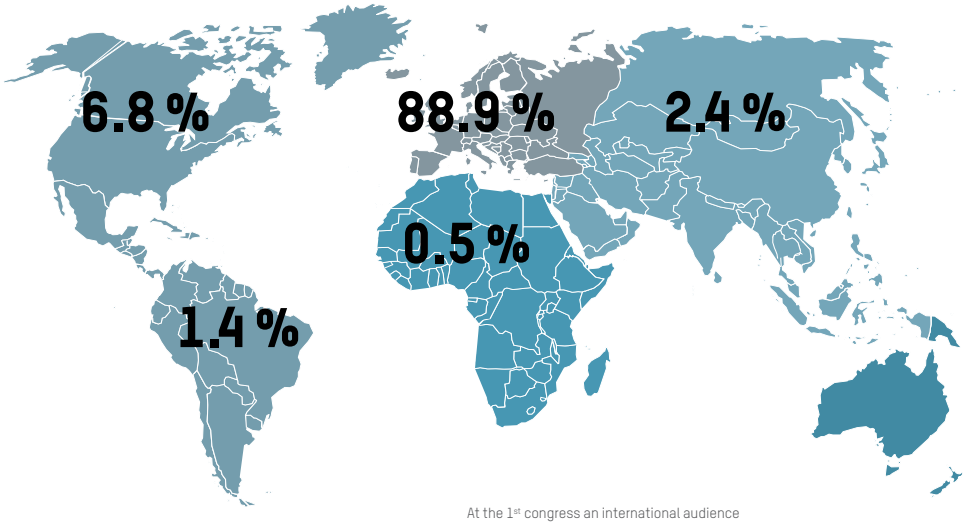
- promoting research on rare and orphan diseases among the general public, industry and policy makers
- bringing together researchers and their knowledge
- helping to understand other more common diseases
- encouraging clear insights positions identifiable from the scientific community in university and industry

MAIN TOPICS

- Stem Cell and Cell Therapy Approaches
- Mapping Diseases and Genome Instabilities
- Pathophysiology and Diagnostics
- Bringing Treatments to the Clinic
- Degenerative Disorders
- Patients and Research

SCIENTIFIC DISCIPLINES INVOLVED

Autoimmunity, biochemistry, cell biology, dermatology, endocrinology, gastroenterology, gene therapy, human genetics, hematology, infectious diseases, inflammation, molecular and cellular biology, neuroimmunology, oncology, orphan drugs, pathology, pharmacology, primary immune deficiency, rheumatology, transplantation, virology.



At the 1st congress an international audience of delegates from more than 30 countries were present.

"Congratulations for a very successful and useful conference! That was a challenge and it seems that you have succeeded. I am happy that EURORDIS could be by your side for this first."

Yann Le Cam, CEO of EURORDIS, Paris, France

"... it was a pleasure to partake in this fantastic meeting. Congratulations to you for putting together this event, and for your relentless efforts towards fostering research on rare diseases."

Professor Didier Trono, Professor and Dean, School of Life Sciences, Ecole Polytechnique Fédérale de Lausanne, Switzerland.

"It was a pleasure to have a taste of an interesting meeting with an original and worth developing format! "

Professor Alain Fischer, Director of the Pediatric Hematology and Immunology Department and Director of the Research Institute of Genetic Diseases (Imagine), Necker University Hospital, Paris, France

"It was such a pleasure to participate at the RE(ACT) Congress. You did a wonderful job and the meeting was a great success."

Dr Bernd Wollnik, E-RARE granted project coordinator; Center for Molecular Medicine Cologne; University Hospital of Cologne Department of Medicine, Germany

"Congratulations again for your wonderful meeting, one of the highest quality I've ever attended."

Professor Mehdi Tafti, Center for Integrative Genomics, University of Lausanne, Switzerland

RE(ACT) COMMUNITY

Research efforts on rare diseases are still scattered and very often implemented with little coordination between laboratories. This lack of coordination is particularly detrimental to a field where the resources are limited and the patient population is small. For this reason, we decided to create the RE(ACT) Community, a virtual platform for rare disease stakeholders that offers the opportunity to meet other researchers and find new collaborations, share scientific knowledge, learn from other experiences and support research projects through crowdfunding mechanisms and grants.

The RE(ACT) Initiative, which includes the congress and the community, wants to facilitate the cooperation in rare disease research worldwide and to contribute to an increased delivery in the market of new molecules and therapies for millions of patients.

OBJECTIVES

The RE(ACT) Community's ultimate goal is to accelerate the delivery of new molecules and therapies for rare and orphan diseases. To accomplish this final objective, the Community has put in place a multi-pronged strategy which includes the following specific objectives:

- Meeting other researchers to improve scientific collaboration;
- Intensifying communication among all stakeholders which are related to different extent to rare diseases such as: patient organizations, academic institutions, centres of expertise, health industry and policy makers;
- Sharing information and improve the access to scientific publications;
- Supporting the implementation of research projects through crowdfunding mechanisms;
- Increasing public awareness about rare diseases and the achievements and goals of research;
- Facilitating communication between scientists and patients;
- Identifying research proposals, provide grants, fellowships and awards;
- Advocating with policy makers and regulators.

react-community.org
#REACTCommunity

BASEL

THE CONGRESS CITY OF SHORT DISTANCES

Basel will astonish you: its central location, first-class transport connections and infrastructure as well as the compactness of the city make Basel one of the most important exhibition and congress cities in Europe. All this, combined with a huge range of leisure activities, attracts hundreds of thousands of guests every year to Art Basel, the world's largest art exhibition, or to Baselworld, the world's leading watch and jewellery show, and many other top events.

EVEN THE MIND NEEDS A REST SOMETIMES

Discovering Basel is a treat for the senses: all the world's cuisines are represented in the city, from the glittering gourmet restaurant to the takeaway around the corner. The city centre is also a gigantic shopping paradise and includes the traditional daily market in front of the City Hall. And the colourful, vibrant nightlife has something to offer for everyone.

WELCOME TO OUR NEIGHBOURHOOD

Let yourself be seduced away from the daily grind by the culinary pleasures and numerous leisure activities to be found at picturesque locations in the lovely surrounding countryside of Basel. The cantons of Baselland and Solothurn, the Alsace and the Black Forest together form a vast recreation area – you can quickly be in the Roman town of Augusta Raurica, at a feast in Alsace or in one of the famous wine cellars of Baden.

EVEN IN THE FUTURE, YOU CAN ENJOY THE PAST

Experience a journey through history in the Old Town of Basel: as one of the best maintained and most beautiful Old Towns of Europe, it is much more than a pretty backdrop. It is the heart of the city, where history can be sensed all around. Wander between imposing medieval buildings made of typical Basel red sandstone and past elegant patrician houses from the Baroque period.

WHERE ARCHITECTURE HAS FOUND A STRONGHOLD

Draw inspiration from a unique mix of modern and historical architecture. Many contemporary buildings by world-renowned architects such as Herzog & de Meuron, Mario Botta, Renzo Piano, Frank O. Gehry, Richard Meier, Burckhardt+Partner and others, prove that the tradition-conscious city also loves the new, and present an interplay between the exciting image of a tolerant international metropolis and the venerable Old Town.

THE ART OF SO MUCH ART

It is almost unbelievable how much art you can enjoy in Basel. You will come across it while wandering through the city as well as in almost forty museums. All tastes are catered for – from the world-renowned Fondation Beyeler to the Museum Tinguely, the Kunstmuseum Basel (Museum of Fine Arts), the Schau-lager and the Doll House Museum. The sensational three-section theatre is also known well beyond the city limits.

IN A PARTY MOOD BY NATURE

Celebrate festivals with the people of Basel as they happen: join the life-loving and enthusiastic residents as they celebrate carnival like nowhere else! It may last for only three days, but the city prepares for it 362 days of the year. Besides this, the keenly loved FCBasel football club or the Swiss Indoors Basel as one of the most important indoor tennis tournaments in the world and many festivals and occasions always give good reason for letting enthusiasm overflow. There is always something going on in Basel!

SIGHTSEEING IN BASEL

You don't need to search for the sights in Basel. As you wander through the city, you will find them with every step you take. Whether you are in the picturesque Old Town or in the midst of world class architecture – the city offers something for every taste. In hardly any other city do 15th century buildings complement internationally renowned modern architecture to create such a dynamic yet harmonious cityscape. The narrow alleyways and hidden squares with over 180 fountains as well as the many century-old buildings and eye-catching sights such as the City Hall or the Cathedral combine to make Basel's Old Town one of the most beautiful and intact of its kind in Europe.

CATHEDRAL AND PFALZ

Basel's landmark must be the Cathedral. This former Episcopal Church was built between the 12th and the 15th century in romanesque and gothic style. Today, the square around the church is a meeting place and is often used for events. From the observation platform, known as the "Pfalz", you can enjoy a spectacular view overlooking the Rhine, the Kleinbasel district, the Black Forest and the Vosges.

CITY HALL

The City Hall is the seat of the Basel government and its parliament. In the midst of the Old Town, it is particularly eye-catching with its red facade, the characteristic tower and playful frescoes. The oldest part of this imposing structure was built in the years between 1504 and 1514. In the centre court, you will find the statue of Munatius Plancus, the founder of the first Roman settlement in the Basel region. Basel Tourism offers regular tours through this historical building.

FERRIES

A trip on one of the four ferries across the Rhine is not to be missed. Traditionally one calls the "Fährimaa" with a bell from the landingstage. Experience how time seems to stand still during the short crossing. Without sound, driven solely by the current, the ferries will take you to the other side of the river throughout the whole year.

TINGUELY FOUNTAIN

In summer, it cheerfully shovels water, in winter, an enchanting ice sculpture: the unique fountain designed by the Swiss artist Jean Tinguely attracts tourists as well as passers-by, strollers, and Basel inhabitants wishing to enjoy their lunch break outside. With its central location in the city centre, it is the best starting point for a tour of the outdoor works of art of Basel.

ARTS & CULTURE IN BASEL

Basel is widely acknowledged as Switzerland's city of culture and for good reason, with visitors confronted by art at every turn - whether simply wandering through the streets of the Old Town or visiting one of the city's nearly forty museums. The sheer number of museums alone indicates that Basel is not a city that lovers of art and culture can explore in a day. With their themed collections, the museums of Basel have something for every taste and many have reputations that stretch far beyond the Swiss border. And then there are the countless galleries scattered liberally throughout the city. There are also many high-class cultural events that take place throughout the year, underlining Basel's reputation as a cultural hot-spot. Of course we should not forget that the city also has a lively theatre and music scene.

FONDATION BEYELER

With the construction of the museum building, designed by Renzo Piano, in 1997, the Beyeler collection has been made permanently accessible to the public. Around 230

works of art reflect the views of art collectors Ernst and Hildy Beyeler on the art of the 20th century.

→ www.fondationbeyeler.ch

KUNSTMUSEUM BASEL

The Kunstmuseum Basel is the oldest publicly accessible art collection in the world. The focus of the museum is on paintings and graphic art by artists from the Upper Rhine region from 1400 to 1600 and the art of the 19th to 21st century.

→ www.kunstmuseumbasel.ch

THEATER BASEL

The largest mixed-programme theatre company in Switzerland offers a broadly diverse repertoire, including dance, opera and theatre. The conferring of the award "Opera House of the Year" for both 2009 and 2010 shows the high quality of the productions of this theatre.

→ www.theaterbasel.ch

CLASSICAL MUSIC

You may have seen one of Basel's famous orchestras in concert in your home country or on tour either elsewhere in Switzerland or abroad. The internationally-renowned Basel Chamber Orchestra and Basel Symphony Orchestra perform classical works at the highest level.

→ www.kammerorchesterbasel.ch
→ www.sinfonieorchesterbasel.ch

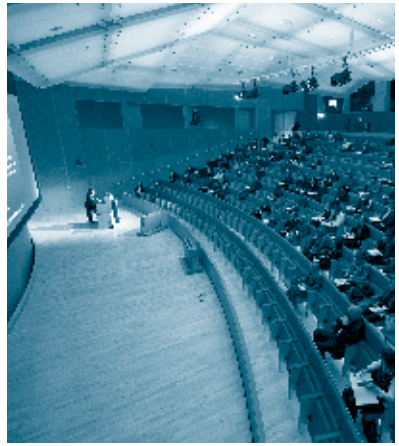
CONGRESS VENUE

THE GEHRY BUILDING – NOVARTIS CAMPUS

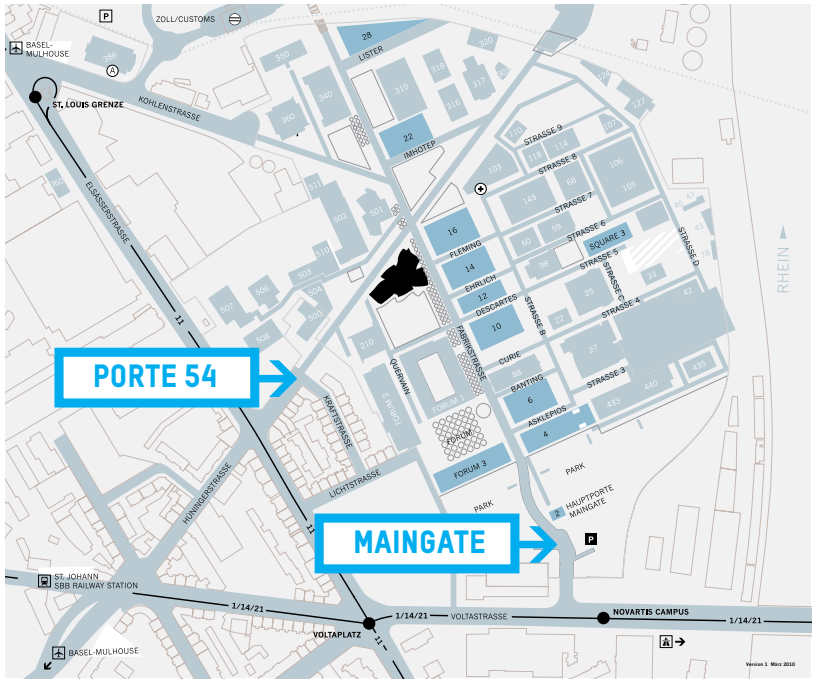
The Novartis building by Gehry Partners is part of the Masterplan for Novartis, designed by Vittorio Magnano Lampugnani, that will transform the St. Johann site, its headquarters in Basel, from an industrial complex to a campus of innovation, knowledge and encounter.

The new campus will offer Novartis employees and visitors an environment for intensive levels of communication and work, which is ultra-modern, very functional, and aesthetically pleasing. The concept of openness, spaces flowing together, played a major factor in the design. The public areas, a restaurant and café, are located on the ground floor, which opens to the Campus Green. The Human Resources Departments occupy the five upper levels with a number of small public areas to encourage people to meet spontaneously for coffee or to hold informal meetings. A central atrium unites the building sections and reinforces visibility by allowing natural light to flow from the roof through all office floors and down to the underground levels where the auditorium lobby is located. The concept of openness and transparency is reinforced by the use of glass in the building's exterior design. Below ground is the Learning Factory for all campus employees, and a 600-seat auditorium with a glass ceiling and skylight connecting it to the Campus Green above. The auditorium can be divided into two separate rooms to hold simultaneous functions. The large sail-like shades inside reduce solar gain and glare and operable windows and large sliding glass doors on the ground floor encourage natural ventilation on warm summer days.

The development of the architecture and the materials used exemplifies Novartis's commitment to the environment. To reduce direct solar heat gain the glass facades are coated with ceramic frits and the glass roof panels contain photovoltaic cells that generate the energy necessary to power artificial lighting for the building.



THE ENTRANCE OF THE CAMPUS IS ORGANIZED AS FOLLOWS:



FOR CONGRESS DELEGATES:

→ **Wednesday, March 5**, 2014, 12 am to 10 pm
PORTE 54 / Hüningerstrasse, Tramstation Hüningerstrasse

→ **Thursday, March 6**, 2014, 8 am to 8 pm
PORTE 54 / Hüningerstrasse, Tramstation Hüningerstrasse

→ **Friday, March 7**, 2014, 8 am to 8 pm
PORTE 54 / Hüningerstrasse, Tramstation Hüningerstrasse

→ **Saturday, March 8**, 2014, 8 am
Novartis MAINGATE, Tramstation Novartis Campus

FOR PARTICIPANTS OF THE PUBLIC SESSIONS:

→ **Wednesday, March 5**, 2014, 17 am
Novartis MAINGATE, Tramstation Novartis Campus

→ **Saturday, March 8**, 2014, 8 am
Novartis MAINGATE, Tramstation Novartis Campus

CONGRESS PROGRAM

SCHEDULE AT A GLANCE

WEDNESDAY, MARCH 5TH, 2014

12:00		Registration opens
14:00	SESSION A:	STEM CELL AND CELL THERAPY APPROACHES
17:00		POSTER SESSION A Gehry Building, level -2
18:00		Public OPENING CEREMONY
20:00		WELCOME RECEPTION

THURSDAY, MARCH 6TH, 2014

08:45	SESSION B:	MAPPING DISEASES AND GENOME INSTABILITIES
12:00		Lunch
12:00		LUNCH-SYMPOSIUM: SWISS RESEARCH SHOWCASE
13:00		POSTER SESSION B + C Gehry Building, level -2
14:00	SESSION C:	PATHOPHYSIOLOGY AND DIAGNOSTICS
17:15		POSTER SESSION B + C Gehry Building, level -2

FRIDAY, MARCH 7TH, 2014

08:45	SESSION D:	BRINGING TREATMENTS TO THE CLINIC
12:00		Lunch
12:00		LUNCH-SYMPOSIUM: NEUROCOGNITIVE DISORDERS
13:00		POSTER SESSION D + E + F Gehry Building, level -3
14:00	SESSION E:	DEGENERATIVE DISORDERS
17:00		POSTER SESSION D + E + F Gehry Building, level -3
18:00		Delegates' Dinner with Apéro (registration requested)

SATURDAY, MARCH 8TH, 2014

09:00	SESSION F:	PATIENTS AND RESEARCH
12:00		End of Congress

CONGRESS PROGRAM

WEDNESDAY, MARCH 5TH, 2014

12:00 Registration opens

14:00 to 17:00 **AFTERNOON SESSION A:**

Stem Cell and Cell Therapy Approaches

CHAIRWOMAN: DR. MARISA JACONI [CH]

14:00 • PROF. GIULIO COSSU [UK]; BIOGRAPHY PAGE 36; ABSTRACT PAGE 77
CELL THERAPY FOR MUSCULAR DYSTROPHIES

14:30 • PROF. ALAN TYNDALL [CH]; BIOGRAPHY PAGE 70; ABSTRACT PAGE 99
STEM CELL THERAPIES OF AUTOIMMUNE DISEASES

15:00 • PROF. MARC PESCHANSKI [FR]; BIOGRAPHY PAGE 54; ABSTRACT PAGE 89
HARNESSING PLURIPOTENT STEM CELLS DERIVATIVES TO DECIPHER MECHANISMS AND IDENTIFY TREATMENTS FOR MONOGENIC DISEASES

15:30 Coffee Break

16:00 • PROF. YANN BARRANDON [CH]; BIOGRAPHY PAGE 32; ABSTRACT PAGE 75
A CLONAL STRATEGY FOR SAFE EX VIVO GENE THERAPY OF EPIDERMIS

16:30 • Dr. SARAH DECEMBRINI (ABSTRACT NO 20); PAGE 104
DERIVATION OF TRACEABLE AND TRANSPLANTABLE PHOTORECEPTORS FROM MOUSE EMBRYONIC STEM CELLS

17:00 to 18:00 **POSTER SESSION A**

18:00 to 20:00

Public Opening Ceremony

MODERATION: PROF. SUSAN GASSER [CH]

18:00 **WELCOME**

- DR. JÖRG REINHARDT, NOVARTIS, CHAIRMEN OF THE BOARD OF DIRECTORS

18:15

- DR DAVID M. LEE BIOGRAPHY PAGE 49

NOVARTIS INSTITUTES FOR BIOMEDICAL RESEARCH, CH

RARE DISEASE RESEARCH: THE PROMISES AND THE CHALLENGES

18:35

- YANN LE CAM, EURORDIS [FR]; BIOGRAPHY PAGE 48

EUROPEAN RARE DISEASE RESEARCH AGENDA: THE PATIENTS' PERSPECTIVE

19:00

- PROF. STEPHEN C. GROFT, NIH-ORDR [USA]; BIOGRAPHY PAGE 42

GLOBAL RESEARCH COLLABORATIONS: ARE WE REACHING OUR GOALS FOR RARE DISEASES?

19:30 **ROUNDTABLE WITH THE 3 KEYNOTE SPEAKERS**

MODERATION: PROF. SUSAN GASSER [CH]

20:00 **WELCOME RECEPTION**

THURSDAY, MARCH 6TH, 2014

08:45 to 12:00 **MORNING SESSION B:**

Mapping Diseases and Genome Instabilities

CHAIRMAN: PROF. STYLIANOS ANTONARAKIS [CH]

08:45

- PROF. THADDEUS DRYJA [USA]; BIOGRAPHY PAGE 37; ABSTRACT PAGE 78

SPECIAL CONSIDERATIONS FOR PHASE I TRIALS OF GENE THERAPIES FOR RETINITIS PIGMENTOSA AND ALLIED RETINAL DEGENERATIONS

09:15

- PROF. NICHOLAS KATSANIS [USA]; BIOGRAPHY PAGE 46; ABSTRACT PAGE 84

MODELLING THE MORBID PEDIATRIC GENOME

09:45

- PROF. STANISLAS LYONNET [FR]; BIOGRAPHY PAGE 52; ABSTRACT PAGE 87

NON-CODING GENOME ALTERATIONS IN RARE DEVELOPMENT ANOMALIES

10:15 Coffee Break

10:45

- PROF. ALEXANDRE REYMOND [CH]; BIOGRAPHY PAGE 60; ABSTRACT PAGE 92

CHROMATIN LOOPS AND CNVS: THE COMPLEX SPATIAL ORGANIZATION OF THE 16P11.2 LOCUS

11:15

- DR. DAVIDE GABELLINI [IT]; BIOGRAPHY PAGE 39; ABSTRACT PAGE 80

FSHD MUSCULAR DYSTROPHY PROVIDES A MOLECULAR UNDERSTANDING OF THE REPETITIVE (EPI)GENOME

11:45

- Dr. TERRENCE MEEHAN [ABSTRACT NO32] PAGE 110

INFORMING RARE DISEASE MECHANISMS: INFORMATICS FOR THE INTERNATIONAL MOUSE PHENOTYPING CONSORTIUM

12:00 to 13:00 Lunch

12:00 to 14:00 **LUNCH-SYMPOSIUM:** SWISS RESEARCH SHOWCASE → PAGE 26

13:00 to 14:00 **POSTER SESSION B + C**

14:00 to 17:15 **AFTERNOON SESSION C:**

Pathophysiology and Diagnostics

CHAIRMAN: DR. MIKE MORRIS [CH]

14:00
- PROF. DENNIS LO [HK]; BIOGRAPHY PAGE 51; ABSTRACT PAGE 86
  NONINVASIVE PRENATAL TESTING USING CELL-FREE FETAL DNA IN MATERNAL PLASMA

14:30
- PROF. CÉCILE JANSSENS [USA]; BIOGRAPHY PAGE 45; ABSTRACT PAGE 83
  HOW PREDICTIVE IS OUR DNA?

15:00
- PROF. EPHRAT LEVY-LAHAD [IL]; BIOGRAPHY PAGE 50; ABSTRACT PAGE 85
  FROM MUTATION TO PATHOGENESIS IN RARE DISEASES

15:30 Coffee Break

16:00
- DR. ANNE PUEL [FR]; BIOGRAPHY PAGE 56; ABSTRACT PAGE 90
  INBORN ERRORS OF HUMAN IL-17 IMMUNITY UNDERLIE CHRONIC MUCOCUTANEOUS CANDIDIASIS

16:30
- PROF. ORLY ELPELEG [IL]; BIOGRAPHY PAGE 38; ABSTRACT PAGE 79
  WHOLE EXOME SEQUENCING IN RARE DISEASES

17:00
- DR. FRANCISCA MARÍA SÁNCHEZ-JIMÉNEZ [ABSTRACT NO34]; PAGE 116
  SEARCHING FOR BIOMEDICAL RELATIONSHIPS AMONG GENES AND DISEASES: A GREAT ALLY FOR RARE DISEASES

17:15 to 19:00 **POSTER SESSION B + C**

FRIDAY, MARCH 7TH, 2014

08:45 to 12:00 **MORNING SESSION D:**

Bringing Treatments to the Clinic

CHAIRMAN: DR. JORDI SURRALLÉS [ES]

08:45
- PROF. MARC TARDIEU [FR]; BIOGRAPHY PAGE 68; ABSTRACT PAGE 98
  DEVELOPMENT OF AN INTRA-CEREBRAL GENE THERAPY TRIAL IN SANFILIPPO DISEASE TYPE A

09:15
- PROF. MICHAEL SINNREICH [CH]; BIOGRAPHY PAGE 64; ABSTRACT PAGE 94
  NOVEL TREATMENT STRATEGIES FOR MUSCULAR DYSTROPHY

09:45
- PROF. LAKSHMINARAYAN RANGANATH [UK]; BIOGRAPHY PAGE 57; ABSTRACT PAGE 91
  ADVANCES IN THE TREATMENT OF ALKAPTONURIA

10:15 Coffee Break

10:45
- PROF. COLIN MCKERLIE [CAN]; BIOGRAPHY PAGE 53; ABSTRACT PAGE 88
  SYSTEMATIC LARGE-SCALE GENE FUNCTION ANALYSIS OF THE MOUSE GENOME

11:15
- DR. CORINNE KOSTIC [ABSTRACT NO29]; PAGE 127
  OPTIMIZATION OF RPE65-GENE TRANSFER USING A LENTIVIRAL VECTOR FOR LCA TREATMENT

11:30
- DR. MATTHIAS SCHÄFER [ABSTRACT NO35]; PAGE 129
  ACTIVATION OF NRF2 IN KERATINOCYTES CAUSES CHLORACNE (MADISH)-LIKE SKIN DISEASE IN MICE

11:45
- DR. JORDI SURRALLÉS [ABSTRACT NO21]; PAGE 125
  FANCONI ANEMIA: FROM GENE DISCOVERY TO GENE THERAPY

12:00 to 13:00 Lunch

12:00 to 14:00 **LUNCH-SYMPOSIUM:** NEUROCOGNITIVE DISORDERS → PAGE 28

13:00 to 14:00 **POSTER SESSION D + E + F**

14:00 to 17:00 **AFTERNOON SESSION E:**

Degenerative Disorders

CHAIRMAN: PROF. DENIS MONARD [CH]

14:00
- PROF. JOSE-ALAIN SAHEL [FR]; BIOGRAPHY PAGE 63; ABSTRACT PAGE 93
  VISION RESTORATION STRATEGIES IN BLINDING RETINAL DYSTROPHIES

14:30
- PROF. ROBERT D. GOLDMAN [USA]; BIOGRAPHY PAGE 40; ABSTRACT PAGE 81
  ALTERED INTERMEDIATE FILAMENT NETWORKS ARE THE HALLMARKS OF MANY RARE DISEASES

15:00
- PROF. COLIN L. STEWART [SG]; BIOGRAPHY PAGE 66; ABSTRACT PAGE 96
  ANALYZING PROGERIA TO PROVIDE INSIGHTS INTO THE MECHANISMS OF AGEING

15:30 Coffee Break

16:00
- PROF. GISELE BONNE [FR]; BIOGRAPHY PAGE 34; ABSTRACT PAGE 76
  LAMINOPATHIES OF THE STRIATED MUSCLE: FROM GENE DEFECTS TO WARDS PATHOPHYSIOLOGICAL MECHANISMS

16:30
- DR. CATERINA GIACOMINI [ABSTRACT NO16]; PAGE 135
  ABNORMAL LAMIN B1 LEVELS AFFECT NEURONAL VIABILITY AND DIFFERENTIATION

16.45
- DR. SIMON WADDINGTON [ABSTRACT NO27]; PAGE 138
  PERINATAL GENE THERAPY RESCUES ACUTE NEONATAL LETHAL NEURONOPATHIC GAUCHER DISEASE IN MICE

17:00 to 19:00 **POSTER SESSION D + E + F**

18:00 **DELEGATES' DINNER WITH APÉRO**

SATURDAY, MARCH 8TH, 2014

09:00 to 12:00 **MORNING SESSION F:**

Patients and Research

CHAIRMAN: DR. NICK SIREAU [UK]

09:00
- KAREN AIACH [FR]; BIOGRAPHY PAGE 30; ABSTRACT PAGE 74
  LESSONS LEARNED FROM A PIONEERING PHASE I/II GENE THERAPY TRIAL IN SANFILIPPO SYNDROME

09:30
- DR. MARTINE ZIMMERMANN [CH]; BIOGRAPHY PAGE 72; ABSTRACT PAGE 100
  REGULATORY FRAMEWORKS AND INCENTIVES FOR DEVELOPMENT OF ORPHAN MEDICINAL PRODUCTS

10:00
- DR. NICK SIREAU [UK]; BIOGRAPHY PAGE 65; ABSTRACT PAGE 95
  CURING BLACK BONE DISEASE: LESSONS FROM A MAJOR CLINICAL TRIAL

10:30 Coffee Break

11:00
- PROF. PHILIPPE GORRY [FR]; BIOGRAPHY PAGE 41; ABSTRACT PAGE 82
  ROLE OF ACADEMIC RESEARCH IN THE DISCOVERY OF ORPHAN DRUGS

11:30
- PROF. MARSHALL SUMMAR [USA]; BIOGRAPHY PAGE 67; ABSTRACT PAGE 97
  RARE DISEASE REGISTRIES SUCCESFUL MODELS AND LESSONS

12:00 End of Congress

LUNCH-SYMPOSIUM

THURSDAY, MARCH 6TH, 12:00 TO 14:00

Swiss Research Showcase

This lunch event is initiated and organized by two Swiss Rare Diseases Research Programs: radiz – Rare Disease Initiative Zurich, a clinical research priority program of the University of Zurich and "Rare Diseases – New Approaches" an initiative of Gebert Rüf Stiftung.

PROGRAM

Learn about the research programs by attending the presentation of short pitches followed by a networking lunch.

- PROF. DR. MATTHIAS BAUMGARTNER BIOGRAPHY PAGE 31
  METHYLMALONIC ACIDURIA – FROM PATHOPHYSIOLOGY TOWARDS NOVEL THERAPIES
- PD DR. THORSTEN HORNEMANN BIOGRAPHY PAGE 43
  ATYPICAL SPHINGOLIPIDS AS THERAPEUTIC TARGETS IN RARE DISEASES
- PROF. DR. JEFFREY HUBBELL BIOGRAPHY PAGE 44
  TOLERANCE INDUCTION TO PROTEIN DRUGS THROUGH ERYTHROCYTE BINDING
- PROF. DR. BARBARA PLECKO & PROF. DR. ANITA RAUCH BIOGRAPHY PAGE 55/58
  A COMBINED METABOLIC-GENETIC APPROACH TO UNRAVEL CAUSES OF EPILEPTIC ENCEPHALOPATHIES OF CHILDHOOD
- PD DR. JANINE REICHENBACH BIOGRAPHY PAGE 59
  ROLE OF MACROAUTOPHAGY IN CHRONIC GRANULOMATOURS DISEASE AND CORRECTION OFT HE DEFECT
- PROF. DR. BOTOND ROSKA BIOGRAPHY PAGE 61
  OPTOGENIC VISION RESTORATION
- PROF. DR. DIDIER TRONO BIOGRAPHY PAGE 69
  DISEASES OF IMPRINTING
- PROF. DR. GISOU VAN DER GOOT BIOGRAPHY PAGE 71
  TOWARDS PREVENTING NODULE FORMATION IN HYALINE FIBORMATOSIS PATIENTS

RADIZ

radiz – the Rare Disease Initiative Zurich is a clinical research priority program of the University of Zurich. radiz is a joint effort of the University Children's Hospital Zurich, the University of Zurich, and the University Hospital Zurich in the fight against rare diseases. By building a strong interdisciplinary network of researchers and clinicians focused on rare diseases in Zurich, radiz aims to bridge the gap between basic and clinical research in rare diseases. Several translational rare disease research projects are being funded by radiz. Continuing education is being offered in order to raise awareness for rare diseases among physicians, researchers, and the general public.

radiz - Rare Disease Initiative Zürich
Clinical Research Priority Program for Rare Diseases University of Zurich

Universität Zürich[UZH]
Zentrum für Stiftungsrecht

RARE DISEASES – NEW APPROACHES

Gebert Rüf Stiftung is a private Swiss science foundation, active in various fields of innovation. Since 2009 it runs the program «Rare Diseases – New Approaches» based on annual calls. The program aims at developing and implementing innovative technologies or approaches in the diagnosis and treatment of rare diseases. 2 million Swiss Francs are invested annually; 26 projects out of 338 applications have been accepted with a budget totalling CHF 10.3 million.

GEBERT RÜF STIFTUNG
WISSENSCHAFT.BEWEGEN

PROGRAMME
RARE DISEASES
NEW APPROACHES

LUNCH-SYMPOSIUM

FRIDAY, MARCH 7TH, 12:00 TO 14:00

Neurocognitive Disorders

Many disorders affecting higher brain functions show a remarkable overlap both at a clinical as well as a pathophysiological level. Conversely, the identical disorder may show a high variability between different patients. Since recently, progress in genetics is contributing significantly to our understanding of what causes variation in neurocognitive disease. This workshop will highlight some of the insights gained on the genetics and pathophysiology of selected neurodevelopmental and neurocognitive disorders. The event is initiated and organized by NPSuisse, the Swiss Association for Niemann-Pick Diseases.

PROGRAM

- CHRISTOPH POINCILIT / HEIKO RUNZ: **INTRODUCTION**
- NICOLAS CHARLET-BERGUERAND BIOGRAPHY PAGE 33
  RNA AND PROTEIN GAIN OF FUNCTION IN FRAGILE X TREMOR ATAXIA SYNDROME (FXTAS)
- SVEN CICHON BIOGRAPHY PAGE 35
  COMMON AND RARE GENETIC RISK FACTORS IN NEUROPSYCHIATRIC DISORDERS
- MICHEL KOENIG BIOGRAPHY PAGE 47
  ATAXIA BY PARTIAL LOSS OF FUNCTION: A COMMON THEME
- HEIKO RUNZ BIOGRAPHY PAGE 62
  GENETIC AND PHENOTYPIC COMPLEXITIES IN THE RARE MENDELIAN DISORDER NIEMANN-PICK TYPE C (NP-C)

NPSUISSE (www.npsuisse.ch) is the Association of Niemann-Pick disease (NPD) families in Switzerland, is managed by parents, relatives and friends of patients with NPD types A,B or C. NPSuisse aims to inform and support researchers interested in NPD and similar disorders. The association has initiated the Loire Valley Meeting on NP-C as a unique forum for therapy-related NP-C research and participates in the International Niemann Pick Disease Alliance (INPDA).

Niemann-Pick type C disease (NP-C) is a rare, progressive lysosomal lipid storage disorder affecting the brain and visceral organs. Thanks to fundamental research, knowledge on this disease has improved considerably during the recent years, but development of curative therapies remain a challenge (www.inpda.org).

SPONSOR

Actelion Pharmaceuticals Inc. (Basel)

SPEAKERS' BIOGRAPHIES

Disclaimer: The Speakers' Biographies are printed as received by the authors.

Karen Aiach

Karen Aiach is founding president and CEO of LYSOGENE a clinical stage biotechnology company specialized in intracerebral gene delivery for the treatment of neurological diseases. In less than five years, Karen brought LYSOGENE's first product SAF-301 into the clinic. SAF-301 is a gene therapy product aiming at treating a fatal lysosomal storage disease known as Mucopolysaccharidosis type 3 or Sanfilippo Syndrome. Before creating LYSOGENE, Karen's entrepreneurial experience already included successfully founding and running a business consultancy specialized in the financial industry. Prior to that, Karen was a manager at Arthur Andersen where she began her carrier. At Andersen, she specialized in international M&A related transaction services for major tier one clients. From 2008 to 2009, Karen served as a Member of the Pediatric Committee of the European Medicine Agency as a patient representative. In 2008, she served on the Ethical Review Board CCPPRB IDF 8 – Hôpital Ambroise Paré (Boulogne-Billancourt, France), AP-HP Assistance Publique – Hôpitaux de Paris. Karen has also been involved with several not-for-profit organizations engaged in advocacy and research in the field of rare diseases such as Alliance SANFILIPPO and EURORDIS, where she served on Board as Treasurer from 2010 to 2011. Karen received her M.S. ("Grande Ecole") and MBA from ESSEC, France.

PROGRAM PAGE 25; ABSTRACT PAGE 74

Matthias R. Baumgartner

Prof. Dr. med. Matthias R. Baumgartner studied Medicine at the University of Basel, Switzerland, where he earned his degree as a medical doctor in 1992. He then went on to do a postgraduate course in experimental medicine and biology at the University of Zurich followed by laboratory work at the Biocentre of the University of Basel. After completing his residency in pediatrics at the University Children's Hospital Basel and at Hôpital Necker – Enfants Malades in Paris, Prof. Baumgartner continued his training in the United States, where he worked as postdoctoral und clinical fellow at the Mc Kusick-Nathans Institute of Genetic Medicine at Johns Hopkins University, Baltimore, from 1999 – 2001. He returned to Basel to lead the Metabolic Unit at the University Children's Hospital. 2 years later Prof. Baumgartner joined the Division of Metabolism & Molecular Pediatrics at the University Children's Hospital in Zurich. After his habilitation in 2005 he was elected as professor for metabolic diseases at the University of Zurich in 2008. Prof. Baumgartner is head of the Division for Metabolic Diseases und Medical Director of the Swiss Newborn Screening Program at the Kinderspital Zürich. Since 2012 he leads the clinical research priority program "Rare Disease Initiative Zurich – radiz" at the University of Zurich.

PROGRAM PAGE 26

Yann Barrandon

Yann Barrandon, MD-PhD, is joint professor in Stem Cell Dynamics at the EPFL and at the Lausanne University (Unil), and head of the Department of Experimental Surgery at the CHUV since 2002. He has made major contributions in basic epithelial stem cell biology and in stem cell therapy. YB is a member of the EMBO and the Academia Europaea. He is also a member of the EPFL research committee, EPFL Ethical committee and the Canton de Vaud Ethical committee. He was elected twice best teacher in Life Sciences at EPFL. In 2011, he co-founded gymetrics SA. Since 2012, he is "Initiative director" for the doctoral training cooperation initiative signed between the EPFL and AStar Singapore.

PROGRAM PAGE 19; ABSTRACT PAGE 75

Nicolas Charlet-Berguerand

Nicolas Charlet-Berguerand, PhD (IGBMC Strasbourg, France). Since 2007, Dr. Charlet-Berguerand heads an independent research group at IGBMC Strasbourg. Followig a PhD at University of Paris on RNA metabolism in cancer, his current research adresses two distinct areas: First, studying the biogenesis and roles of non-coding RNAs and RNA binding proteins and their implications in human genetic diseases. And second, how expanded non-coding RNA repeats cause RNA gain-of-function diseases such as Fragile X-associated tremor/ataxia syndrome (FXTAS), myotonic dystrophies or spinocerebellar ataxias. Dr. Charlet-Bergerand's goal is to elucidate the molecular causes of these diseases and to identify drugs able to restore a normal function in patient models.

PROGRAM PAGE 28

Gisèle Bonne

Gisèle Bonne, PhD. Team leader at Research Center for Myology, Institut de Myologie, Université Pierre et Marie Curie, Inserm, CNRS, Paris, France. Gisèle Bonne research interest focuses on the analyses of skeletal and cardiac striated muscles in normal and pathologic conditions. She performed PhD thesis (1990 – 1994) on the human cytochrome C oxidase complex during development and in mitochondrial myopathies. To complete her training in genetics, she went to Ketty Schwartz lab for my post-doctoral training where she identified the first mutation in the MYBPC3 gene encoding the cardiac myosin binding protein C, responsible to familial hypertrophic cardiomyopathy (1995). Since 1996, date at which she obtained a position at Inserm as senior researcher, she conducted her research program on the genetics and pathophysiology of Emery-Dreifuss muscular dystrophy (EDMD). She identified the first mutation of LMNA gene encoding Lamins A/C (1999). Mutations of this gene have been since linked to wide spectrum of disorders, the Laminopathies. Her research program has evolved with time and results towards genetics and pathophysiology of Laminopathies and their related disorders and to reach now the genetics and physiopathology of several neuromuscular disorders, as she is now leading a team of 20 persons working not only on EDMD, but also collagen VI related myopathies at the Myology Institute (Paris, France). The field of laminopathies has grown over the years, and is now a quite competitive and simulating research area. Her team has created 2 knock-in mouse models reproducing LMNA mutations identified in patients, models that mimics quite well some of the human disease features and thus represents unique tools to test therapeutic strategies. Gisèle Bonne is vice-chair of the French Society of Myology, member of the European NeuroMuscular Center (ENMC) research committee, and of the World Muscle Society (WMS) executive board.

PROGRAM PAGE 24; ABSTRACT PAGE 76

Sven Cichon

Sven Cichon, PhD (University of Basel, Switzerland). In 2013, Dr. Cichon was appointed Director of the Division of Medical Genetics at Basel University. After a PhD and postdoc on CNS-receptor/transporter genes and their impact on neuropsychiatric disorders at the Institute of Human Genetics in Bonn, Dr. Cichon conducted research at Millennium Pharmaceuticals Inc. (Cambridge, USA) and University of Antwerp (Belgium). He returned to Bonn in 2004 as Head of Molecular Genetics at the Life&Brain centre of excellence in translational biomedicine and a group leader for Genomic Imaging at Research Center Juelich and University of Bonn. His ongoing research aims to identify genetic factors influencing complex neuropsychiatric disorders as well as structural and functional variability of the human brain.

PROGRAM PAGE 28

Giulio Cossu

Professor of Regenerative Medicine, University of Manchester.
2012 – 2013:
Professor of Human Stem Cell Biology, University College London.
2009 – 2011:
Director, Division of Regenerative Medicine, San Raffaele Hospital, Milan
2005 – 2011:
Professor of Histology and Embryology, University of Milan
2000 – 2001:
Director, Stem Cell Research Institute, San Raffaele Hospital, Milan.
1994 – 2005:
Professor of Histology and Embryology, University of Rome Sapienza
1993 – 1994:
Visiting Professor, Dept. of Molecular Biology, Istitut Pasteur, Paris
1986 – 1993:
Associate Professor of Histology, University of Rome Sapienza
1983 – 1986:
Researcher, Institute Histology, University of Rome *La Sapienza*
1980 – 1983:
USPHS Fogarty Fellow Wistar Institute, University of Pennsylvania
1978 – 1980:
CNR Fellow, Institute Histology, University of Rome *La Sapienza*

PROGRAM PAGE 19; ABSTRACT PAGE 77

Thaddeus (Ted) Dryja

Thaddeus (Ted) Dryja earned an MD degree from Yale University School of Medicine (1976) and subsequently did an ophthalmology residency at Harvard Medical School (1978 – 1981). After fellowships in ophthalmic pathology and in molecular genetics, in 1983 he joined the faculty at Harvard Medical School and the staff at the Massachusetts Eye and Ear Infirmary in Boston. He headed a research lab studying the molecular genetics of hereditary diseases of the retina, and he practiced general ophthalmology and ophthalmic pathology. Major accomplishments from his research laboratory included compelling evidence for the recessive nature of oncogenic mutations at tumor suppressor genes like the retinoblastoma gene, the identification and cloning of the retinoblastoma gene, and the identification of 17 different genes responsible for forms of retinal degeneration (e.g., retinitis pigmentosa) and retinal dysfunction (e.g., stationary night blindness). He became the David G. Cogan Professor of Ophthalmology at Harvard in 1993 and a member of the U.S. National Academy of Sciences in 1996. In December, 2006, he joined the Novartis Institutes for Biomedical Research in Cambridge, Massachusetts, where he is now the Global Head of Ophthalmology Research. Dr. Dryja is also currently a Clinical Professor of Ophthalmology at Harvard Medical School and is one of the attending eye pathologists in the Cogan Eye Pathology Laboratory at the Massachusetts Eye and Ear Infirmary.

PROGRAM PAGE 21; ABSTRACT PAGE 78

Orly Elpeleg

Prefessor Orly Elpeleg is a Professor of Pediatrics at the Hebrew University (1999) and the head of the Department of Genetic and metabolic diseases at Hadassah. She graduated the Medical School in the Hebrew University, Jerusalem in 1981 and completed pediatric residency in 1988. During 1986 – 1987 she was a research fellow in inborn errors of metabolism in the Royal hospital in Copenhagen. In 1997 and 2003 she spent Sabbaticals in Neurology and Genetics in Great Ormond St children hospital in London. Her main research interest was metabolic disorders and especially mitochondrial respiratory chain defects. However, over the past decade she focused on gene discovery in a large array of rare disorders, and published 29 novel disease-associated genes with a similar number in the pipeline. She has extensive national and international collaborations, coauthored 150 peer-reviewed articles and is currently supported by DFG, AFM, and the Israeli Ministry of health.

PROGRAM PAGE 22; ABSTRACT PAGE 79

Davide Gabellini

Personal Statement

I have extensive background in performing research on epigenetic gene regulation and FSHD. We were the first to made a connection between deletion of the FSHD-associated D4Z4 repeat and transcriptional de-repression of nearby genes (Cell 110: 339, 2002). Next, we generated the only available mouse model of the disease (Nature, 439: 973, 2006). More recently, we have identified the lncRNA DBE-T as a key regulator of the FSHD locus (Cell, 149: 819, 2012) and we have developed the first RNAi-based gene therapy for dominant muscular dystrophies (Molecular Therapy, 19, 2055, 2011).

Positions

2008 – present:
Senior HSR Researcher, Division of Regenerative Medicine, Ospedale San Raffaele, Milano, Italy

2006 – present:
Assistant Telethon Scientist, Dulbecco Telethon Institute (DTI), San Raffaele Scientific Institute, Milano, Italy

2000 – 2006:
Postdoctoral Research Associate, HHMI, University of Massachusetts Medical School, Worcester, MA, USA

PROGRAM PAGE 21; ABSTRACT PAGE 80

Robert D. Goldman

Robert D. Goldman, PhD, is the Stephen Walter Ranson Professor and Chairman of the Department of Cell and Molecular Biology at Northwestern University Feinberg School of Medicine. He is an authority on the structure and function of the cytoskeletal and nucleoskeletal intermediate filament systems. He and his colleagues have published over 240 scientific articles. His work has led to a number of honors and awards, including an Ellison Foundation Senior Scholar Award in human aging and a MERIT award from the National Institute of General Medical Sciences. Dr. Goldman is a Fellow of the American Association for the Advancement of Science, and served on its board of directors from 1997 – 2001. He has held numerous positions in the scientific community, including organizing meetings and editing monographs and lab manuals for the Cold Spring Harbor Laboratory and has served on review committees for the American Cancer Society and the NIH. He was President of the American Society for Cell Biology and of the American Association of Anatomy, Cell Biology and Neuroscience Chairpersons. Goldman founded and for many years directed the Science Writers Hands On Fellowship Program at the Marine Biological Laboratory (MBL) and served on the MBL Board of Trustees, as Director of the MBL's Physiology Course and was Director of the MBL's Whitman Research Center. He is an Associate Editor of the FASEB Journal, the Molecular Biology of the Cell and Bioarchitecture.

PROGRAM PAGE 24; ABSTRACT PAGE 81

Philippe Gorry

Philippe Gorry MD-PhD, Associate Prof., past-funding & executive director of the technology transfer office of the University of Bordeaux, has been Vice-Dean for technology transfer at University of Bordeaux Ségalen for 10 years, and is currently the CFO of the university incubator. Trained in medical genetic, his research field was on cancer-prone rare diseases & he was an inventor of several patents on transgenic mice. Member of several national and international, scientific and tech transfer societies, is working as an expert on biotechnology and technology transfer, for governmental or private organization (ESHG, ERC, NIH-OTT, OECD, WIPO, ...). He has been board member of the of the Licensing Executive Society (France), and President of the association of French university technology offices, "Réseau C.U.R.I.E." At the present time, he is a research associate in the Dpt. of Economics, University of Bordeaux, focusing on economics of innovation & the pharmaceutical industry with a particular interest in the market of orphan drugs. He is teaching mainly science forecasting, patent landscaping and competitive intelligence, and management of innovation in biotech and pharma industry at the undergraduate as well graduate level at the Faculty of Economics, Pharmacy and Life Sciences at the University of Bordeaux.

PROGRAM PAGE 25; ABSTRACT PAGE 82

Stephen C. Groft

Stephen (Steve) C. Groft, Pharm. D. is the Director of the Office of Rare Diseases Research (ORDR) in the National Center for Advancing Translational Sciences at the National Institutes of Health (NIH). His major focus is on stimulating research with rare diseases and developing information about rare diseases and conditions for health care providers and the public. To help identify research opportunities and establish research priorities, the Office has co-sponsored over 1200 rare diseases-related scientific conferences with the NIH research Institutes and Centers. Current activities include establishing patient registries for rare diseases, developing an inventory of available bio-specimens from existing bio-repositories, developing an educational module on rare diseases for middle school children, establishing a public information center on genetic and rare diseases, developing an international rare diseases research consortium, maintaining the Rare Diseases Clinical Research Network, and providing a special emphasis clinic with senior clinical staff for patients with undiagnosed diseases at NIH's Clinical Research Center Hospital.

Steve received the B.S. degree in Pharmacy in 1968 and the Doctor of Pharmacy degree from Duquesne University in 1979.

PROGRAM PAGE 20

Thorsten Hornemann

PD Dr. Thorsten Hornemann studied Biology at the University of Konstanz, Germany. He carried out his thesis in the laboratory of Prof. Eppenberger and Prof. Wallimann, researching energy metabolism and muscle physiology. He received his Ph.D. from ETH Zurich, Switzerland in 2000. He then worked as a postdoctoral fellow at the University of Potsdam, Germany, before returning to the ETH Zurich for further postdoctoral work. In 2002 he joined the Institute of Clinical Chemistry at the University Hospital Zurich as a group leader, where he is researching sphigolipid metabolism and lipidomics. He earned his habilitation from the University of Zurich in 2011.

PROGRAM PAGE 26

Jeffrey Hubbell

Jeffrey Hubbell, PhD, is Professor of Bioengineering and Chemical Engineering at the Ecole Polytechnique Fédérale de Lausanne (EPFL). Trained as a chemical engineer, his research activities are in matrix and morphogen engineering for regenerative medicine and biomaterials and protein engineering in immunotherapy, including immunotherapies for induction of antigen-specific tolerance in protein drugs and autoimmunity. He is author of more than 325 papers in peer-reviewed journals and inventor on more than 100 patents. He is a member of the National Academy of Engineering, USA. Previous to moving to Lausanne, he taught at the Swiss Federal Institute of Technology Zurich, at the California Institute of Technology, and at the University of Texas in Austin. He holds a BS from Kansas State University and a PhD from Rice University.

PROGRAM PAGE 26

A. Cecile J.W. Janssens

Prof. A. Cecile J.W. Janssens, PhD is professor of translational epidemiology at the department of Epidemiology at Emory University, Atlanta, USA. Her research concerns the translation of genomics research to applications in clinical and public health practice. Her work focuses on the prediction of multifactorial diseases (e.g. diabetes, cardiovascular disease, asthma) using genetic risk models and on the assessment of the predictive ability and utility of genetic testing.

Cecile Janssens has published over 150 papers in international scientific journals and was awarded several personal grants, including the Erasmus MC Young Investigator Fellowship in 2006, the Vidi grant from the Netherlands Institute for Scientific Research in 2007 and the European Research Council Starting grant in 2012. Prior to her move to the USA, Cecile Janssens was the chair of the Dutch Association of Community Genetics and Public Health Genomics and board member of the Netherlands Association for Human Genetics. She chaired a European workshop on quality criteria for health checks and co-chaired an international workshop on guidelines for the reporting of genetic risk prediction studies, the latter which were published in 10 scientific journals simultaneously. She still is an active member of the Dutch Health Council and a member of the Evaluation of Genetic Applications in Prevention and Practice (EGAPP) working group.

PROGRAM PAGE 22; ABSTRACT PAGE 83

Nicolas Katsanis

Dr. Nicolas Katsanis obtained his first degree in Genetics from UCL in London in 1993 and his doctorate from Imperial College, University of London in 1997. He then joined the laboratory of Dr. Lupski at Baylor College of Medicine, where he initiated his studies on Bardet-Biedl syndrome. In 2002, he relocated to the Institute of Genetic Medicine, Johns Hopkins University where he led studies that unified several allied conditions under the ciliopathy umbrella. In 2009, he moved to Duke University to establish the Center for Human Disease Modeling, where he is the Director; this new structure aims to facilitate collaboration across disciplines and to develop physiologically relevant tools to study variation found in human patient genomes. As part of that effort, Dr. Katsanis leads the Taskforce for Neonatal Genomics. This multidisciplinary group of physicians and basic scientists strives to synthesize genomic and biological data for the faster diagnosis, improved/focused clinical care, and potential therapeutic paradigms, for infants and neotates with genetic conditions. In parallel, the Katsanis lab pursues questions centered on the signaling roles of vertebrate cilia, the translation of signaling pathway defects on the causality and possible treatment of ciliary disorders, and the dissection of second-site modification phenomena as a consequece of genetic load in a functional system. In recognition of his work, Dr. Katsanis was awarded the Young Investigator Award from the American Society of Nephrology in 2009, the E. Mead Johnson Award from the Society for Pediatric Research in 2012 and has delivered several Distinguished lectures. Dr Katsanis is a Professor in the Departments of Cell Biology and Pediatrics and holds the Brumley Distinguished Professorship. He has published over 190 research papers, reviews, and book chapters, serves on several advisory, editorial, and organizational boards and has delivered over 140 lectures in 18 countries.

PROGRAM PAGE 21; ABSTRACT PAGE 84

Michel Koenig

Michel Koenig, MD/PhD (University of Montpellier, France). Dr. Koenig is a newly-appointed group leader at the Institute of Human Genetics at University of Montpellier. He received his MD/PhD at University of Strasbourg, followed by a postdoc in the Department of Pediatrics and Genetics at Harvard Medical School (Boston, USA). Until 2013, Dr. Koenig was an independent Investigator at IGBMC and Professor of Human Genetics at University of Strasbourg. Since 1990, Dr. Koenig has been dedicated to the unraveling of the autosomal recessive ataxias and has made break-through discoveries in this field.

PROGRAM PAGE 28

Yann Le Cam

Yann Le Cam, MBA, Chief Executive Officer, European Organisation for Rare Diseases – EURORDIS has dedicated 25 years of professional and personal commitment to health and medical research non-governmental organisations in France, Europe and the United States in the fields of cancer, HIV/AIDS and rare diseases. He was one of the founding members of EURORDIS in 1997, and was nominated Chief Executive Officer in 2001. He has participated to the revision and adoption of European regulations having an impact on rare disease patients' life, including the EU Regulation on Orphan Drugs, December 1999. Yann was one of three patient representatives appointed to the Committee for Orphan Medicinal Products (COMP) at the European Medicines Agency (EMA) for 3 mandates, and served as its elected Vice Chairman from 2000 to 2006. He served on the Management Board and Executive Committee of the French HTA agency ANAES now called HAS for 5 years.

He has been nominated Vice-Chair of the EU Committee of Experts on Rare Diseases (EUCERD). Yann holds an Executive MBA from the Hautes Etudes de Commerces – HEC – Jouy-en-Josas France (2000) and an MBA from the Institut Superieur de Gestion (1984), Paris, France. Yann has three daughters, the eldest of whom has cystic fibrosis. He lives in France, Paris, and in Belgium, Brussels.

PROGRAM PAGE 20

David Lee

David Lee leads the Autoimmunity, Transplant and Dermatology Translational Medicine group and is responsible for generating and implementing the global disease area TM strategy to efficiently advance Novartis compounds through Proof of Concept to full Development.

David joined Novartis in 2010. He led Translational Research in the Autoimmunity, Transplantation and Inflammation disease area between 2010 and December 2011, covering development of target / pathway / mechanism-based assays, identifying target activity in human disease, building pre-clinical rationale for Disease Area compound Proof of Concept studies, and promoting 'back translation' of insights from disease cohorts to identify novel targets for drug discovery.

Before joining Novartis David was an Associate Professor at Harvard Medical School and Associate Physician at Brigham & Women's Hospital, focusing on translational studies of autoimmune and inflammatory mechanisms in arthritis. David obtained his medical and graduate degrees from Duke University School of Medicine and post-graduate medical residency and Rheumatology fellowship at Brigham & Women's Hospital, Harvard Medical School.

PROGRAM PAGE 20

Ephrat Levy-Lahad

Prof. Ephrat Levy-Lahad, MD is Director of the Medical Genetics Institute at Shaare Zedek Medical Center in Jerusalem, Israel and Associate Professor of Internal Medicine and Medical Genetics at the Hebrew University-Hadassah Medical School. She received her MD degree from Hebrew University-Hadassah Medical School (1989; Jerusalem, Israel), and trained in Internal Medicine at Shaare Zedek Medical Center and in Medical Genetics at the University of Washington in Seattle. She is board certified in Internal Medicine (Israel) and in Clinical and Clinical Molecular Genetics (USA and Israel). Prof. Levy-Lahad's clinical laboratory includes a large preimplantation diagnosis service, and cancer genetics diagnostics. Her research laboratory focuses on genetics of breast cancer, in particular the BRCA1 and BRCA2 genes, and on genetic and environmental factors that affect the risk associated with these mutations. During her fellowship Levy-Lahad discovered a gene for Alzheimer's disease gene (presenilin-2). In recent years and her laboratory is also involved in elucidating the genetic basis of rare diseases, including recent discoveries of novel genes for microcephaly, ovarian dysgenesis and polyarteritis nodosa. Prof. Levy-Lahad is also active in bioethical aspects of genetic research, and is currently co-Chair of the Israel National Bioethics Council. She is currently a member of the Israeli National Council for Women's Health and the National Council for Gynecology, Perinatology and Genetics. She was a member the Israeli Ministry of Health's committee on regulation of fertility treatments and of a Ministry of Justice advisory committee on wrongful birth. Internationally, she was a member of UNESCO's IBC (International Bioethics Committee) (2006 – 2009), and is a member of the Clinical Trials Task Force of the International Society of Stem Cell Research (ISSCR).

PROGRAM PAGE 22; ABSTRACT PAGE 85

Y. M. Dennis Lo

Prof. Lo is the Director of the Li Ka Shing Institute of Health Sciences and the Chairman of the Department of Chemical Pathology of The Chinese University of Hong Kong. In 1997, Prof. Lo and his co-workers reported the presence of cell-free fetal DNA in the plasma of pregnant women. Since then, Prof. Lo has elucidated the fundamental biological characteristics regarding circulating fetal DNA as well as its clinical applications in noninvasive prenatal diagnosis. In 2008, Prof. Lo and his team demonstrated that next-generation sequencing of maternal plasma DNA would allow fetuses with Down syndrome to be detected robustly and noninvasively. In 2011, Prof. Lo and his team published the first large-scale validation of this technology for Down syndrome detection. This technology has since then been rapidly introduced into clinical practice in late 2011. Prof. Lo was also the first to demonstrate in 2010 that the fetal genome could be sequenced noninvasively from maternal plasma. Taken as a whole, Prof. Lo's work has created a paradigm shift in prenatal diagnosis, making such testing safer for the fetuses and less stressful for the pregnant mothers. In recognition of his work, Prof. Lo has won numerous awards and was elected to the Royal Society in 2011.

PROGRAM PAGE 22; ABSTRACT PAGE 86

Stanislas Lyonnet

After training in paediatrics and genetics, Pr. Stanislas Lyonnet became a full Professor of genetics at University Paris Descartes Medical School in 1995. He is a clinical geneticists in the Department of Medical Genetics at Hôpital Necker-Enfants Malades.

As a principal investigator of an INSERM research group ("Genetics and embryology of congenital malformations"), Pr Lyonnet has conducted several studies aiming to localize and identify the genes involved in congenital malformation and inborn errors of development, mostly neurocristopathies. This group belongs to the recently created Foundation Imagine, Institut des Maladies Génétiques (Necker campus).

Pr Lyonnet is responsible for the European Master of Genetics (Paris Descartes-Paris Diderot Universities). He is a member of the INSERM Scientific Advisory Board, and has been a member of the board of the European Society of Human Genetics and its scientific programme committee. Pr Lyonnet was also responsible for the Rare Disease Research Programme in the frame of the French national agency for research (ANR).

He is a section editor of the European Journal of Human Genetics, and belongs to the editorial boards of Human Molecular Genetics and Clinical Dysmorphology. He was awarded the Jean Hamburger prize of Ville de Paris in 2006 and the Research Price of INSERM in 2009. He is the elected President of the European Society of Human Genetics (2012 – 2013).

PROGRAM PAGE 21; ABSTRACT PAGE 87

Colin McKerlie

Dr. Colin McKerlie DVM, DVSc, MRCVS is a Senior Associate Scientist at The Hospital for Sick Children and Professor in the Department of Laboratory Medicine & Pathobiology at the University of Toronto. A Veterinary Pathologist and Phenogenomic Scientist, he is also Director of Research Partnerships at the Toronto Centre for Phenogenomics (TCP) and Staff Scientist with the Samuel Lunenfeld Research Institute of Mount Sinai Hospital.

His research focuses on developing and using mouse models to discover and understand the function of genes that cause disease in children and adults; particularly the comparative pathology and tissue changes related to genetic manipulation in the mouse. Dr. McKerlie is project leader of the NorCOMM2 project, Canada's contribution to the International Mouse Phenotyping Consortium (IMPC) that aims to produce and phenotype up to 20,000 mutant mouse lines and make the repository of models and data publically available as a hypothesis-generating resource. The IMPC's mission is to get its data and resources into the hands of the research community to support their hypothesis-driven research, and generate collaborations where the mouse biology, production, phenotyping, and pre-clinical application knowledge and expertise it has can help. The NorCOMM2 project within the IMPC has established expertise in imaging and pathology-based phenotyping, particularly suited for characterization of embryo & neonatal lethal (congenital) phenotypes for comparative analysis to human disease.

PROGRAM PAGE 23; ABSTRACT PAGE 88

Marc Peschanski

Marc Peschanski, Scientific Director I-STEM (INSERM/UEVE 861, AFM), founder and scientific director of I-Stem is a medical doctor in Neurosciences. Entered at INSERM in 1982, he first worked on the neurophysiology and anatomy of pain in Paris and San Francisco. From 1985 his work was oriented towards the study of neuroplasticity and transplantation of foetal neurons, with which his team conducted the first clinical studies in France, starting in 1991 in patients with Parkinson's disease, and the first world trial in Huntington's patients from 1996, followed by a European study of Phase II in a hundred patients, currently in 4 countries. Co-founder of the Clinical Investigation Centre at the Henri-Mondor Hospital and to its associated Biotherapy branch, he was also a founder of the European neurotransplantation Network (NECTAR) and its first chairman in 1991 – 1992. He has coordinated several European research networks for gene therapy and cell therapy of neurodegenerative diseases, as well in most recent years pluripotent stem cells. He currently coordinates the Scr&Tox network of FP7.

The Institute for Stem cell Therapy and Exploration of Monogenic diseases (I-Stem), has been created the first of January 2005. It is a centre for research and development, dedicated to the development of treatments based on the potential offered by Stem cells and applicable to rare diseases of genetic origin. Defined by three key words, "therapeutics", "monogenic diseases" and "stem cells", the activity of I-Stem extends from basic biological research and pathological mechanisms up to the transfer of new therapies to clinical research. The objective of I-Stem is the development of treatments intended for monogenic diseases, founded on the strong potential of stem cells for substitutive and regenerative therapies. A second original objective of I-Stem is the development of cell models representative of pathologies on the basis of human embryonic stem cell lines each carrying a mutant gene associated with a given disease. These should help elucidate mechanisms of pathogenesis, and consequently, reveal possible therapeutic targets. These models can also be used as a basis for screening compounds libraries in order to discover new potential drugs.

PROGRAM PAGE 19; ABSTRACT PAGE 89

Barbara Plecko

Prof. Dr. med. Barbara Plecko studied Medicine at the University of Graz, Austria, where she earned her degree as a medical doctor in 1985. She continued her medical training in general medicine and pediatrics at the University Hospital Graz. In 1995, she was appointed senior consultant in Child Neurology and Inborn Errors of Metabolism at the Department of Pediatrics at the Medical University Graz. From 1999 to 2001 she worked as a research fellow in the Metabolic Laboratory at the Department of Pediatrics at the University Hospital Vienna, Austria. She earned her habilitation from the Medical University Graz, in 2003. In 2004, she became the head of Child Neurology and Service for Inborn Errors of Metabolism at the University Children's Hospital Graz, and in 2007 worked as an Associate Professor at the Division of Biochemical Diseases at Children's and Women's, Vancouver, UBC – joint neurometabolic clinic, Canada. Since 2011, Prof. Plecko is the head of Child Neurology at the University Children's Hospital Zurich, Switzerland and professor of Child Neurology at the University of Zurich, Switzerland. Her main field of interest in clinical research is in neurometabolism, with a focus on pyridoxine dependent seizures.

PROGRAM PAGE 26

Anne Puel

Anne Puel NSERM, Senior Researcher, Genetic determinism of idiopathic severe bacterial and fungal infections is an INSERM CR1 senior scientist in the Laboratory of Human Genetics of Infectious Disease (Necker Hospital, Imagine Institute, Paris). I am co-leading the team working on the genetic determinism of bacterial infections in children and leading the team working on the genetic determinism of severe fungal infections in humans. In particular, within the last five years, we have contributed in deciphering the pathogenesis of chronic mucocutaneous candidiasis (CMC) in primary immunodeficiencies, with the discovery of autoantibodies against IL-17 cytokines in autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED or APS-1) patients or impaired Th17 cells in autosomal dominant hyper IgE syndrome (AD-HIES) patients (J. Exp. Med. 2008 and J. Exp. Med. 2010). In 2011, we have discovered the first three genetic etiologies of CMC disease (CMCD) with autosomal recessive IL-17 receptor (IL-17RA) deficiency, autosomal dominant IL-17F deficiency and autosomal dominant STAT1 gain-of-function (Science 2011, J. Exp. Med. 2011). We are now investigating "idiopathic" invasive fungal infections and have identified CARD9 as a key player in immunity to various invasive fungal infections (N. Engl J Med, in press, manuscript in preparation). Our project aims at deciphering the molecular and cellular mechanisms of human immunity to fungi. The elucidation of the pathogenesis of CMCD and idiopathic invasive fungal infections will also benefit patients and their families (molecular diagnoses and genetic counselling), and should help in developing new immunotherapeutic treatments for these diseases, in addition to antifungal agents.

PROGRAM PAGE 22; ABSTRACT PAGE 90

Lakshminarayan Ranganath

Professor Lakshminarayan Ranganath is a busy clinician working in the Department of Clinical Biochemistry and Metabolic Medicine, Royal Liverpool University Hospital. He obtained a research degree (PhD) from the University of Surrey and was the first to show deficiency of incretin (GLP-1) in obesity, maintaining a continuing interest and continuing to make a contribution to this area. He became interested in Alkaptonuria serendipitously in 2003 and in close collaboration with a number of like-minded colleagues, is continuing to advance the clinical care and research into Alkaptonuria. He is the Clinical Director of the National Alkaptonuria Centre based in Liverpool allowing nitisinone to used in treating patients in the centre. He is also the co-ordinator and Chief Investigator for the EC-funded project DevelopAKUre. He has supported a number of Research degrees in his department.

PROGRAM PAGE 23; ABSTRACT PAGE 91

Anita Rauch

Prof. 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.

PROGRAM PAGE 26

Janine Reichenbach

Prof. Dr. med. Janine Reichenbach is Co-Head of the Division of Immunology at University Children's hospital Zurich, and Head of the research laboratory immunodeficiency/gene therapy, University Zurich. She studied medicine at the Universities of Frankfurt (DE), Lyon and Paris (F). She has been trained in pediatrics, pediatric immunology, hematopoietic stem cell transplantation (HSCT) and gene therapy at the Universities Frankfurt and Bonn, Université René Descartes / Hôpital Necker – Enfants Malades Paris, and University Zurich. She earned her Habilitation for pediatrics, spec. immunology/HSCT, from University Zurich in 2009, and has obtained the science award of the Walther and Gertrud Siegenthaler Trust in 2010. She was elected Assistant Professor of Pediatric Immunology at University Zurich in 2013. Her research is centred on inborn errors of the immune system and development of gene therapy for these defects. She is PI in an EU-FP7 funded multi-centre clinical phase I/II gene therapy trial for treatment of patients with Chronic Granulomatous Disease (CGD).

PROGRAM PAGE 26

Alexandre Reymond

Alexandre Reymond carried out his thesis in the laboratory of Dr. Viesturs Simanis at the Swiss Institute for Experimental Cancer Research (ISREC) and received his Ph.D. from the University of Lausanne in 1993. After completion of his postdoctoral training with Dr Roger Brent in the Department of Molecular Biology, Massachusetts General Hospital and in the Department of Genetics, Harvard Medical School in Boston, he moved to the Telethon Institute of Genetics and Medicine (TIGEM) in Milan in 1998 to lead a research group. He joined in 2000 the Department of Genetic Medicine and Development, University of Geneva Medical School. He moved to the Center for Integrative Genomics in October 2004.

PROGRAM PAGE 21; ABSTRACT PAGE 92

Botond Roska

Botond Roska, MD PhD, co-founder (of Gensight), is a senior group leader at the Friedrich Miescher Institute in Basel Switzerland. He was educated at University of California Berkeley, Harvard University and Harvard Medical School as well as at Semmelweis Medical School. His group studies the structure and function of the retina. His group pioneered retina cell type specific optogenetic vision restoration (Lagali et al., Nature Neuro. 2008, Busskamp et al, Science, 2010). He received several international prizes and awards: EMBO member (2011) Alcon Award (2011) VIVA Award (2010) ERC Starting Investigator (2010) EMBO Young Investigator (2009) Marie Curie Excellence Grant (2006) HFSP Young Investigator (2003) Harvard Society Fellow (2002) HFSP Short Term Fellow (2001) Bearden Memorial Award for biophysics (2001) Fulbright Fellow (1997).

PROGRAM PAGE 26

Heiko Runz

Heiko Runz, MD (University of Heidelberg, Germany and Massachusetts General Hospital, USA). Dr. Runz is a group leader at the Institute of Human Genetics, University of Heidelberg and the MMPU, a translational research unit between Heidelberg University and the European Molecular Biological Laboratories (EMBL). Since 2012, he also conducts research at the Mass. General Hospital in Boston, USA. Following a postdoc at EMBL and clinical training as a specialist in medical genetics, Dr. Runz' research centers around the mechanisms that cause variability in human genetic disease and how such variability may lead to novel therapies. His research bridges the genetics of common complex conditions with that of rare neurocognitive syndromes such as Niemann-Pick type C disease (NP-C).

PROGRAM PAGE 28

José-Alain Sahel

José-Alain Sahel is Professor of Ophthalmology at Pierre and Marie Curie University Medical School, Paris, France and Cumberlege Professor of Biomedical Sciences at the Institute of Ophthalmology, University College London, UK. He chairs a Department of Ophthalmology at the Quinze-Vingts National Ophthalmology Hospital and at the Rothschild Ophthalmology Foundation. He coordinates the Ophthalmology Clinical Investigation Centre and the National Reference Centre for Retinal Dystrophies. Dr Sahel is Director of the Vision Institute that comprises more than 17 research teams and more than 250 members focused on understanding the mechanisms associated with eye diseases and developing novel therapeutic strategies for currently untreatable retinal diseases. A key focus of his research is extending the functional life of cone photoreceptors in retinal degenerations.

Dr Sahel published over 250 peer-reviewed articles in specialty and general audience peer-reviewed journals and co-authored more than 20 patents. He has been the recipient of several awards, including Foundation Fighting Blindness Trustee Award, Alcon Research Institute Award, CNRS Medal of Innovation ... He is a Member of the Academy of Sciences, Institut de France. He sits on several editorial boards, including the Journal of Clinical Investigation, Science Translational Medicine, Progress in Retinal and Eye research and Archives of Ophthalmology.

PROGRAM PAGE 24; ABSTRACT PAGE 93

Michael Sinnreich

Prof. Dr. med. Dr. phil. Michael Sinnreich is head of the Neuromuscular Center in the Departments of Neurology and Biomedicine at the Basel University Hospital, where patients with neuromuscular diseases are treated by an interdisciplinary team. His research lab is located in the Pharmacenter of the University of Basel and focuses on the development of therapeutic strategies for muscular dystrophies. Michael Sinnreich studied Medicine and Biochemistry at Basel University, he did his PhD at the Friedrich Miescher Institute in Basel, his Neurology residency training at the University Hopsitals of Basel and Geneva, and fellowships in Neuromuscular diseases at the Mayo Clinic, Rochester, MN, and at the Montreal Neurological Institute, Montreal, where he subsequently joined the Faculty of McGill University.

In 2009 he was appointed Extraordinarius for Neurology at the University Hospital Basel.

PROGRAM PAGE 23; ABSTRACT PAGE 94

Nicolas Sireau

Dr Nicolas Sireau is Chairman and CEO 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) 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, turning them black – hence it is also called Black Bone Disease. The AKU Society is a fast growing international patient movement. We work with AKU research teams, clinical centres, biotech and pharma partners across the world. We launched in November 2012 a major five-year programme of international clinical trials for a promising new treatment called Nitisinone as part of an EC-funded consortium. The website of the AKU Society is www.akusociety.org. Dr Sireau is on the Management Committee of Rare Disease UK, the national alliance for people with rare diseases. He is the editor of the book 'Rare Diseases: Challenges and Opportunities for Social Entrepreuneurs' (Greenleaf, 2013). He is also the Founder and Chairman of Findacure (www.findacure.org.uk), a foundation that seeks to change conventional thinking about rare diseases by funding scientific research into fundamental diseases: rare diseases that are gateways to understanding common diseases.

PROGRAM PAGE 25; ABSTRACT PAGE 95

Colin Stewart

Colin Stewart received his D.Phil from the University of Oxford where he studied interactions between teratocarcinomas, the forerunners of ES cells, and early mouse embryos. He was the first to show that mouse chimeras can be produced by aggregation of EC and ES cells with 8-cell stage embryos, a now widely used technique in experimental mouse genetics. During postdoctoral work with Rudolf Jaenisch he showed EC cells and early embryos have a powerful mechanism, associated with de novo DNA methylation at transcriptionally silencing retroviruses. Subsequently as a staff scientist at the EMBL he was instrumental in discovering the role of the cytokine LIF in maintaining mouse ES cells in an undifferentiated state. There he also initiated an interest in the nuclear lamins and nuclear architecture. Following relocation to Hoffman-La-Roche, he showed that, paradoxically, LIF was not essential for embryonic development. Rather LIF, produced in the uterus, was essential at regulating embryo implantation. In 1996, he moved to the ABL research program in Frederick, Maryland and in 1999 was appointed Chief of the Laboratory of Cancer and Developmental Biology at the National Cancer Institute. Since June 2007 he has been Research and Assistant director at the Institute of Medical Biology at the Singapore Biopolis. His current research interests centre on the functional architecture of the cell's nucleus and the lamins, in stem cells, epigenetics, regeneration and disease.

PROGRAM PAGE 24 ABSTRACT PAGE 96

Marshall Summar

Dr. Marshall Summar, Chief, Genetics and Metabolism; Margaret O'Malley Professor of Genetic Medicine, internationally known for his pioneering work in caring for children diagnosed with rare diseases, including urea cycle and related disorders, joined Children's National in 2010. Previously, at Vanderbilt University School of Medicine he directed the Program in Translational Genetics, the DNA Core program, and started the inborn errors of metabolism program. The ability to study rare diseases and apply the findings to common diseases, especially in intensive care and emergency room settings, is a hallmark of Dr. Summar's work. Currently, his research focuses on the interaction between common genetic variations and the environment. This involves research in heart disease, asthma, pulmonary hypertension, oxident injury and aging, Down syndrome and liver disease. Dr. Summar is board-certified in Pediatrics, Clinical Genetics, and Biochemical Genetics and has been listed with Best Doctor's in America since 2004. He serves on the editorial board of The Journal of Pediatrics and is the president-elect for the Society of Inherited Metabolic Disorders.

PROGRAM PAGE 25; ABSTRACT PAGE 97

Marc Tardieu

Marc Tardieu is Professor of paediatrics (neurology), head of paediatric neurology service, head of research laboratory INSERM unit 1012, Université Paris South, Assistance publique-hôpitaux de Paris, Hôpitaux Universitaires Paris Sud.

He has been trained in pediatrics, paediatric neurology, immunology and virology, at Université Paris-Sud, Université Catholique de Louvain and Harvard Medical School, Boston. He has been a professor of paediatrics at Université Paris South since 1990. His main interest has been in the infectious and inflammatory diseases of the child brain, their patho-physiology and their epidemiology. He had published close to 300 papers in this field especially on HIV-1 infection, multiple sclerosis, acute disseminated encephalomyelitis, haemophagocytic lymphohistiosis, herpes encephalitis. More recently he developed an intra-cerebral gene therapy trial and recently published a study on the incidence and natural history of MPSIII subtypes.

PROGRAM PAGE 22; ABSTRACT PAGE 98

Didier Trono

Born in 1956, Didier Trono obtained his M.D. from the University of Geneva in 1981. After completing a clinical training in pathology, internal medicine and infectious diseases in Geneva and at Massachusetts General Hospital in Boston, he joined in 1986 David Baltimore's laboratory at the Whitehead Institute for Biomedical Research of MIT as a post-doctoral fellow. In 1990, he moved to the Salk Institute for Biological Studies of Jolla to launch, as an assistant professor, a center for AIDS research. Promoted to associate professorship in 1995, he returned two years later to the University of Geneva as a full professor within the Department of Genetics and Microbiology. He took the head of this department in 2000 and, a year later, the presidency of the Basic Sciences Section of the Faculty of Medicine. In 2004 he joined the Ecole Polytechnique Fédérale de Lausanne (EPFL) as dean of its newly launched School of Life Sciences, a position he held for eight years. Didier Trono's past research has focused on interactions between viral pathogens and their hosts, and on exploring genetics from both fundamental and therapeutic perspectives. This led him to epigenetics, the current topic of his investigations.

PROGRAM PAGE 26

Alan Tyndall

Alan Tyndall was born on 3/8/1948 in Newcastle Australia and achieved his undergraduate medical degree at the University of Sydney in 1972. His post graduate qualifications are FRACP, FRCP(Ed), with post graduate experience in Canberra, Sydney and London. In 1991 he was appointed professor and head of the Dept of Rheumatology in the University of Basel, and his recent interests are stem cell therapy of autoimmune diseases and systemic sclerosis (scleroderma). He has participated in the working party of the ESF sponsored study of investigator initiated trials and the EMA study group regarding third country clinical trials. He has served on the boards of the EBMT and EULAR and was a founding member and secretary of the EULAR Scleroderma Trials and Research (EUSTAR) group. He is currently secretary and founding member of the World Scleroderma Foundation (based in Basel), chairman of the safety committees of two of 2 NIH sponsored stem cell trials and is an adjunct professor at the University of Florence, Italy. Prof Tyndall has published over 230 peer reviewed papers, 100 of which relate to stem cell therapy and 25 book chapters.

PROGRAM PAGE 19; ABSTRACT PAGE 99

Gisou van der Goot

Gisou van der Goot is full Professor in Life Sciences at the Swiss Institute of Technology in Lausanne. After an engineering training at the Ecole Central in Paris and a PhD from Univ. Paris V, she performed a postdoc at the EMBL in Heidelberg. She started her independent career at the University of Geneva, first in Biochemistry and then at the Medical School. She obtained an EMBO Young Investigator award (2001), a Howard Hughes International Scholar award (2005), was elected EMBO member (2009) and received the Swiss Prix Marcel Benoist in 2009. She is a leader in the molecular and cellular understanding bacterial toxins, in the organization of mammalian membranes and in organelles biology.

PROGRAM PAGE 26

Martine Zimmermann

Martine Zimmermann is currently Executive Director for Global Regulatory Affairs at Alexion Pharma International. She is based In Lausanne Switzerland. Dr Zimmermann has gained extensive experience in international pharmaceutical industry for more than 18 years in roles at Daiichi Pharmaceuticals R&D center in Tokyo (Japan) where she started her carrier as researcher in immunology, Rhone-Mérieux (Lyon), Aventis Pharma (Paris) and Les Laboratories Servier (Paris) before joining Alexion in 2009. Her professional background crosses a broad spectrum of activities, having worked in the areas of research and drug development, regulatory affairs, and compliance with good clinical practice.

In addition she is a member of EUCERD. Dr Zimmermann is a French citizen. She is a Pharm D specialized in immunology and graduated from Louis Pasteur University, Strasbourg, France

PROGRAM PAGE 25; ABSTRACT PAGE 100

SPEAKERS' ABSTRACTS

SPEAKERS' ABSTRACTS

Disclaimer: The speakers' abstracts are printed as received by the authors

Lessons Learned from a Pioneering Phase I/Ii Gene Therapy Trial in Sanfilippo Syndrome

Karen Aiach

LYSOGENE is a leading gene therapy biotechnology company developing breakthrough treatments targeting severe genetic pathologies with high unmet medical needs.

In 2013, LYSOGENE successfully completed its Phase I/II gene therapy study using its lead product (SAF-301) in patients with Sanfilippo Syndrome type A (http://clinicaltrials.gov/ct2/show/NCT01474343?term=sanfilippo&rank=2).

Sanfilippo Syndrome is a lethal pediatric neurodegenerative disorder with currently no treatment. It is an autosomal recessive condition belonging to the group of Lysosomal Storage Disorders (Gaucher, Fabry, Hunter, Niemann-Pick ...) and affects 1:100,000 live births – it is likely to be underdiagnosed-. The condition is characterized by progressive neurodegeneration, neurocognitive impairement, severe invasive behavioral disorders, and a cohort of milder peripheral symptoms. Patients with Sanfilippo syndrome generally do not live beyond their second decade. Impacts on quality of life of patients and their families are numerous and devastating.

Sanfilippo Syndrome has since long been considered an ideal model for AAV-based gene transfer. In a complex regulatory environment, LYSOGENE translated it rAAVrh10-SGSH-SUMF1 from bench to bedside in 5 years for Sanfilippo A. The Company now aims to expeditiously advance the clinical development and worldwide commercialization of its lead product, while leveraging on lessons learn to expand its pipeline to additional monogenic diseases with high unmet medical needs.

PROGRAM PAGE 25; BIOGRAPHY PAGE 30

A Clonal Strategy for Safe Ex Vivo Gene Therapy of Epidermis

Yann Barrandon

Joint Chair of Stem Cell Dynamics School of Life Sciences
Ecole Polytechnique Fédérale Lausanne and Department of Experimental Surgery
Lausanne University Hospital, 1015 Lausanne Switzerland

Safety is critical when it comes to ex vivo autologous gene therapy but current stem cell technology makes it difficult to thoroughly investigate the properties of human recombinant stem cells before cells are transplanted. Epidermal stem cells have the remarkable property to be massively expanded ex vivo and it is theoretically possible to completely reconstruct the epidermis of an adult human from the progeny of a single autologous epidermal stem cell. We have explored the feasibility of a single cell approach for ex vivo gene therapy of skin using recessive dystrophic epidermolysis bullosa (RDEB), a horrendous blistering genodermatosis, as a model system. This approach allows for a full characterization of the recombinant clone(s) both for stem cell capabilities (long term production of the medicinal protein, long term regeneration of a cured human epidermis onto immunodeficient mice) and for safety criteria (determination of proviral insertions, absence of tumorogenicity and dissemination). The combination of a clonal approach with high throughput technologies should permit to thoroughly evaluate the properties of the genetically corrected stem cells before the patient is transplanted and brings safety to a level that is difficult to achieve otherwise.

PROGRAM PAGE 19; BIOGRAPHY PAGE 32

Laminopathies of the Striated Muscle: from Gene Defects towards Pathophysiological Mechanisms.

Gisèle Bonne

1. Inserm, U974, Paris, F-75013, France;
2. Université Pierre et Marie Curie-Paris 6, UM 76; CNRS, FRE; Institut de Myologie, Paris, F-75013, France;
3. AP-HP, Groupe Hospitalier Pitié-Salpêtrière, U.F. Cardiogénétique et Myogénétique Moléculaire, Service de Biochimie Métabolique, Paris, F-75013, France.

Laminopathies are due to mutations in the LMNA gene encoding A-type Lamins (or Lamin A and C) and comprise highly heterogeneous human disorders including cardiac and muscular dystrophies, lipodystrophies and progeria. Lamins A/C are constituents of the nuclear lamina, a meshwork of proteins underneath the nuclear envelope first described as scaffolding proteins of the nucleus. Since the discovery of the first LMNA mutation in the Emery-Dreifuss muscular dystrophy, more than 450 different LMNA mutations were reported (www.umd.be/LMNA/) and the number of functions described for lamins A/C has expanded. Lamins A/C are notably involved in the regulation of chromatin structure and gene transcription, and in the resistance of cells to mechanical stress. In order to dissect the pathomechanisms of LMNA mutations and understand mutations in a gene encoding ubiquitously expressed proteins could give rise to tissue specific disorders; our group has created knock-in mouse models that reproduced LMNA mutation indentified in patients presenting with cardiac and muscular dystrophies of different severity. These models are excellent tools to explore the pathomechanisms of the mutations, identify therapeutical targets as well as test therapeutic approaches.

PROGRAM PAGE 24; BIOGRAPHY PAGE 34

Cell Therapy for Muscular Dystrophies

Giulio Cossu

Napolitano S1, Cicalese MP1, Previtali S1, Marktel S1, Venturini M1, Politi L1, Noviello M. 1, Tedesco FS1,2, Bonini, C1., Torrente Y3, Ciceri F1 and Cossu G1,2.
1Division of Regenerative Medicine, Department of Neurology and Bone Marrow Transplantation Unit, San Raffaele Scientific Institute,
Institute of Inflammation and Repair, University of Manchester.
Department of Neurological Sciences, University of Milan.

Mesoangioblasts are progenitor cells, associated with the vasculature and able to differentiate into different types of mesoderm, including skeletal muscle (Minasi et al. Development 129, 2773, 2002). When mesoangioblasts were delivered intra-arterially to muscles of dystrophic mice and dogs they resulted in a significant functional amelioration (Sampaolesi et al. Science 301, 487, 2003; Nature 444, 574, 2006). Human adult mesoangioblasts, isolated and expanded in vitro from muscle biopsies, were shown to correspond to a subset of pericytes (Dellavalle et al. Nature Cell Biol. 9, 255, 2007).

Based on these results, a mono-centre, prospective, non-randomized, clinical phase I/II study of cell therapy with HLA-matched donor human mesoangioblasts in DMD patients started in June 2009, after a one year preliminary study (involving 28 DMD patients, aged 5 – 10), required to validate outcome measures. Starting on March 2011, three out of these patients (with an HLA-identical donor) underwent successive intra-arterial transplantations at escalating doses of cells, under a continuous regime of immune suppression. Two more patients have been treated the following year. Although the results from the last two patients are still being analyzed, preliminary results indicated safety, a transient stabilization of functional measures and the presence of donor cells and donor derived dystrophin in younger patients, Despite this encouraging trend, clinical efficacy appears still to be reached and new strategies are being devised to this aim and will be discussed.

PROGRAM PAGE 19; BIOGRAPHY PAGE 36

Special Considerations for Phase I Trials of Gene Therapies for Retinitis Pigmentosa and Allied Retinal Degenerations

Thaddeus P. Dryja

In the initial, phase I clinical trials of a new therapy, the novel drug or agent is administered to small cohorts of subjects (typically about 6-8 subjects per cohort). The first cohort is given the smallest dose, called the maximum recommended starting dose, which is determined from testing the drug in animals. If that dose appears to be safe and does not appear to be optimally efficacious, a higher dose is administered to the next cohort of subjects. Successive cohorts with increasing doses are enrolled until a dose-limiting toxicity is observed, the maximum practical dose is achieved, or satisfactory efficacy is apparent.

Special considerations are required for gene therapies for hereditary photoreceptor degenerations such as forms of retinitis pigmentosa. Viral gene therapy vectors such as recombinant adeno-associated viruses (AAV) or lentiviruses permanently transduce cells. Toxicity might take years to become apparent and may be irreversible. Without the confidence that a dose has long-term safety, phase I clinical trials must be able to find the smallest dose that is likely to be efficacious, based on results from only a 1 – 6 patients in a cohort. Most photoreceptor degenerations progress slowly, with only about 5 – 10 % deterioration in visual function tests per year. Test-retest variability can be 10 – 30 % in visual function tests such as visual fields or electroretinograms, so it can require many treated patients followed for many years before one can determine if a therapy slows degeneration. This duration of evaluation for each cohort can be impractical because the dose-escalation can require many years. In consequence, phase I trials of new gene therapies for photoreceptor degenerations should be confined to diseases where the therapy is expected to acutely increase some aspect of visual function, or where there is a biomarker of sufficient transduction of the therapeutic gene. This talk will exemplify the principles involved in phase I trials by reviewing prior clinical trials using AAV vectors for RPE65-associated retinitis pigmentosa and congenital amaurosis, as well as an AAV vector to express cellular retinaldehyde binding protein planned for testing in patients with retinitis punctata albescens due to mutations in RLBP1.

PROGRAM PAGE 21; BIOGRAPHY PAGE 37

Whole Exome Sequencing in Rare Diseases

Orly Elpeleg

Reaching the correct molecular diagnosis in rare disease is of utmost importance. The economical and emotional burden on the family and the society is vast, especially in traditional societies, where these disorders are more common. Elucidating the molecular basis of a rare disease would not only allow the family genetic counseling but would also pave the way for drug development.

Whole Exome analysis has turned to be a powerful tool but with current technology, is far from perfect. Incomplete coverage and missed indels are the leading causes of failure to reach a final diagnosis. Ethnic variant databases and causality laboratories are needed, and a new subspecialty in Genetics training should be considered.

PROGRAM PAGE 22; BIOGRAPHY PAGE 38

FSHD Muscular Dystrophy Provides a Molecular Understanding of the Repetitive (Epi)Genome

Davide Gabellini

Dulbecco Telethon Institute and Division of Regenerative Medicine, San Raffaele Scientific Institute, Milano, Italy

Only about 1 % of the genome encodes for the 20000 human proteins, which are similar in number and largely orthologous to those found in organisms of significant lower complexity. On the contrary, the proportion of non protein-coding DNA has increased with developmental complexity reaching 98.5 % in humans. Interestingly, up to two thirds of the human genome is composed of non protein-coding repetitive sequences. Furthermore, a significant portion of the epigenetic modifications is present in these regions and DNA repeats are dynamically transcribed in different cells and developmental stages producing a vast pool of non protein-coding RNA (ncRNA) molecules. Thus, ncRNAs produced by DNA repeats may hold the key to understanding the regulatory complexity inherent in advanced biological networks.

Long ncRNAs (lncRNAs) represent the most numerous and functionally diverse class of RNA produced by mammalian cells. Despite the growing interest on lncRNAs, they still remain poorly explored in terms of biological relevance, cellular function, mechanism of action and involvement in disease. We have recently contributed to this field through the identification of the first activating lncRNA involved in a human genetic disease: facioscapulohumeral muscular dystrophy (FSHD).FSHD is one of the most important genetic diseases affecting the skeletal muscle. It is an autosomal dominant disorder with a strong epigenetic component. Unlike the majority of genetic diseases, FSHD is not caused by mutation in a protein-coding gene. Instead, the disease is associated with a reduced copy number of the D4Z4 macrosatellite repeat mapping to 4q35. Despite years of intensive research, the molecular pathogenesis of FSHD remains largely unknown. We recently identified DBE-T, a chromatin-associated lncRNA produced preferentially in FSHD patients. DBE-T mediates a Polycomb to Trithorax epigenetic switch at the FSHD locus, driving chromatin remodeling and transcription of FSHD candidate genes.

Here, I will discuss our recent results regarding the regulation of DBE-T expression, the mechanism responsible for DBE-T tethering to chromatin and how this lncRNA regulates the epigenetic status of the FSHD locus.

PROGRAM PAGE 21; BIOGRAPHY PAGE 39

Altered Intermediate Filament Networks are the Hallmarks of Many Rare Diseases

Robert Goldman

In humans, there are ~65 genes encoding a large family of Intermediate Filament (IF) proteins. Three of these genes give rise to a complex of nucleoskeletal intermediate filaments, the nuclear lamins. We have shown that the lamins play important roles in DNA replication, gene transcription, chromatin organization and nuclear assembly, size and shape.. Over the past decade, there have been reports of hundreds of mutations in the gene encoding lamin A. These mutations cause a remarkably wide range of rare human diseases collectively known as the "laminopathies", which include lipodystrophies muscular dystrophies, cardiomyopathies and the premature aging disease Hutchinson Gilford Progeria Syndrome (HGPS). To date our studies have focused on HGPS. Although the incidence of this devastating disease is only about 1 in 8 million, it has been thought to represent a model for normal human aging for over 100 years. Children are typically born normal in appearance but there is rapid onset of aging phenotypes such as hair loss, growth arrest, hip dysplasia and atherosclerosis which causes heart attacks and strokes. Our studies of progeria have provided insights into not only the cause and treatment of this disease, but also the roles of lamins in regulating the positioning and epigenetic modifications of chromatin and in cell growth and senescence. The other IF genes encode proteins which assemble into cytoskeletal networks . These networks determine a cell's shape and mechanical properties and are involved in signal transduction, motility and adhesion. There are numerous rare diseases caused by mutations in cytoskeletal IF genes such as skin blistering diseases, muscular dystrophies and neurodegenerative diseases. There are also diseases which lead to the abnormal accumulation or aggregation of IF such as the rare neurological disorder, giant axonal neuropathy (GAN). GAN is an untreatable genetic disorder of the nervous system of children who typically have difficulties walking by ~ age 3, are using wheelchairs by age 10, and ultimately require feeding and breathing tubes before dying at 20-30 years. GAN is caused by mutations in the gene which encodes gigaxonin, an E3 ligase-like adaptor. We have found that gigaxonin targets several types of cytoskeletal IF proteins for degradation by the proteasome. The malfunctioning of gigaxonin prevents the normal turnover of cytoskeletal IF causing large aggregates to form. In nerve cell axons these aggregates appear to impede axonal transport causing neurodegeneration. These findings provide a framework for drug development and have opened up new opportunities for research into the normal regulation of a major cytoskeletal system. Funded by the NIH, the NCI, the Ellison Medical Foundation, Hannah's Hope Fund and the Progeria Research Foundation.

PROGRAM PAGE 24; BIOGRAPHY PAGE 40

Role of Academic Research in the Discovery of Orphan Drugs

Philippe Gorry

MD-PhD, Asso. Prof.; Research Unit in Theoretical and Applied Economics, UMR CNRS 5113, University of Bordeaux, Pessac – FRANCE

Rare Diseases drug development has been limited by a lack of understanding of the pathophysiology mechanisms, as well the prohibitive cost of investing in a novel drug with poor market potential. To encourage the development, Orphan Drug (OD) legislation was put in place in US in 1983 and in the EU in 2000, bringing incentives such as market exclusivity and tax credit, which have contributed to the registration of many OD designations by the pharma and biotech companies. But the number of approved drugs is small compare to the total number of rare diseases. There is a growing concern that the industry will not be able to sustain research pipelines that bring enough new compounds into drug development that fulfill the expectation of patients. Historically academic science has always performed basic research that elucidated the underlying mechanisms of disease, whereas company researchers have performed applied research resulting in discovery of drugs and transfer to market. However, the boundaries between the roles of the public and private sectors have shifted substantially. The pharma industry is adopting an open innovation paradigm seeking to complement internal R&D with external global expertise. The academia is pushing technologies from basic research to the marketplace.This changing landscape demands a better understanding of the role of academia in translational research and suitable technology transfer terms in rare diseases. We undertook the objective to map research on rare diseases and evaluate the effective contribution of academia to OD approved in the EU & US market. We run a worldwide literature search of large scientific database using text-mining techniques, and gather OD information from different sources (scientific publications, patents, "drug pipeline", clinical trials, orphan status, market authorization). With the help of data visualization tools and network analysis software, we examine trends, rank the actors and determine the patterns of scientific collaboration in order to gain an understanding of the contribution of academia to OD pipeline. In the light of the results, we will discuss integrated approach to accelerate OD R&D and alternative business model with strategic partnerships between charity, academia and industry.

PROGRAM PAGE 25; BIOGRAPHY PAGE 41

How Predictive is our DNA?

Cecile Janssens

The rapid and continuing progress in gene discovery for complex diseases is fuelling interest in the potential implications of this knowledge for clinical and public health practice. One of the prominent expectations is that preventive and therapeutic interventions can be more effectively administered when they are targeted to individuals on the basis of their genetic risks. An essential prerequisite for such applications is that DNA has appreciable predictive ability. The number of studies assessing the predictive ability is steadily increasing. This lecture will give a review of the recent developments in genetic risk prediction studies and a preview on the predictive ability of future DNA testing including whole genome sequencing: how well can we predict diseases when we know all genetic risk factors?

PROGRAM PAGE 22; BIOGRAPHY PAGE 45

Modelling the Morbid Genome-Wide Sequencing

Nicolas Katsanis

Genome-wide sequencing is emerging as a powerful tool as a first-pass diagnostic test. This has heightened the need for interpretive assays to determine the pathogenic potential of genetic variation. To address these challenges, and to capitalize on the opportunity to shorten the time to secure molecular diagnoses, we have created the Task Force for Neonatal Genomics at Duke University. The Task Force targets a uniquely vulnerable patient cohort: infants and neonates whose developmental anomalies are more likely to be within a timeframe for treatment. Our efforts harness the full spectrum of clinical, genetics and cellular biology expertise, including the use of transient model organisms (primarily zebrafish). I will discuss: 1) the interdisciplinary nature of our efforts; 2) our methodology for recruitment, data generation and analysis, and communication strategies between researchers and clinicians; 3) our analysis progress to date; and 4) our evolving approach to returning primary and secondary molecular findings to clinicians and family members. In phenotype-appropriate patients, we couple whole exome sequencing of trios, a multi-tiered bioinformatic prioritization strategy, and functional modeling of novel variants in physiologically relevant vertebrate and cell-based models to inform allele pathogenicity. Strikingly, in our first year, we have achieved definitive diagnoses for 41 % of our patients and strong candidate diagnoses that typically involved novel disease genes and/or complex genetic interactions in 90 % of our cohort. This initiative provides an unprecedented model for communication across an interdisciplinary research/clinical team with the ultimate goal of responsible and timely integration of new genetic technologies into clinical care.

PROGRAM PAGE 21; BIOGRAPHY PAGE 46

From Mutation to Pathogenesis in Rare Diseases

Ephrat Levy-Lahad

Disease causing mutations in humans provide invaluable information on gene function in vivo. Although genomic analysis has rapidly increased the number of genes identified to be mutated in various conditions, no such mutations are known for the majority of human genes. As the process of coupling human genes with associated human diseases accelerates, the next challenge is to assess the pathogenic potential of variants, and to understand the role of genes in disease pathogenesis. Addressing this issue will be discussed using recent examples from our lab, including the role of VRK1, a gene previously implicated mainly in cancer, in brain development and the role of ADA2, the extracellular adenosine deaminase, in vascular integrity.

PROGRAM PAGE 22; BIOGRAPHY PAGE 50

Noninvasive Prenatal Testing Using Cell-free Fetal DNA in Maternal Plasma

Y.M. Dennis Lo

Li Ka Shing Institute of Health Sciences and Department of Chemical Pathology, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Hong Kong SAR, China.

In 1997, our group showed that cell-free fetal DNA is present in the plasma of pregnant women. This discovery has opened up new possibilities for noninvasive prenatal diagnosis. Cell-free fetal DNA represents a mean of 15 % of the DNA that is present in maternal plasma and is present from the first trimester of pregnancy. The recent advances in massively parallel sequencing have allowed fetal DNA analysis to be carried out with unprecedented precision. In 2010, we described a method for the noninvasive whole genome sequencing of the fetus from maternal plasma DNA. This strategy has recently been confirmed by two other groups. Furthermore, we have demonstrated that this approach can be used for the noninvasive prenatal diagnosis of many genetic disorders, using beta-thalassemia as our first model system. We have since then shown that with targeted sequencing, one could implement such a strategy for multiple genetic diseases in a relatively cost-effective fashion. Thus, noninvasive prenatal testing is likely to play an increasingly important role in obstetrics care.

PROGRAM PAGE 22; BIOGRAPHY PAGE 51

Non-coding Genome Alterations in Rare Development Anomalies

Stanislas Lyonnet

Université Paris Descartes and Imagine Institute, Hôpital Necker-Enfants Malades, Paris, France

One of the key discoveries of vertebrate genome sequencing projects was the unexpected amount of DNA that remained evolutionarily conserved under selective pressure, and thus likely functional. Two-thirds of it do not correspond to coding sequences (exons and UTRs); they have been named conserved non-coding sequences (CNCs) and represent a vast amount of DNA (3 % of the human genome). Interestingly, enrichment for CNCs has been demonstrated within gene deserts nearest to physically isolated genes known or suspected to be important developmental regulators. It has been thus suggested that, in these cases, CNCs may represent regulatory elements (enhancers or suppressors) necessary for the correct spatiotemporal expression of these genes needed for embryonic development, and acting as modular, sometimes combinatorial, tissue-specific enhancers of gene transcription. In that context, we will discuss a number of findings, following the seminal discovery of long-distance genomic alterations altering the expression of the SHH (Sonic Hedgehog) gene. Recent examples involve:

- Mutation of non-coding RNA genes, such as the deletions observed at the mir17-92 cluster in Feingold syndrome, or mutation of a long non-coding RNA in RAVINE encephalopathy.
- Enhancer variants located within or close to a gene, such as a genomic variant in a highly conserved sequence located in a non-coding region of the RET gene, altering the binding of a transcription factor expressed in neural crest cell precursors to the enteric nervous system, which predispose to Hirschsprung disease.
- Long-distance disruption of CNCs, whatever their function, such as those observed on both side of the SOX9 gene coding sequences in either Pierre Robin sequence (PRS), a common orofacial cleft anomaly with mandibular hypoplasia, or isolated disorders of sex determination (DSDs). In these cases, the disruption of distant tissue-specific regulatory elements, required for the normal development of either the mandibula or the gonads, perturbs embryonic expression of SOX9 and could account for the PRS or DSD phenotypes respectively, as these evolutionarily constrained regions may be disrupted in a modular fashion.

Collectively, these observations suggest that the domains to study for genomic alterations, resulting in tissue-specific misregulation of a developmental gene and a subsequent malformation, should be much broader than traditionally investigated.

PROGRAM PAGE 21; BIOGRAPHY PAGE 52

Systematic Large-Scale Gene Function Analysis of the Mouse Genome:

An opportunity for new mouse models of rare diseases for research and drug discovery

Colin McKerlie

There are >7,000 genetic disorders listed at the OMIM registry. Approximately half of them are associated with an identified genetic variant but therapeutics are only available for a very small proportion of those. The genes or mutations that cause the other 3,500 disorders are unknown, making diagnosis of patients difficult, and discovery of therapeutic targets extremely challenging. These rare genetic disorders typically result from mutation of a single gene and often present with either congenital or early onset. The mouse can be a powerful model system to reproduce disease symptoms, explore mechanisms, and evaluate potential therapies when a known gene is mutated. Systematic production and characterization of mouse models with mutations in genes with unknown function can potentially discover the genes that cause a particular disorder, and identify therapeutic targets. All of these mouse models should be available to every scientist.

Towards this goal, the International Knockout Mouse Consortium (IKMC) is mutating all 20,000 protein-coding genes in the genome in mouse embryonic stem (ES) cells. Currently, the IKMC resource contains targeted alleles for over 3/4s of all protein-coding genes with complete genome coverage expected in a few years. The production and characterization of mice from this resource is underway by members of the International Mouse Phenotyping Consortium (IMPC). Each mouse strain with a mutation in a single gene undergoes a standardized battery of clinical phenotyping tests in order to assess the phenotypic consequence of the targeted allele, thereby generating biologically relevant models of mutations in known genes and functional annotation of genes with unknown function. An imaging, gene expression, and pathology pipeline is used to characterize phenotypes in embryo lethal or perinatal lethal genes. All of the biological resources and phenotyping data are openly available to the scientific community through web based interfaces. An overview of the tools and resources, opportunities for the research and development community to engage, and some examples of our resources as tools for interrogating known and novel gene biology, disease mechanism, and therapeutic discovery for rare diseases will be presented.

PROGRAM PAGE 23; BIOGRAPHY PAGE 53

Harnessing Pluripotent Stem Cells Derivatives to Decipher Mechanisms and Identify Treatments for Monogenic Diseases

Marc Peschanski

I-Stem Institute Evry 91030 France

Pluripotent stem cell lines derived from donors who carry a mutant gene at the origin of a monogenic disease can be obtained currently either from embryos characterized as gene-carriers during a pre-implantation genetic diagnosis procedure, or else through genetic reprogramming of donors' sample cells. Both can be used to screen libraries of compounds, in a search for new treatments. Currently, the ES cell bank at I-Stem comprises over 30 PGD-derived cell lines, representing over 15 diseases. IPS cell lines are derived at request. Robust read-outs relevant to the pathological mechanisms should first be identified. On this basis, screening platform either in high throughput or in high content can be implemented, as derivatives of pluripotent stem cells can be obtained at near homogeneity and are amenable to miniaturization and standardization of cell processes. At I-Stem, we have exploited this potential for several monogenic pathologies, already, including Huntington's disease, myotonic dystrophy type I, Progeria and Lesch-Nyhan disease. In parallel, functional genomics can also be implemented on large-scale platforms, in a search for yet unknown mechanisms and proteins involved in pathological signaling pathways. Using a subset of siRNA, we have in particular been able to identify one gene, the down-expression of which tended to normalize abnormal gene splicing and functional defects associated to myotonic dystrophy type 1. We eventually found out that the protein encoded by this gene is druggable, which opened a path toward a clinical trial now ongoing.

PROGRAM PAGE 19; BIOGRAPHY PAGE 54

Inborn Errors of Human IL-17 Immunity Underlie Chronic Mucocutaneous Candidiasis

Anne Puel

Chronic mucocutaneous candidiasis (CMC) is characterized by recurrent or persistent symptomatic infection of the nails, skin and mucosae mostly by Candida albicans. CMC is common in patients with profound primary T-cell immunodeficiency, who often display multiple infectious and autoimmune diseases. Patients with syndromic CMC, including autosomal dominant hyper IgE syndrome (AD-HIES), autosomal recessive (AR) CARD9 deficiency, and AR autoimmune polyendocrinopathy syndrome type I (APS-I), display fewer other infections. Patients with isolated CMC (CMCD) rarely display any other severe disease. Low IL-17 T-cell proportions were reported in patients with AD-HIES bearing heterozygous STAT3 mutations, prone to CMC and staphylococcal diseases, in a kindred with autosomal recessive CARD9 deficiency, prone to CMC and other fungal infections. High levels of neutralizing autoantibodies against IL-17 cytokines were documented in patients with APS-I presenting with CMC as their only infectious disease. The first three genetic causes of CMCD were recently reported: AR IL-17RA and AF IL-17F deficiencies and AD STAT1 gain-of-function, all associated with impaired IL-17 immunity. Inborn errors of human IL-17 immunity underlie CMC. Impaired IL-17 immunity may therefore account for CMC in other settings, including patients with acquired immunodeficiency.

PROGRAM PAGE 22; BIOGRAPHY PAGE 56

Bringing Treatments to the Clinic

Advances in the treatment of Alkaptonuria: the nitisinone experience

Lakshminarayan Ranganath

Professor/Consultant in Clinical Biochemistry and Metabolic Medicine
Royal Liverpool University Hospital, Prescot Street, Liverpool, UK, L7 8XP

Alkaptonuria (AKU) is a rare autosomal recessive condition, caused by the lack of the enzyme homogentisate 1, 2-dioxygenase (HGD). The absence of HGD results in patients being unable to fully metabolise the amino acids tyrosine and phenylalanine, resulting in high levels of HGA in biological fluids. In AKU from birth there is darkening of urine on standing owing to oxidation of the HGA. A black pigment produced by oxidation of HGA in connective tissues especially cartilage occurs, termed ochronosis. Premature severe arthritis affecting the spine and large weight-bearing joints follows ochronosis, leading to multiple joint replacements and a wheelchair-bound existence. Other common features besides arthritis are aortic valve stenosis, stone formation (renal, prostate, gall bladder and salivary), osteopenia (leading to fractures and complications during joint replacement surgery), and ruptures of tendons, muscle and ligaments. Overall, patients suffering from alkaptonuria-induced ochronosis experience pain, incapacity and disability. Until recently, there was no effective treatment for alkaptonuria. Dietary modifications to restrict intake of tyrosine and phenylalanine have met with limited success owing to the difficulty in maintaining such a restrictive diet for the whole of a person's life. There is some indication that ascorbic acid might have a protective effect but results have been variable. Nitisinone, a potent inhibitor of the enzyme responsible for converting hydroxyphenylpyruvate to HGA, reduces HGA levels but is not licensed for AKU. The creation of a National AKU Centre in Liverpool, funded by the United Kingdom Department of Health, has allowed supervised use of nitisinone in people with AKU older than 16 years. Clinical trials of nitisinone are needed to allow this drug to be licensed for the routine care of AKU patients. The licensing of nitisinone should enable the drug to be used more widely in the EC. To enable all of this to occur in AKU, we are carrying out studies to better understand the disease, and have developed better assessment tools to identify optimal outcome measures. An important goal is to address not only efficacy but also safety. These challenges are being successfully overcome by an excellent committed team that has allowed remarkable progress in a short space of time. The current presentation will highlight approaches to using the unlicensed drug in a clinic as well as developments that could allow routine use of this drug in AKU in the future.

PROGRAM PAGE 23; BIOGRAPHY PAGE 57

Chromatin Loops and CNVs

Alexandre Reymond

Maria Nicla Loviglio1, Marion Leleu2, Nele Ghedolf1, Eugenia Migliavacca1, Katrin Mannik1, 16p11.2 European Consortium, Jacques S. Beckmann3, Sébastien Jacquemont3, Jacques Rougemont2, Alexandre Reymond1
1. Center for Integrative Genomics, University of Lausanne, Lausanne, Switzerland
2. EPFL, Lausanne, Switzerland
3. Service de Génétique Médicale, CHUV, Lausanne, Switzerland

Hemizygosity of the 16p11.2 ~600 kb BP4-BP5 region (29.5 to 30.1Mb) is one ofthe most frequent known genetic etiology of autism spectrum disorder (ASD). It isalso associated with a highly penetrant form of obesity and a significant increasein head circumference. Mirror phenotypes are observed in carriers of thereciprocal duplication, who present a high risk of being underweight,microcephalic and/or schizophrenic. The just distal 16p11.2 220 kb BP2-BP3deletion is similarly associated with obesity and neuropsychiatric disorders. Weassessed possible chromatin interplays between these regions via long-rangeacting regulatory elements using high-resolution Chromosome ConformationCapture Sequencing (4C-seq) technology. We compared the three dimensionalorganization at the 16p11.2 locus between normal copy number and 600kbdeletion or duplication state. The analysis of normal copynumber samples highlights complex chromatin looping between genes located inthe 600kb and 220kb regions.
To gauge whether the presence of a rearrangement alters any of the identified chromatin interactions along chromosome 16, we compared interaction profile signals of deletion and duplication of the 600kb BP4-BP5 region and controls. Considering all viewpoints we identified 342 and 378 regions whose looping intensities are significantly modified in deleted and duplicated samples, respectively. In parallel, we profiled the transcriptome of lymphoblastoid cell lines of 50 600kb BP4-BP5 deletion, 32 reciprocal duplication and 29 control individuals and identified 1188 differentially expressed (DE) genes using a numerical variable to reflect a dosage effect. 27 of the 74 DE genes (36.5%) mapping on chromosome 16 show concomitant significant changes in chromatin interaction. Our results show that relevant chromatin conformation changes may arise from copy number variants. They suggest a link between the observed chromatin perturbations and gene expression and a possible contribution of the chromosome conformation to the disease phenotype.

PROGRAM PAGE 21; BIOGRAPHY PAGE 60

Vision Restoration Strategies in Blinding Retinal Dystrophies

José-Alain Sahel

1. Institut de la Vision/INSERM/UPMC Univ Paris 06/CNRS/CHNO des Quinze-Vingts;
2. Fondation Ophtalmologique Adolphe de Rothschild;
3. Académie des Sciences–Institut de France, Paris, France;
4. Institute of Ophthalmology, University College of London, UK.

Inherited retinal degenerations (IRDs) are major cause of yet untreatable vision loss. Based on better understanding of the complex pathophysiology of IRDs and recent technological advances, significant progress towards innovative therapeutic strategies has been made. Major advances in gene therapy in experimental models of human blinding diseases have been achieved and clinical translational studies are currently under way to evaluate the safety and clinical efficacy of gene therapies in inherited and complex retinal dystrophies, including Leber congenital amaurosis (LCA), Stargardt disease, age-related macular degeneration. The most notable gene-replacement approach (AAV-RPE65) demonstrated safety and vision restoration not only in rodents and large animal models but also in patients with LCA. Prevention the secondary degeneration of cones (by trophic factors and antioxidants) is a very promising approach for sigh restoration, as it could be applied in a wide range of mutations expressed in rods, even at late stages of disease. Recently discovered rod-derived cone viability factor (RdCVF) has been shown to induce cone survival in animal models of IRDs and is now in translation as a potential therapeutic agent. Restoring cone function by optogenetic is another innovative approach for treating retinal degeneration, currently under pre-clinical evaluation. It is based on the possibility to convert different retinal cell types into "artificial photoreceptors" by targeting their genetically encoded light sensors. In IRDs, "artificial retina" can be designed to take over the function of the lost photoreceptors. The epiretinal prosthesis Argus II and subretinal retina implant AG's Alpha IMS have recently obtained market authorisation. Retinal cell transplantation (retinal cells or retinal sheets) to replace the degenerating retinal cells with healthy photoreceptor cells and stem cells to create new retinal cells are nowadays areas of intensive research. Pluripotent stem cells like human embryonic stem cells (hESCs) or induced pluripotent stem cells (hiPSCs) have the ability to be expanded indefinitely in culture and could be used as an unlimited source of retinal cells for treatment of IRDs. iPSCs derived retinal cells have been generated by different laboratories worldwide and some groups are currently setting up human clinical trials with human iPSc derived RPE for treatment of AMD.

PROGRAM PAGE 24; BIOGRAPHY PAGE 63

Novel Treatment Strategies for Muscular Dystrophy

Michael Sinnreich

No treatment is currently available for patients with muscular dystrophies. Finding therapies is imperative as these disabling neuromuscular diseases have a high personal and socioeconomic impact. Dysferlin is a transmembrane protein implicated in surface membrane repair of muscle cells. Mutations in dysferlin lead to progressive muscle membrane damage and cause the muscular dystrophies Miyoshi Myopathy, Limb Girdle Muscular Dystrophy Type 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 dysferlin 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 cellular quality control system. Experiments in cultured patient-derived muscle cells indicate that inhibition of the degradation pathway of mis-sense mutated dysferlin restores membrane resealing function. Such therapeutic strategy could therefore be used for patients with specific dysferlin mis-sense mutations, and may be applicable also for other genetic diseases in which a mutated, but potentially functional protein is prematurely degraded by the cell's quality control system.

PROGRAM PAGE 23; BIOGRAPHY PAGE 64

Discovering Drugs for and with Patients

Nicolas Sireau

The AKU Society, a UK-based patient advocacy group, has worked in close partnership with the Royal Liverpool University Hospital (RLUH) and the University of Liverpool (UoL) over the past nine years to develop a major programme of research and treatment that works closely with international partners across the EU (Italy, Slovakia, Sweden, France, etc) and the USA. This started with the post-mortem of an AKU patient, funded through sponsored events, followed by the funding of a PhD programme that developed an in vitro model of AKU. Thanks to support from the Big Lottery Fund, the AKU Society then funded a four-year programme at UoL that successfully created an animal model of AKU, in which new therapies (small molecule, gene therapy and enzyme therapy) are being tested. The AKU Society and RLUH in parallel launched a global campaign to identify AKU patients, starting with three patients in the UK and reaching more than 1,000 patients globally by 2012. This was important in order to prepare for clinical trials. AKU patients and their families set up formal AKU Societies in the UK, France, Germany, the Netherlands, Italy, the USA and Canada in order to build the patient movement. A study was carried out to find out the average cost of an AKU patient to the National Health Service: £100,000 a year. This was used to build a case to the NHS for funding the National Alkaptonuria Society at RLUH and launching it in June 2012, where a treatment is now being used off label as part of an observational study. The AKU Society and its partners led the creation of an international consortium including 15 pharma companies, biotechs, universities, clinical trial centres, patient groups and contract research organisations in eight countries across Europe and North America. Thanks to funding from the European Commission, this consortium launched in late 2012 a five-and-a-half year clinical development programme to develop and obtain marketing authorisation for nitisinone, a small molecule that inhibits the accumulation of homogentisic acid. Further AKU research centres have also been established in Jordan and South India.

PROGRAM PAGE 25; BIOGRAPHY PAGE 65

Analyzing Progeria to Provide Insights into the Mechanisms of Ageing

Colin L. Stewart

Institute of Medical Biology, The Biopolis, Singapore 138648.

Progeria is a rare disease that manifests some aspects of premature ageing, particularly in the vascular system. In a mouse model for progeria, a mutation in the Lmna gene, that results in a truncated and farnesylated form of Lamin A, affects the postnatal, but not embryonic fibroblast's production of a functional extracellular matrix (ECM). Production of the ECM is necessary for fibroblast survival in vitro and is associated with defective Wnt signaling. In vivo, the Lmna mutation results in apoptosis of the vascular smooth muscle of the postnatal great vessels, as well skeletal abnormalities, pathologies that characterize progeria.

Using induced pluripotential stem (iPSC) cells derived from Progeria patient fibroblasts we found that different lineages exhibit different levels of the mutant lamin A protein, Progerin, with mesenchymal stem cells (MSCs) and vascular smooth muscle (VSMCs) expressing the highest levels and neuronal cells the lowest. The levels of expression broadly correlated with Progerin having the greatest deleterious effects on cell proliferation and viability of the MSCs and VSMCs that also were associated with a defective ECM and Wnt signaling.

Many LMNA mutations are associated with increased levels of another nuclear envelope protein SUN1. We derived Lmna mutant mice that lack Sun1 and found that loss of Sun1 markedly improves the viability of mice carrying the different Lmna mutations, including our progeria model. SUN1 loss to some extent also improves progeric cell viability in vitro.

Overall our studies reveal that VSMC and MSCs are particularly vulnerable to Progeroid mutations and provide insights into aging, particularly as to what factors may affect the vascular system as we age. These findings also suggest potential novel approaches to treating Progeria by either manipulating the Wnt signaling pathway or by inhibiting Sun1 expression

PROGRAM PAGE 24; BIOGRAPHY PAGE 66

Rare Disease Registries Succesful Models and Lessons

Marshall Summar

As the field of rare disease research and therapeutics expands, the need for a better understanding of the natural history and outcome grows. For designing clinical trials and comparing treatment models, the rarity of patients means that each one is an important source of information and changes the nature of conducting research in this field. We have over 10 years of experience with the NIH's Rare Disease Clinical Research Network and have observed the impact of data collection on therapeutics, community, and even outcomes. I will present some of the findings from our study and discuss many of the lessons we have learned for our families with urea cycle disorders.

PROGRAM PAGE 25; BIOGRAPHY PAGE 67

Development of an Intra-cerebral Gene Therapy Trial in Sanfilippo Disease Type A

Marc Tardieu

Marc Tardieu1 Michel Zerah3 and Olivier Danos3
Université Paris Sud 1, Université René Descartes2,
Assistance Publiques Hôpitaux de Paris 1& 2 Lysogène3.

Mucopolysaccharidosis type III or Sanfilippo diseases are a group of 4 lysosomal storage diseases. MPSIIIA is caused by an autosomal recessive genetic defect of lysosomal sulfamidase, N-sulfoglycosamine sulphohydrolase (SGSH). There is currently no available treatment for Sanfilippo syndromes and the direct delivery of the missing enzyme within brain through gene therapy was an appealing approach supported by numerous preclinical studies.

We initially defined in an epidemiological study the natural course of the diseases (Amer J Med Genet 2011, 155A:58-68).Two years ago we initiated an open label, single arm, monocentric, phase I/II clinical study evaluating the tolerance and the safety of intra-cerebral administration of adeno-associated viral vector serotype 10 carrying the human SGSH and SUMF1 cDNA for the treatment of Sanfilippo A syndrome. Four patients have been included and followed. The final results of the first year follow-up will be presented.

PROGRAM PAGE 22; BIOGRAPHY PAGE 68

Stem Cell Therapies of Autoimmune Diseases

Alan Tyndall

Alan Tyndall Dept of Rheumatology
University of Basel

In the past 15 years, more than 1,500 patients worldwide have received a hematopoietic stem cell transplant, mostly autologous, as treatment for a severe autoimmune disease (AD). A recent retrospective analysis of 900 patients showed that the majority had multiple sclerosis, systemic sclerosis, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and juvenile idiopathic arthritis (JIA; n = 65) and idiopathic cytopenic purpura. An overall 85 % 5-year survival and 43 % progression-free survival was seen, with 100-day transplant-related mortality (TRM) ranging between 1 % (RA) and 11 % (SLE and JIA). Around 30 % of patients in all disease subgroups had a complete response, despite full immune reconstitution. In many patients, morphological improvement was documented beyond any predicted known effects of intense immunosuppression alone. The ASTIS (Autologous Stem cell Transplantation In Scleroderma) trial is completed and showed a significantly improved event free survival in the transplanted patients. It is hoped that the results of three ongoing large prospective, randomized, controlled trials will allow modification of the protocols to reduce the high TRM, which relates to regimen intensity, age of patient, and comorbidity.

Multipotent mesenchymal stromal cells (MSCs), including autologous MSCs, have recently been tested in various ADs, exploiting their immune-modulating properties and apparent low acute toxicity. Despite large numbers of encouraging in vitro, animal model and small phase I/II studies, only one randomised clinical trial has been published in AD (RA) which showed a modest positive outcome.

The emerging issues surrounding stem cell therapy of autoimmune disease and possible solutions will be discussed.

PROGRAM PAGE 19; BIOGRAPHY PAGE 70

Regulatory Frameworks and Incentives for Development of Orphan Medicinal Products

Martine Zimmermann

The presentation will describe regulatory frameworks and incentives from FDA and EMA for development of Orphan Medicinal Products (OMPs).

Additionally, an overview of the different options to develop a regulatory pathway for rare/ultra rare disease settings.

Learning Objectives:
- Identify the main features of the different Orphan legislations including opportunities and challenges
- Get an overview on how to Develop a regulatory strategy for development of OMPs

PROGRAM PAGE 25; BIOGRAPHY PAGE 72

ABSTRACTS

Disclaimer: The abstracts are printed as received by the authors

Tissue Engineering Approaches and Non-invasive Optical Tools to Address the Diagnosis and Therapy of Rare Diseases in Women

AUTHORS: **BRAUCHLE EVA**, eva.brauchle@igb.fraunhofer.de, Germany; **HINDERER SVENJA**, svenja.hinderer@igb.fraunhofer.de,Germany; **VOTTELER MIRIAM**, Miriam.Votteler@med.uni-tuebingen.de, Germany; **EISENBEIS SIMONE**, Simone Simone.Eisenbeis@med.uni-tuebingen.de, Germany; **WALLWIENER DIETHELM**, diethelm.wallwiener@med.uni-tuebingen.de, Germany; **BRUCKER SARA**, sara.brucker@med.uni-tuebingen.de, Germany; **SCHENKE-LAYLAND KATJA**, katja.schenke-layland@igb.fraunhofer.de, Germany; **RALL K. KATHARINA**, katharina.rall@med.uni-tuebingen.de, Germany

KEYWORDS: Female genital malformations, Stem cells, Biomaterials, Multiphoton imaging, Raman spectroscopy

BACKGROUND: Female rare diseases are often connected to individual forms of genital malformations such as Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, which is the congenital absence of the vagina and uterus, occurring in approximately 1 of 4,500 female live births. While several projects are ongoing worldwide, the etiology for most female genital malformation is still unknown. The Women's University Hospital in Tübingen successfully established surgical therapies to correct certain malformations, but in complex malformations like cervical and partial vaginal aplasia, there is still no ideal implant that could replace missing or malformed genital tissues in women. Our goal is to design implantable tissue equivalents that can support or replace malformed female sex organs. We aim to illuminate pathways that are responsible for uterovaginal agenesis and other malformations and which can be translated into tissue constructs with stem cell technologies. We will characterize healthy vaginal and uteruine tissue, analyzing their biomechanical and functional properties, which are determined by the interaction of extracellular matrix (ECM) and specific cell phenotypes. Key proteins of the ECM will be identified and will serve as constituents to manufacture new biomaterials by electrospinning or bioprinting technologies. These processes enable the design of biomaterials with complex multi-layered compositions, defined fiber alignments and pore sizes; parameters that are related to biocompatibility and cell-material interactions of the manufactured materials. In addition, we will investigate the use of non-invasive optical technologies that can assess biochemical information of healthy and in vitro constructed genital tissues. Multiphoton imaging visualizes the three-dimensional organization of collagen as well as elastin fibers and can characterize cells based on their intrinsic fluorescent metabolites. Raman spectroscopy, another laser-based technique, reflects the global molecular constitutions within tissues and can identify ECM components. Due to their non-invasive character, both Raman spectroscopy and multiphoton imaging could potentially serve as diagnostic tools to detect tissue remodeling processes, which are related to rare disease in women. Ultimately, our findings will assist in the development of new diagnostic tools and therapies for women affected with in uterovaginal agenesis and other genital malformations.and help to identify the underlying etiology.

Muscle Gene Transfer Mediated by Episomal Plasmid Vectors and the Piggy Bac Transposon System

AUTHORS: **IYER PAVITHRA**, pavithra.iyer@unil.ch, Switzerland; **VAN ZWIETEN RUTHGER**, ruthger.vanzwieten@unil.ch, Switzerland; **LEY DÉBORAH**, deborah.ley@unil.ch, Switzerland; **PUTTINI STEFANIA**, stefania.puttini@epfl.ch, Switzerland; **MERMOD NICOLAS**, nicolas.mermod@unil.ch, Switzerland

KEYWORDS: Duchenne muscular dystrophy, mesoangioblasts, PiggyBac transposon system, non-replicating episomal plasmid, cell therapy

BACKGROUND. Duchenne muscular dystrophy (DMD) is a frequently occurring lethal X-linked disease in which dysfunctional dystrophin leads to muscle wasting. Autologous transplantation of myogenic stem cells genetically modified to express a functional dystrophin is an attractive therapeutic option for treatment of the disease. There has been very modest success in cell therapy for muscular dystrophy due to several factors; some of them being the difficulty to achieve efficient gene transfer due to the large size of the dystrophin gene and the transgene silencing. The present study investigates the potential use of non-viral gene transfer in mesoangioblasts for cell therapy for DMD. Mesoangioblasts are muscle progenitor cell in the embryonic dorsal aorta wall of vertebrates, including mice and humans, with reported ability to fuse with myofibres.

METHODS: This study focuses on two approaches for muscle gene expression with mesoangioblasts. The first approach is using non-replicating episomal plasmid vectors, which are hypothesized to remain in the post-mitotic muscle tissue. The second approach is to induce genomic integration of the transgene by the PiggyBac transposon system. Muscle gene expression is studied by transplantation of genetically modified mesoangioblasts in the tibialis anterior of mice. Results: Intramuscular transplantation of mesoangioblasts containing the integrating transposon system or the episomal plasmid in mouse tibialis anterior muscles led to widespread and sustained eGFP expression in myofibres for at least up to two months after transplantation. It is likely that the episomal plasmid follows the same mechanism of long-term persistence as for muscle electroporated in vivo, but without the limitations of in vivo electroporation. In case of the transposon based approach, transposition in mesoangioblasts allowed sustained expression in mouse muscle, even after mesoangioblast fusion with resident myofibers.

CONCLUSIONS: These findings provide a proof-of-principle that the episomal plasmid vectors as well as the PiggyBac transposon system may have the potential to improve cell-based therapies of DMD. The same approaches will be further used with dystrophin containing vectors to test improvement of functionality of murine muscles and confirm potential use in therapy. It is hypothesized that the mesoangioblasts expressing dystrophin would be able to fuse with the myofibres and improve muscle functionality.

SESSION A: GEHRY BUILDING LEVEL -2

STEM CELL AND CELL THERAPY APPROACHES

ABSTRACT n° A020_2014

Derivation of Traceable and Transplantable Photoreceptors from Mouse Embryonic Stem Cells

AUTHORS: **DECEMBRINI SARAH**, sarah.decembrini@fa2.ch, Switzerland; **KOCH UTE**, ute.koch@epfl.ch, Switzerland; **RADTKE FREDDY**, freddy.radtke@epfl.ch, Switzerland; **MOULIN ALEXANDRE**, alexandre.moulin@fa2.ch, Switzerland; **ARSENIJEVIC YVAN**, yvan.arsenijevic@fa2.ch, Switzerland;

KEYWORDS: Photoreceptor, Tranplantation, ESCs

Retinal degenerative diseases resulting in the loss of photoreceptors are a major cause of blindness. Recently, different groups validated the possibility to reactivate dormant retinal circuits of degenerating retinas using retinal prosthesis, gene therapy, cell replacement therapy. Photoreceptor replacement therapy may be feasible since transplanted photoreceptors, collected directly from the developing or the adult retina, have been shown to restore some visual function in mice affected by retinal degeneration. Because the developing retina is not a suitable source of renewable photoreceptors, we focused on embryonic stem cells (ESC) for their capacity to generate retinal progenitors and photoreceptor cells in vitro.
In this study, we derived a new transgenic ESC line in which the reporter gene, the Crx-GFP transgene, is expressed in both post-mitotic immature and mature photoreceptors, and assessed the extent to which this protocol recapitulates photoreceptor development in vitro.
Various oxygen concentrations were tested at different development stages to improve photoreceptor production. As observed during the retinogenesis, the optimized 3D-retina induction protocol allows the production of GFP-positive photoreceptors between 12 and 14 days of culture which reach the peak of birth between day 18 and 20 of culture. Similarly the intensity of the GFP signal and their alignment increased over time. We observed that hyperoxic condition improved photoreceptor survival only when present since photoreceptor differentiation onset. Up to ten layers of photoreceptors can be formed in each in vitro-generated retinas. In addition we proved that transplantation of ESC-derived photoreceptors is feasible. No appearance of tumour formation was detected after transplantation of sorted photoreceptor cells. Many Crx-GFP-positive cells show the presence of outer-segments, ribbon synapses, and light signal transduction pathway proteins.
These experiments show the feasibility to reliably generate a large quantity of integration-competent photoreceptors from ESC. A further characterization of the transplanted photoreceptors to reveal their capacity to mediate light stimuli is underway.

PROGRAM PAGE 19

SESSION B: GEHRY BUILDING LEVEL -2

MAPPING DISEASES AND GENOME INSTABILITIES

ABSTRACT n° A002_2014

Hunting for New Developmental Mutations with Dogs

AUTHORS: **HYTÖNEN MARJO**, marjo.hytonen@helsinki.fi, Finland; **ANU LAPPALAINEN**, anu.k.lappalainen@helsinki.fi, Finland; **ARUMILLI MEHARJI**, meharhi.arumilli@helsinki.fi, Finland; **LUKINMAA PIRJO-LIISA**, Pirjo-Liisa.Lukinmaa@helsinki.fi, Finland; **SARKIALA-KESSEL EVA**, eva.sarkiala-kessel@helsinki.fi, Finland; **NIEMINEN PEKKA**, pekka.nieminen@helsinki.fi, Finland; **LOHI HANNES**, hannes.lohi@helsinki.fi, Finland

KEYWORDS: Gene mapping, mutation, dog, developmental

ABSTRACT: Dogs have emerged as clinically and genetically relevant large animal models for human inherited disorders. Selective breeding has created more than 400 different breeds each representing genetic isolates with breed-specific morphological and behavioral characteristics as well as disease profile. Majority of the over 600 genetic disorders that have been described in dogs are similar to human conditions. Most of the canine disorders are Mendelian. Unique breed structure facilitates gene discovery and provides new candidate genes for corresponding human conditions. Methods: We have used various clinical and pathological techniques such as radiography and histology to characterize the novel canine phenotypes. To identify the genetic causes, we have applied both genome wide association and whole genome resequencing approaches.
RESULTS: We have established a large dog DNA bank with over 50 000 samples from 300 breeds. This provides a major resource for various genetic studies, including developmental disorders. We have initiated a significant multidisciplinary program to clinically and genetically characterize many congenital traits, including hip dysplasia, vertebral anomalies, craniomandibular osteopathy, mucopolysaccharidosis, chondrodysplasia and dental anomalies. We study here two recessive previously unknown disorders: a congenital syndrome characterized by severe mandibular prognathism, patellar subluxation and mental disturbances, and a disease with vigorous tooth attrition caused by abnormal hard tissue structure.
CONCLUSIONS: The identification of the mutations causing these diseases will provide new candidate genes for corresponding human conditions, will establish the affected breeds as models to further explore disease mechanisms and develop therapeutic approaches. Furthermore, it will enable the development of genetic tests for breeding purposes in dogs. The presence of a large range of different breed-specific developmental defects in dogs provides a remarkable resource to facilitate the gene discovery in rare disorders of comparative interest in human.

Is the Genetic Basis of Li- Fraumeni Syndrome Fully Deciphered?

AUTHORS: **AKOUCHEKIAN MANSOUREH**, m-akouchekian@tums.ac.ir; Iran

KEYWORDS: Li-frameni syndrome, P53 gene, germline mutation

BACKGROUND: The definitions of predisposition syndromes for cancer have been characterized due to the occurrence of a non-random aggregation of cancers in families. Careful epidemiological studies are needed to distinguish between environmental and genetic causes, and in many cases this has confirmed the existence of inherited predisposition. Li-Fraumeni syndrome (LFS1; MIM# 151623) is one of the cancer predisposition syndromes, which was initially proposed in 1969 and subsequently confirmed by a number of epidemiological studies. LFS is one of the most serious hereditary cancer syndromes with high risk of malignancy already in childhood. This syndrome knows as an autosomal dominant cancer predisposing syndrome due to a germline mutation in the p53 tumor suppressor gene.
METHODS: We describe a representative case of Li Fraumeni syndrome. The case is a 43 years old male who had Osteosarcoma in Mandible and positive family history of cancer. In the other words his mother died at the age of 29 for brain cancer. His sister died at the age of 18 for breast cancer. His brother died at the age of 36 for liver cancer and also he has had a sister died by leukemia at the age of 16. Complete sequence analysis of P53 gene in this patient was performed. After following detailed analyse of the family history and also medical records of affected individuals, we used standard diagnostic tools, e.g. sequencing and multiplex ligation dependent probe amplification (MLPA) to analyse the P53 gene in this family. Results: We have done whole gene sequencing for P53 gene. We performed a germline mutation in this patient that previously reported as somatic mutation in LFS in IARC database.
CONCLUSIONS: Genomic modifications for tumor risk and genotype-phenotype correlations in LFS are still to be identified. We believe every new finding in this area can provide new insights into the pathogenesis and progression of Li-frameni syndrome.

Copy Number Analyses in Five Monozygotic Discordant Twin Pairs Reveal MMP14, LRP10 and Genes Relevant for Extra-Cellular Matrix and Neoangiogenesis as Candidate Genes in Uterovaginal Aplasia (MRKH Syndrome)

AUTHORS: **RALL K. KATHARINA**, katharina.rall@med.uni-tuebingen.de, Germany; **EISENBEIS SIMONE**, simone.eisenbeis@med.uni-tuebingen.de, Germany; **BARRESI GIANMARIA**, g.barresi@student.uni-tuebingen.de, Germany; **WALTER MICHAEL**, michael.walter@med.uni-tuebingen.de, Germany **POTHS SVEN**, sven.poths@med.uni-tuebingen.de, Germany; **WALLWIENER DIETHELM**, diethelm.wallwiener@med.uni-tuebingen.de, Germany; **RIESS OLAF**, olaf.riess@med.uni-tuebingen.de, Germany; **BRUCKER SARA**, sara.brucker@med.uni-tuebingen.de, Germany; **BONIN MICHAEL**, michael.boni@med.uni-tuebingen.de, Germany

KEYWORDS: uterovaginal aplasia, MMP14, monozygotic twins, LRP10, CNV

BACKGROUND: The Mayer-Rokitansky-Küster-Hauser syndrome (MRKHS) affects at least 1 in 4,500 female live births. It is characterized by vaginal and uterine aplasia in individuals with a normal 46, XX karyotype and normal secondary characteristics. The syndrome has been considered as sporadic anomaly for long time but familial clustering occurs and supports the hypothesis of a genetic origin. However the identification of any locus using standard genetic linkage analysis was impossible so far and cases of monozygotic, discordant twins challenged the purely genetic basis.
METHODS: In our study we had the unique opportunity to genetically analyze five pairs of monozygotic twins discordant for MRKHS comprising the advantage that already one pair of twins can reveal the genetic cause of the syndrome. We used copy number variations (CNVs) in order to identify differences between the affected and unaffected twin. Results: In total, 64 CNVs were detected but none of the CNVs was differential between the discordant twin pairs. Additional detailed analysis revealed differences in CNV-patterns in one out of the five twin pairs which have never been listed within the Database of Genomic Variants. In twin 1 who had MRKH type II with unilateral kidney agenesis and a duplicated ureter we identified three duplications and one deletion. None of the deleted genes had any known relevance for the development of the female genital tract. However the duplication found on chromosome 14 comprised two genes namely MMP14 and LRP10 which have known functions within uterine endometrium and embryology. Additional network analysis revealed important connections to differentially expressed genes in MRKH patients found in earlier studies. These genes include several molecules involved in remodelling of the extracellular matrix like MMP14, SPOCK3, ITIH5, PI3K and neoangiogenesis like VEGFC, KDR, FLT1 and neuropilin.
CONCLUSION: The occurrence of these clusters gives evidence of a deficiency in vascularization during the uterine development and/or disturbed reorganization of ECM components especially during the elongation of the Müllerian duct singed by the influence of the embryological relevant (PI3K)/AKT pathway in the network.This scenario allows us to reason that the genes are probably involved in the onset of the anomaly. Therefore these genes could be seen as new candidates for the MRKHS.

Epigenetic Differences as a Causing Mechanism of the MRKH Syndrome: Analysis of Differentially Expressed MicroRNAs in Uterine Rudiments of MRKH Patients Compared with Uterine Tissue from Control

AUTHORS: **RALL K. KATHARINA**, katharina.rall@med.uni-tuebingen.de, Germany; **EISENBEIS SIMONE**,simone.eisenbeis@med.uni-tuebingen.de, Germany; **HENNINGER VERENA**, verena.henninger@med.uni-tuebingen.de, Germany; **RÜCKNER DANIEL**, rueckner@gmx.de, Germany; **WALTER MICHAEL**, michael.walter@med.uni-tuebingen.de, Germany; **POTHS SVEN**, sven.poths@med.uni-tuebingen.de, Germany; **WALLWIENER DIETHELM**, diethelm.wallwiener@med.uni-tuebingen.de, Germany; **RIESS OLAF**, olaf.riess@med.uni-tuebingen.de, Germany; **BRUCKER SARA**, sara.brucker@med.uni-tuebingen.de,Germany; **BONIN MICHAEL**, michael.bonin@med.uni-tuebingen.de, Germany

KEYWORDS: uterovaginal aplasia, microRNA, MRKH, ESR, epigenetic

BACKGROUND: The Mayer-Rokitansky-Küster-Hauser syndrome (MRKHS) is a malformation of the female genital tract characterized by congenital aplasia of the uterus and the upper part of the vagina. It is present in at least 1 out of 4,500 women with functional ovaries and a normal 46, XX karyotype. To date the etiology is largely unknown. In a previous study, where we used a combined whole-genome expression and methylation approach we came to the hypothesis that either deficient estrogen receptors or the ectopic expression of certain HOXA genes could lead to this malformation. Epigenetic causes are futher supported by the existence of five monozygotic, phenotypically discordant twin pairs in our collective.

METHODS: In order to determine differences on the level of gene expression between MRKH patients and non-MRKH-controls microRNA-sequencing experiments were carried out. Uterine rudiments of 10 MRKH patients and uterine tissue samples from 10 control patients were obtained and used for microRNA isolation. Differentially expressed microRNAs between both tissue groups were detected by sequencing using Illumina Genome Analyzer IIx. The validation of this results were performed by qRT- PCR.

RESULTS: The sequencing revealed 33 significantly differential expressed microRNAs. Associated candidate genes coincide partly with genes identified in the previous whole-genome and methylation approach. All results were validated by qRT-PCR. After comparing the preliminary data and the current literature, especially 5 microRNAs are in a special focus with 4 being significantly downregulated in MRKH patients and one significantly upregulated. These candidate genes such as ESR1, FGF 7, SPOCK3 and HOXA 5 are known to play an important role in embryonic kidney and uterine development and the onset of menarche.

CONCLUSION: With the analysis of differentially expressed microRNAs we were able to confirm some of the previously described candidate genes for MRKHS and to identify new genes likely involved in the onset of the syndrome. Currently pending trials, such as the UTR cloning will provide further insights into their influence of the disease origin .

Canine Models of Human Rare Diseases

AUTHORS: **LOHI HANNES**, hannes.lohi@helsinki.fi, Finland

KEYWORDS: dog, gene mapping, comparative genetics, GWAS, association

BACKGROUND: The annotation of the canine genome and subsequent development of new genomic tools have established purebred dogs as a powerful model for gene discovery. Over 600 genetic conditions often enriched in certain breeds have been described and many of them are Mendelian and represent clinically relevant models to corresponding human disorders. We have established a large collaborative genomic programme to establish resources and identify the genetic causes in various disease groups. We have collected blood samples in over 50 000 dogs in 300 breeds including more than 100 phenotypes in various disease groups, including neurological, vision, autoimmune, musculoskeletal, metabolic and behavioral conditions. Our aim is to discover the clinical and genetic backgrounds of the canine conditions as models for the human disorders.

METHODS: Clinical diagnoses have been established through multiple protocols in collaboration with specialized veterinarians. We have established large pedigrees with the help of a public registry to define the modes of inheritance of the conditions, to establish proper study design for genetic analyses. To identify the genetic causes behind the disorders, we have used canine-specific high-density SNP arrays, exome or whole genome resequencing methods. Various bioinformatics, statistical and validation methods have been used to map new disease loci and confirm candidate mutations.

RESULTS. We have identified mutations in canine syndromic and idiopathic epilepsies, progressive ataxia, progressive retinal atrophy, various storage diseases (Pompe disease, MPS VII) and chondrodysplasia. In addition, we have mapped new loci for late-onset glaucoma, different neurobehavioral traits such as noise and social phobia, skeletal conditions including hip dysplasia and dwarfism. Our ongoing exome and resequencing studies aim to establish a significant sequence and variant database to further facilitate gene discoveries in many conditions.

CONCLUSIONS: Our results have several implications. First, we have identified new candidates genes and pathways for mutation screenings in human patients. Second, we have discovered new disease mechanisms and developed new genetic tests for breeding programs. Finally, gene discoveries have established large animal models for the development of novel therapies, such as our ongoing collaborative gene therapy effort in the Pompe disease.

Informing Rare Disease Mechanisms: Informatics for the International Mouse Phenotyping Consortium

AUTHORS: **MEEHAN TERRENCE**, tmeehan@ebi.ac.uk, EMBL-EBI, United Kingdom; **BLAKE ANDREW**, A.Blake@har.mrc.ac.uk, MRC Harwell, United Kingdom; **CHEN CHAO-KUNG**, ckchen@ebi.ac.uk, EMBL-EBI, United Kingdom; **DI FENZA ARMIDA**, a.difenza@har.mrc.ac.uk, MRC Harwell, United Kingdom; **EASTY RICHARD**, re4@sanger.ac.uk, Wellcome Trust Sanger Institute, United Kingdom; **FIEGEL TANYA**, t.fiegel@har.mrc.ac.uk, MRC Harwell, United Kingdom; **HORNE ALAN**, ah17@sanger.ac.uk, Wellcome Trust Sanger Institute, United Kingdom; **IYER VIVEK**, vvi@sanger.ac.uk, Wellcome Trust Sanger Institute, United Kingdom; **KARP NATASHA**, nk3@sanger.ac.uk, Wellcome Trust Sanger Institute, United Kingdom; **KOSCIELNY GAUTIER**, koscieln@ebi.ac.uk, EMBL-EBI, United Kingdom; **MASON JEREMY**, jmason@ebi.ac.uk, EMBL-EBI, United Kingdom; **MELVIN DAVID**, dgm@sanger.ac.uk, Wellcome Trust Sanger Institute, United Kingdom; **MORGAN HUGH**, h.morgan@har.mrc.ac.uk, MRC Harwell, United Kingdom; **RETHA AHMAD**, a.retha@har.mrc.ac.uk, MRC Harwell, United Kingdom; **JACOBSEN JULES**, jj8@sanger.ac.uk, Wellcome Trust Sanger Institute, United Kingdom; **SANTOS LUIS**, l.santos@har.mrc.ac.uk, MRC Harwell, United Kingdom; **SNEDDON DUNCAN**, d.sneddon@har.mrc.ac.uk, MRC Harwell, United Kingdom; **TUDOSE ILINCA**, tudose@ebi.ac.uk, EMBL-EBI, United Kingdom; **WARREN JONATHAN**, jwarren@ebi.ac.uk, EMBL-EBI, United Kingdom; **WESTERBERG HENRIK**, h.westerberg@har.mrc.ac.uk, MRC Harwell, United Kingdom; **YAIKHOM GAGARINE**, g.yaikhom@har.mrc.ac.uk, MRC Harwell, United Kingdom; **BROWN STEVE D.**, s.brown@har.mrc.ac.uk, MRC Harwell, United Kingdom; **FLICEK PAUL**, flicek@ebi.ac.uk, EMBL-EBI, United Kingdom; **MALLON ANN-MARIE**, a.mallon@har.mrc.ac.uk, MRC Harwell, United Kingdom; **PARKINSON HELEN**, parkinson@ebi.ac.uk, EMBL-EBI, United Kingdom; **SKARNES WILLIAM C.**, skarnes@sanger.ac.uk, Wellcome Trust Sanger Institute, United Kingdom

KEYWORDS: Disease models, Phenomics, Genetics, Gene function, Informatics

STATEMENT OF PURPOSE: The International Mouse Phenotyping Consortium (IMPC) is building the first truly comprehensive functional catalogue of a mammalian genome that will inform mechanisms of rare disease.

METHODS: The IMPC is coordinating efforts to generate a knockout mouse strain for every protein-coding gene. These mouse strains are characterized using a standardized, broad-based phenotyping pipeline and data is collected and archived centrally by the IMPC-Data Coordinating Centre. Dedicated 'data wranglers' are working with each phenotyping centre to ensure proper transfer and quality control of data. An automated statistical analysis pipeline identifies knockout strains with significant changes in phenotype parameters. Potential disease models are identified by orthologous gene and by orthologous phenotype features.

SUMMARY OF RESULTS: Over 3000 IMPC mouse strains have been produced, with emerging phenotype data available for hundreds of these strains. Users can freely access all data including new gene-phenotype via an intuitive web portal. Annotation with biomedical ontologies allows biologists and clinicians to easily find mouse strains with phenotypic traits relevant to their research. Users can register interest in genes so they may be informed as mouse models and new phenotype data become available. The community is invited to explore and provide feedback as we build this rich resource for rare disease research at: www.mousephenotype.org

PROGRAM PAGE 21

Genomic Instability of Osteosarcoma Cells During in Vitro Culture

AUTHORS: **MUFF ROMAN**, rmuff@research.balgrist.ch, KlinikBalgrist, Switzerland; **FUCHS BRUNO**, bfuchs@research.balgrist.ch, **KLINIKBALGRIST**, Switzerland; Baudis Michael, mbaudis@gmail.com, Switzerland

KEYWORDS: osteosarcoma, metastasis, genomic instability, cell lines, microarray

Osteosarcoma (OS) is a rare bone tumor with poor prognosis in case of metastasis formation. There are only a few established OS cell lines available for the research in the OS field. We have investigated the genomic stability during in vitro culture of three OS cell line systems consisting of a low metastatic parental cell line and a derivative thereof with increased metastatic potential. The OS cell lines (parental/metastatic) SAOS/LM5, HOS/143B and Dunn/LM8 were cultured in vitro for periods to achieve more than 150 cell doublings. Gene expression was analysed by microarray using Agilent microarray kits, and array comparative genomic hybridization (aCGH) by Affymetrix HD CytoScan arrays. All cell lines, except 143B, showed altered gene expression during in vitro culture, with two metastatic cell lines (LM5 and LM8) exhibiting greater instability than the parental cell lines. In parental SAOS and Dunn cells 53 and 79 genes, respectively, were differentially (>2-fold; fdr

Genome-engineering Tools to Establish Accurate Reporter Cell Lines that enable Identification of Therapeutic Strategies to Treat Friedreich's Ataxia

AUTHORS: **VILLASEÑOR RODRIGO**, rodrigo.villasenor@fmi.ch, FMI, Basel, Switzerland

KEYWORDS: Friedreich's Ataxia (FRDA), triplet repeat expansion disorder (TRED), high-throughput screening (HTS), genome engineering, drug discovery

Rodrigo Villaseñor1,2,5, Loren Miraglia3,5, Angelica Romero3, Buu Tu3, Tanel Punga1,2,4, Philip Knuckles1,2, Stephan Duss1,2, Tony Orth3, and Marc Bühler1, 2; 1Friedrich Miescher Institute for Biomedical Research, Maulbeerstrasse 66, 4058 Basel, Switzerland; 2University of Basel, Petersplatz 10, 4003 Basel, Switzerland; 3Genomics Institute of the Novartis Research Foundation, 10675 John J Hopkins Dr., San Diego, CA 92121, USA; 4Present address: Uppsala University, Department of Medical Biochemistry and Microbiology, BMC Box 582, 75123 Uppsala, Sweden; 5These authors contributed equally to this work.; Correspondence should be addressed to M.B. (marc.buehler@fmi.ch), T. O. (aorth@gnf.org)

SUMMARY: Friedreich's Ataxia is a neurodegenerative disease caused by deficiency of the mitochondrial protein frataxin. This deficiency results from expansion of a trinucleotide repeat in the first intron of the frataxin gene. Because this repeat expansion resides in an intron and hence does not alter the amino acid sequence of the frataxin protein, gene reactivation could be of therapeutic benefit. High-throughput screening for frataxin activators has so far met with limited success because current cellular models may not accurately assess endogenous frataxin gene regulation. Here we report the design and validation of genome engineering tools that enable the generation of human cell lines that express the frataxin gene fused to a luciferase reporter gene from its endogenous locus. Performing a pilot high-throughput genomic screen in a newly established reporter cell line, we uncovered novel negative regulators of frataxin expression. Rational design of small molecule inhibitors of the identified frataxin repressors and/or high-throughput screening of large siRNA or compound libraries with our system may yield treatments for Friedreich's Ataxia.

neXtProt, a Knowledge Platform on Human Proteins, its Relevance to the Research on Rare Diseases

AUTHORS: SIB Swiss Institute of Bioinformatics, Rue Michel-Servet 1, 1211 Geneva **PASCALE GAUDET,** pascale.gaudet@isb-sib-ch; **MONIQUE ZAHN** Monique.Zahn@isb-sib.ch; **GHISLAINE ARGOUD-PUY** Ghislaine.Argoud-Puy@isb-sib.ch; **ISABELLE CUSIN** Isabelle.Cusin@isb-sib.ch; **PAULA DUEK** Paula.Duek@isb-sib.ch; **OLIVIER EVALET** olivier.evalet@isb-sib.ch; **ALAIN GATEAU** alain.gateau@isb-sib.ch; **ANNE GLEIZES** anne.gleizes@isb-sib.ch; **PIERRE-ANDRÉ MICHEL** Pierre-Andre.Michel@isb-sib.ch; **MARIO PEREIRA** mario.pereira@isb-sib.ch; **DANIEL TEIXEIRA** daniel.teixeira@isb-sib.ch; **LYDIE LANE** lydie.lane@isb-sib.ch; **AMOS BAIROCH** ab@isb-sib.ch

KEYWORDS: Human protein database, protein variants, protein function, biocuration.

neXtProt (www.nextprot.org/) is a human protein-centric knowledge platform. Developed at the Swiss Institute of Bioinformatics (SIB), it aims to help researchers answer questions relevant to human proteins. neXtProt is built on the extensive corpus of curated knowledge originating from the UniProtKB/Swiss-Prot knowledgebase and is complemented by carefully selected and filtered high-throughput data pertinent to human proteins. We want neXtProt to be of use to researchers working in the field of human health and specifically to help them understand and analyze the growing corpus of variation data. To do so we are integrating information on protein variations either arising from SNPs (mainly from dbSNP), disease-causing mutations (from Swiss-Prot and our own annotation efforts) or somatic variants in cancer samples (from COSMIC). We are interested in contributing to the community efforts to tackle rare diseases and are open to collaborative projects to annotate and organize the type of protein-centric information that would benefit to these efforts.

This presentation will give an overview of the relevance of neXtProt in the context of human protein variations.

A Xenopus Model of Alkaptonuria

AUTHORS: BRANDLI ANDRE, abrandli@med.lmu.de, Ludwig-Maximilians-University Munich, Germany

KEYWORDS: Alkaptonuria, Animal model, Xenopus, Drug development, Nitisinone

Alkaptonuria (AKU) is a rare metabolic disease caused by mutations in the gene encoding homogentisate 1,2-dioxigenase (HGD), an enzyme participating in the catabolism of tyrosine. Patients with HGD deficiencies accumulate homogentisic acid (HGA) in the blood circulation and excrete large amounts in the urine, causing darkening of the urine upon exposure to air. Progressive accumulation of HGA polymers damages cartilages, heart valves, and kidneys. Presently, no approved treatment modality is available for AKU patients.
The full scope of AKU cannot be modeled in cell or organ cultures. A genetic mouse model of AKU was recently established and has been instrumental in the study of the histopathology of AKU and validation of nitisinone as a promising drug candidate for the long-term treatment of AKU. Cost considerations and technical limitations prohibit however the use of the mouse AKU model for large-scale drug screening purposes.
Non-mammalian vertebrates, such as fish and amphibians, typically generate thousands of offspring that can be raised in multi-well dishes and utilized for large-scale drug discovery screens. For example, we have developed a proprietary chemical library screening strategy to identify small organic molecules that interfere in vivo with vascular development and/or functions in embryos of the African clawed frog Xenopus laevis (Kälin et al. 2009 Blood 114, 1110-1122). HGD genes are present in the Xenopus genome, and we have been recently found that Xenopus embryos express HGD transcripts in the developing liver and kidneys. Using antisense morpholino knockdown methodology, we have developed a first Xenopus model of AKU for drug discovery and drug testing purposes. In addition, TALE nuclease (TALENs) and CRISPR/Cas9 technologies are being evaluated to disrupt HGD gene functions in vivo. Mutant Xenopus embryos that adequately recapitulate human AKU pathology will be used for the preclinical testing of promising AKU drug candidates, such as nitisinone. Furthermore, the Xenopus AKU model will be employed for in vivo drug discovery screening to identify novel small organic molecules that suppress the AKU phenotype in vivo.

Molecular Consequences of Defective Serpinh1 in Osteogenesis Imperfecta

AUTHORS: LINDERT USCHI, uschi.lindert@kispi.uzh.ch, Children´s Hospital Zurich, Switzerland; **WEIS MARY ANN**, maweis@u.washington.edu, University of Washington, United States of America; **EYRE DAVID**, deyre@u.washington.edu, University of Washington, United States of America; **SEELIGER FRANK**, Frank.Seeliger@astrazeneca.com, Sweden; **HAUSSER INGRID**, Ingrid.Hausser@med.uni-heidelberg.de, University of Heidelberg, Germany; **LEEB TOSSO**, tosso.leeb@itz.unibe.ch, University of Bern, Switzerland; **ROHRBACH MARIANNE**, Marianne.Rohrbach@kispi.uzh.ch, Children´s Hospital Zurich, Switzerland; **GIUNTA CECILIA**, Cecilia.Giunta@kispi.uzh.ch, Children´s Hospital Zurich, Switzerland

KEYWORDS: connective tissue, osteogenesis imperfecta, collagen, SerpinH1, unfolded protein response

Osteogenesis imperfecta (OI) is a heritable connective tissue disease characterized by bone fragility and increased risk to fractures. Up to now, mutations in at least sixteen genes have been associated with dominant, respectively recessive forms of OI, and have been implicated in altered posttranslational processing of procollagen, or altered bone homeostasis. Among those, SERPINH1 (HSP47) was identified to cause a severe form of OI in Dachshund (Leu326Pro), as well as in humans (1 single case with a Leu78Pro mutation). The gene product, heat-shock protein 47 (HSP47), acts as a chaperon for procollagen folding in the ER. It is speculated to prevent premature lateral aggregation, and to provide a quality control mechanism in collagen biosynthesis.
To elucidate the disease mechanism underlying the SERPINH1 mutation in the Dachshund, we applied a set of biochemical assays, as follows: SDS-PAGE analysis of in vitro produced procollagen of OI-dog and control dog fibroblasts, tandem mass spectrometry of bone collagen, transmission electron microscopy of cultured fibroblasts, and western blot and immunofluorescent staining to access protein expression and stability. SDS-PAGE analysis of in vitro produced procollagen, showed decreased migration of type I and type V collagen and slightly delayed secretion of collagen in the OI-dog compared to control dog, thus suggesting a defect in procollagen processing and/or folding. In line with the migration shift detected on SDS-PAGE, tandem mass spectrometry from bone of the OI-dog and control dog revealed alterations in collagen cross-linking and hydroxylation levels. Interestingly, transmission electron microscopy of cultured fibroblasts of the OI-dog showed enlarged endoplasmic reticulum (ER) cisterns. In contrast to the mutation in the human case causing protein instability, the mutant protein in the Dachshund was detectable by immunofluorescent staining and the protein amount was only slightly decreased in western blot analysis.
Taken together, these results suggest that the SERPINH1 mutation in the Dachshund may lead to delayed folding and secretion of collagen, and to its accumulation in the ER, thus leading to ER-stress and the activation of the unfolded protein response. Indeed, initial experiments using Tunicamycin and Thapsigargin to induce ER-stress showed a stronger activation of the ER-stress markers GRP78 and CHOP in OI-dog fibroblasts compared to control dog fibroblasts.

Searching for Biomedical Relationships among Genes and Diseases: a Great Ally for Rare Diseases

AUTHORS: **SÁNCHEZ-JIMÉNEZ FRANCISCA MARÍA**, kika@uma.es, University of Malaga-CIBER de Enfermedades Raras, Spain; **RODRIGUEZ-LOPEZ ROCIO**, rocio84@gmail.com, University of Malaga-CIBER de Enfermedades Raras, Spain; **REYES-PALOMARES ARMANDO**, armandorp@gmail.com, University of Malaga-CIBER de Enfermedades Raras, Spain; **GARCIA-RANEA JUAN ANTONIO**, ranea@uma.es, University of Malaga-CIBER de Enfermedades Raras, Spain; **MOYA-GARCIA AURELIO A.**, amoyag@uma.es, University of Malaga-CIBER de Enfermedades Raras, Spain; **MEDINA MIGUEL ANGEL**, medina@uma.es, University of Malaga-CIBER de Enfermedades Raras, Spain

KEYWORDS: Bioinformatics, phenotypic space, integrative tool, systems medicine

BACKGROUND: Most of the rare diseases have a genetic origin. Mainly, difficulties for diagnosis, prognosis and treatment of these orphan diseases are the consequence of the reduced number of patients and the fact that each single patient shows the phenotype resulting from his/her own gene interaction/metabolic network. The present knowledge on these interactions is usually based on their co-associations to biological processes, coexistence in cellular locations, coexpression in cell lines, physical interactions and so on. In addition, pathological processes can present similar phenotypes that have mutations either in the same genomic location or in different genomic regions. Thus, integrative resources for all of these complex interactions can help us prioritize the relationships between genes and diseases.
RESULTS: Our group has approached this problem by using different bicomputational solutions. After a brief presentation of the most recent results in the field of rare diseases, this communication will focus mainly in description of PhenUMA (www.phenuma.uma.es), a web application that displays biological networks using information from biomedical and biomolecular data repositories. One of its most innovative features is to combine the benefits of semantic similarity methods with the information taken from databases of genetic diseases and biological interactions. More specifically, this tool is useful in studying novel pathological relationships between functionally related genes, merging diseases into clusters that share specific phenotypes or finding diseases related to reported phenotypes. This framework builds, analyzes and visualizes networks based on both functional and phenotypic relationships. PhenUMA represents an advance for genomics and personalized medicine that should be especially interesting for both basic molecular research and clinical characterization of rare diseases. Enrichment of the tool with supplementary genetic and pharmacological data is in progress. Funded by Grants SAF2011-26518 (MINECO, Spain) and CVI-06585 (PAIDI, Andalusia, Spain) and CIBERER, which is an initiative of Instituto de Salud Carlos III.

PROGRAM PAGE 22

Biochemical Properties of Different SPT Mutations Correlate with Disease Severity Observed in HSAN1

AUTHORS: **BODE HEIKO**, heiko.bode@usz.ch, University Hospital Zurich, Switzerland; **OTHMAN ALAA**, Alaa.Othman@usz.ch, University Hospital Zurich, Switzerland; **ERNST DANIELA**, Daniela.Ernst@usz.ch, University Hospital Zurich, Switzerland; **HORNEMANN THORSTEN**, Thorsten.Hornemann@usz.ch, University Hospital Zurich, Switzerland

KEYWORDS: HSAN1, 1-deoxySL, SPT, Severity, correlation

Serine palmitoyltransferase (SPT) catalyzes the first step of sphingolipid (SL) de novo synthesis, the condensation of palmitoyl-CoA and L-serine. Several mutations in SPT are associated with hereditary sensory and autonomic neuropathy type 1 (HSAN1). Some of these mutations increase the activity of SPT with L-alanine and glycine resulting in the generation of neurotoxic 1-deoxysphingolipids (dSL). Elevated dSL-concentrations were consistently found in plasma of all analyzed HSAN1 patients and correlate with the severity of the neuropathy.
We used mutant overexpressing HEK293 cells to compare the biochemical properties of all known HSAN1 associated and some unrelated SPT mutations. Using metabolic labeling and LC-MS, we measured activity and substrate preference of SPT. The canonical activity was not lower in natural conditions for any of the mutants, three of them were even hyperactive. Eight mutants have significant higher activity with alanine. Principal component analysis revealed a clustering of the different mutants acording to their distinct biochemical properties which correlates with severity of the symptoms in affected patients.
We conclude that dSL formation is a crucial factor for the neuropathy. Changes of SPT´s activity correlate with the severity of the disease. Canonical hyperactivity worsens the effect of dSL formation, causing the most severe pathologies. Analysis of the biochemical properties of the mutations in in vitro allows prediction of the severity and symptoms of the disease in vivo.

Ormdl Proteins as Regulators of the Mammalian Serine Palmitoyltransferase

AUTHORS: **ZHAKUPOVA ASSEM**, assem.zhakupova@usz.ch, UniversityHospitalZurich, Switzerland

KEYWORDS: sphingolipids, neuropathy, regulation, Serine Palmitoyltransferase, mutations

Serine Palmitoyltransferase (SPT) typically catalyzes the condensation of palmitoyl-CoA and L-serine, the first step in de novo sphingolipid synthesis. Several mutations in SPT cause hereditary sensory neuropathy type 1 (HSAN1) shifting the substrate specificity to L-alanine, which results in accumulation of 1-deoxysphingolipids. In yeast it was demonstrated that SPT activity is tightly regulated by a metabolic feedback loop, which is mediated by the Orm1 and Orm2 proteins. At high cellular sphingolipid levels Orm proteins bind to SPT and inhibit its activity. Low sphingolipid levels, in contrast, lead to a phosphorylation of the Orm proteins, which results in their dissociation from SPT and an activation of the enzyme.

However, the role of the ORM proteins in regulating SPT activity in mammalian cells is not understood yet. In contrast to yeast, mammalian cells express three Orm isoforms (ORMDL1-3) and the phosphorylation sites found in yeast are not conserved in the mammalian orthologs. We were therefore interested to see if a similar metabolic feedback inhibition also exists in mammalian cells. We measured SPT activity in HEK293 cells which were treated with increasing amounts of membrane permeable C6-ceramide (C6Cer). We observed an inverse correlation between the amount of the de-novo formed sphingolipids and the intracellular ceramide levels, which indicates that increasing levels of C6Cer inhibit SPT activity. In the reverse approach we treated cells with increasing concentrations of myriocin – a specific inhibitor of SPT. At low concentrations (up to 0.5 nM) myriocin-mediated inhibition of SPT was compensated by a metabolic activation of the enzyme, whereas at higher myriocin concentrations (above 0.5 nM) the inhibition could not be compensated and resulted in a reduced de-novo formation of sphingolipids.

The role of the individual ORMDL isoforms in regulating SPT activity was further tested in HEK293 cells overexpressing ORMDL1-3. We observed reduced de novo sphingolipid synthesis and cell viability in ORMDL1 but not in ORMDL2 and 3 overexpressing cells. However, MEF cells in which ORMDL3 expression was abolished showed an increased SPT activity, whereas enzyme activity was decreased in cells which overexpressed an ORMDL3-GFP construct. This indicates that the role of the individual ORMDL isoforms in regulating SPT activity might be redundant and possibly depends on the cellular or metabolic context.

True Haploinsufficiency in Rare Aortic Diseases: Identification and Characterization of large Deletions using Next Generation Sequencing

AUTHORS: **MEIENBERG JANINE**, meienberg@genetikzentrum.ch, Foundation for People with Rare Diseases, Switzerland; **OKONIEWSKI MICHAL**, michal.okoniewski@fgcz.ethz.ch, Functional Genomics Center Zurich, Switzerland; **PATRIGNANI ANDREA**, andrea.patrignani@fgcz.ethz.ch, Functional Genomics Center Zurich, Switzerland; **SZABELSKA ALICJA**, aszabelska@gmail.com, Functional Genomics Center Zurich, Switzerland; **TSAI YU-CHIH**, ytsai@pacificbiosciences.com, Pacific Biosciences, United States of America; **CARREL THIERRY**, Thierry.Carrel@insel.ch, University Hospital Berne, Switzerland; **STEINMANN BEAT**, beat.Steinmann@kispi.uzh.ch, University Children's Hospital, Switzerland; **TURNER STEPHEN W.**, sturner@pacificbiosciences.com, Pacific Biosciences, United States of America; **KORLACH JONAS**, jkorlach@pacificbiosciences.com, Pacific Biosciences, United States of America; **RÖTHLISBERGER BENNO**, benno.roethlisberger@ksa.ch, Switzerland; **SCHLAPBACH RALPH**, ralph.schlapbach@fgcz.ethz.ch, Functional Genomics Center Zurich, Switzerland; **MATYAS GABOR**, matyas@genetikzentrum.ch, Switzerland

KEYWORDS: rare aortic diseases, array CGH, next generation sequencing

INTRODUCTION: Aortic dilatation/dissection (AD) can occur spontaneously or in association with rare genetic syndromes, such as Marfan syndrome caused by FBN1 mutations, Loeys-Dietz syndrome caused by TGFBR1, TGFBR2, SMAD3, TGFB2 or TGFB3 mutations, and vascular Ehlers-Danlos syndrome caused by COL3A1 mutations. In addition, there are also a substantial number of cases with inherited AD of unknown entity, for which screening for sequence variants and large genomic deletions/duplications in further (candidate) genes is needed. The characterization of large genomic deletions identified by multiplex ligation-dependant probe amplification (MLPA) or microarray analyses can be challenging. We have evaluated the use of next generation sequencing (NGS) for the identification and characterisation of large deletions.

METHODS: Three DNA samples used for the evaluation of breakpoint characterization using NGS harbor hemizygous deletions causing true haploinsufficiency previously characterized using a Sanger sequencing approach. Deletions in two samples of length 26,887 bp and 302,580 bp, respectively, affect the FBN1 gene, while a deletion of 3,408,306 bp comprises the entire COL3A1 gene. Accordingly, purified LR-PCR products containing the deletion breakpoints were sequenced on the PacBio RS sequencing platform (Pacific Biosciences) as well as with the HiSeq 2000 system (Illumina). Furthermore, we have compared array CGH and whole exome sequencing (WES) as well as whole genome sequencing (WGS) data visually to assess the potential of NGS for the detection of large deletions/duplications.

RESULTS: By testing our DNA samples, both NGS platforms were able to characterize the position of deletion breakpoints. However, whereas the long reads of PacBio RS mainly showed a decrease in read depth, in the short Illumina reads it was mainly an increase in mismatches related to the position of the breakpoints. In addition, our results demonstrate the use of NGS for the detection of large deletions.

CONCLUSION: Our approach provides an alternative procedure for the characterisation of large deletions, which is less work intensive and time consuming. Furthermore, NGS data can be successfully used for the identification of large structural variants such as deletions and duplications.

Immune-mediated Activation of Coagulation in Stevens Johnson Syndrome/Toxic Epidermal Necrolysis

AUTHORS: **IQBAL OMER**, Daneyal Syed, BS., **JULIA MALALIS**, MD., **CHRISTINE MATA**, MD., **AMY LIN**, MD::., **MICHAEL MOSIER**, MD., **EDWARD CAMPBELL**, Ph.D††., **SHUHARAZAD ABRO**, MD., **DEBRA HOPPENSTEADT**, Ph.D., **JAWED FAREED**, Ph.D., **CHARLES BOUCHARD**, MD.
†Department of Pathology & Ophthalmology; Department of Pathology; Department of Ophthalmology; Department of Surgery. †† Department of Molecular & Cell Physiology, Loyola University Health System, Maywood, IL. 60153.

KEYWORDS: Immunity, Coagulation, T-cell activation, Cytokines, Granulysin, Granzyme.

BACKGROUND: Stevens Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN) are specific drug hypersensitivity reactions initiated by cytotoxic T-lymphocytes. Augmentation of T-cell activation by positive co-stimulation and Major Histocompatibility Complex-restricted presentation of the culprit drug triggers T-cell activation following interaction with T-cell receptors. This T-cell activation results in expression of cytokines including TNF-α, interferon-γ, and granzyme B from NK cells. At the immunity-coagulation interface, these cytokines cause coagulation activation.
MATERIALS & METHODS: Following an Institutional Review Board approved protocol blood samples were obtained from subjects suspected of SJS/TEN and normal healthy volunteers (n=2). Confirmatory biopsies were performed in all SJS/TEN subjects that confirmed SJS/TEN in 4 subjects and were negative in 7 subjects. Immunohistochemistry was performed on the skin biopsy sections using anti-granulysin, FasL and anti-granzyme B antibodies. Cytokine levels were measured using the cerebral II array biochip from Randox Laboratories Limited (Crumlin, UK). Besides cerebral array II, other parameters such as thrombin-antithrombin (TAT) complexes (Dade®, Marburg, Germany), fibrinopeptide A (F1.2, Dade®), plasminogen activator inhibitor-1 (PAI-1, Diagnostica Stago® and STACHROME antithrombin (Stago®), ZYMUPHEN platelet microparticles activity (Hyphen® Biomed (Neuville-sur-Oise, France), and HEMOCLOT protein C (Stago®) were measured using ELISA kits as per manufacturers' instructions.
RESULTS: Compared to the Normal Human Plasma, the IL-4, IL-6, TNF-α, and MCP-1 levels were increased significantly in biopsy-confirmed SJS/TEN patients (see table). Other parameters measured including IL-2, IL-8, IL-10, VEGF, INF-γ, IL-1α, IL1-β and EGF were not significantly increased. A marked increase in the TAT complexes (6.3±5.9 µg/ml), F1.2 (430.4±202.4 pmol/L), platelet microparticles (13.1±9.3 nM) and protein C levels (90.5±63.4%) with a corresponding decrease in PAI-1 (53.3±18.8ng/ml) and antithrombin levels (80.7±42.4%) compared to normal human plasma were also observed. Biopsy-negative SJS/TEN subjects with less pronounced inflammatory stimulus, demonstrated mild elevation in cytokine levels of IL-4 (1.95±0.59 pg/ml), IL-6 (29.81±25.18 pg/ml), TNF-α (7.20±5.04 pg/ml) and MCP-1 (265.10±159.09 pg/ml)). Immunohistochemical studies revealed high expression of granulysin and granzyme B.
CONCLUSIONS: T-cell activation and release of cytokines especially TNF-α, granulysin and granzyme B evidenced by their increased expression in immunohistochemistry, causes immune-mediated activation of coagulation with increase in TAT, MCP-1, F1.2 and platelet microparticles and corresponding decrease of protein C, antithrombin, and PAI-1. These alterations in coagulation may progress to sepsis associated coagulopathy and overt disseminated intravascular coagulation.

Gorham's Disease of the Calvarium – a Complex Single Step Skull Reconstruction

AUTHORS: **OHLA VICTORIA**; victoria.ohla@uniklinik-freiburg.de; United States of America; **HEFTY MARKUS**; mhefty@bidmc.harvard.edu, United States of America; **ANDERSON MATTHEW**, manderson@bidmc.harvard.edu, United States of America; **KASPER EKKEHARD**, ekasper@bidmc.harvard.edu, United States of America

KEYWORDS: Gorham 's disease, Vanishing bone disease, Osteolytic disorder

BACKROUND: Gorham 's disease is a very rare osteolytic disorder characterized by uncontrolled proliferation of non-neoplastic vascular or lymphatic tissue, leading to progressive resorption and replacement of osseous matrix. Due to the low incidence, unkown cause and unpredictable natural history of the disease, a standardized treatment regimen has not yet been defined. Current treatments are only experimental as no single treatment has proven to be superior in arresting the course of the disease. Trials have included surgery, radiation and medical therapies employing drugs such as calcium salts, vitamin D supplements and hormones. A single step surgery consisting of craniectomy for the diseased bone and reconstructive cranioplasty has not been described in the management of Gorham 's disease. We therefore report our experience of a case with only substantial cranial involvement, which was successfully treated with excision of the diseased bone segment and a CAD/CAM custom-made cranioplasty implant to allow for synchronous repair.
CLINICAL PRESENTATION: A 25- year- old man with an asymptomatic skull defect over the left frontal convexity had noticed a progressive enlargement of the affected site. Physical examination revealed a clearly palpable depression of the fronto-temporal bone. Conventional XR of the skull showed widespread loss of the native calvarial structure, corresponding to an osteolytic process. Subsequent MRI and CT scans disclosed the typical features of a patchy resorptive osteolysis concerning for an active underlying process. Due to the need for a histopathological diagnosis and the existing risk from a large unprotected area of his brain, surgical intervention was chosen. The goal was to obtain a pathological diagnosis as well as complex reconstruction of the afflicted area. A density graded CT scan was used to indicate the relative severity of the affected bone areas and this information was used to design a custom made cranioplasty allograft implant to allow for a single step excisional craniectomy with synchronous repair. Pathological results revealed Gorham 's disease and the patient has been recurrence free for 2 years since surgery.
CONCLUSION: Based on this report and available information in the literature, a single stage surgery with excisional craniectomy and a custom-made cranioplasty allograft implant appears to be an effective therapy for patients suffering from Gorham 's disease limited to vault involvement.

Enzyme Replacement Therapy for Homocystinuria

AUTHORS: **KRAUS JAN**; jan.kraus@ucdenver.edu, United States of America; **BUBLIL EREZ**, erez.bublil@ucdenver.edu, United States of America; **PARK INSUN**, nsun.Park@ucdenver.edu, United States of America; **SALZMAN ANDREW**, salzman@nlsv.net, United States of America

KEYWORDS: homocysteine, pyridoxine, cystathionine, sulfur metabolism, stroke

BACKGROUND: Cystathionine beta synthase (CBS) deficient homocystinuria is the most common inherited defect of sulfur amino acid metabolism. CBS condenses homocysteine and serine to cystathionine, which is then cleaved to cysteine by cystathionine gamma lyase. Homocystinuria is characterized by very high levels of plasma Hcy, S-Adenosylhomocysteine and reduced concentrations of cystathionine and cysteine. These abnormalities are manifested in thrombotic vascular disease, connective tissue aberrations, and mental retardation. About 40 % of the patients respond to pyridoxine therapy and the remaining ones are subjected to a low methionine diet supplemented with betaine to promote the re-methylation of homocysteine to methionine. This therapy is difficult to comply with and has little impact on downstream metabolites. We envisioned that administration of recombinant CBS to the circulation may positively impact the cellular equilibrium of sulfur amino acids.
METHODS: We have expressed and purified human truncated CBS in E. coli and pegylate it. The enzyme was injected subcutaneously to our H0 mouse model of homocystinuria at a dose of 5 mg/kg weight.
RESULTS: We found that administration of a PEGylated truncated human CBS enzyme to homocystinuric mice resulted in a ~80 % decrease in Hcy, ~900 % increase in cystathionine, and normalization of cysteine concentrations, indicative of re-activation of the intracellular transsulfuration pathway.
CONCLUSIONS: The data strongly suggest that CBS enzyme replacement therapy is a promising approach for treatment of homocystinuria, and that ERT for metabolic deficiencies may not necessitate introduction of an ¬enzyme into its native intracellular environment.

Elimination of HIV Sequences from Lentiviral Gene Therapy vector DNA Delivered to Target Cells: the LTR-1 System.

AUTHORS: **HOWE STEVEN**, s.howe@ucl.ac.uk, United Kingdom; **VINK CONRAD**, c.vink@ucl.ac.uk, United Kingdom

KEYWORDS: gene therapy, lentivirus, HIV, vector, virus;

AIM: To reduce the amount of remaining HIV-1 sequence from lentiviral gene delivery vectors to improve safety and efficacy of the viruses for gene therapy of rare diseases. Background: Lentiviral vectors (LV) are useful tools for gene therapy approaches to treating rare diseases. Current vectors based on HIV-1 effectively deliver genes to a range of cells, but current clinically approved viral backbones contain almost 20 % wild-type HIV sequence. LV packaging sequences (Ψ, Rev Response Element) up to 2kb long are necessary for viral RNA genome packaging into viral particles in producer cells. In standard LVs, these sequences are reverse transcribed into DNA and persist in target cells after transduction. This persistence creates several known and potential problems for LV gene therapy applications. Splice sites within packaging sequences have been shown to splice with nearby host genes, creating aberrant fusion transcripts. The CpG island within the packaging sequence undergoes DNA methylation in some target cells, potentially contributing to transgene silencing. Packaging sequences enable remobilisation of LV genomes in cells expressing viral proteins, which could be problematic in HIV-positive patients. Large packaging sequences within the reverse transcript may reduce the size of the transgene cassette which can be accommodated.
RESULTS: In standard LVs, packaging sequences are located between the two viral long terminal repeats (LTRs), within the region of the vector that is reverse transcribed. We have developed a novel 'LTR-1' transfer vector in which the packaging sequences are located downstream of a single 3' LTR, so are present in the RNA genome during virion packaging but are outside of the region of the genome that is reverse transcribed into DNA in the target cell. For the first time these minimal HIV sequence vectors can now be produced at high titre (3x108 TU/ml by eGFP flow cytometry of 293Ts, pCCL parallel preparation 1x109 TU/ml) and the proportion of eGFP+ cells is stable between 3 and 14 days post-transduction. Conclusion: This configuration eliminates most of the remaining viral DNA delivered into target cells and could be a feature of the next generation of gene therapy vectors based on HIV-1 and other retroviruses.

Partnerships for New Medicines-Repositioning for the Treatment of ALS

AUTHORS: **KALOULIS KOSTAS**, kostas.kaloulis@gmail.com, Switzerland; **VOM BAUR ELMAR**, elmar.vombaur@remedys.net, Switzerland

KEYWORDS: Therapies, Partnerships, Drug Development, Innovation, Patients

To overcome the gap between academia originating promising therapeutic opportunities without commercial interest, on one side, and industrial partnering, clinical development and availability to patients, on the other side, we founded the ReMedys Foundation. ReMedys is a not-for-profit, patient-centric entity, based in Geneva, Switzerland, committed in developing innovative therapeutic ideas into clinically testable therapies for patients with severe disease without effective treatment – independent of commercial potential. ReMedys has been founded by seasoned industry experts and maintains a broad network of pharmaceutical industry experts in all fields required for effective drug development. ReMedys is directed by a Board consisting of representatives of renowned academic institutions, R&D experts, professionals in Technology Transfer and R&D investment. ReMedys works, as an expertise hub, based on strong partnerships, to coordinate and drive a virtual R&D process, closely together with the originators of projects, patients and clinicians. We believe it is essential to keep the accumulated scientific know-how in the projects and to produce what patients and clinicians need, via sharing with our partners our drug development know-how and expertise. Our priority goal is to add therapeutic value to our projects, and thus consequently genuine commercial interest. In cases where new therapies, originated at academic institutions, are developed to marketed drugs, it is usually thanks to the pharmaceutical industry stepping in. Any industry interest in any project is proportional to the commercial prospect, leaving smaller indications, such as rare diseases, or innovative but risky therapeutic approaches without support. The pharmaceutical industry is under significant public pressure due to perceived excessive margins, inefficiencies, and for taking advantage of the distress of patients, directly or indirectly. Rare are the innovative models out there to help patients, especially in rare indications, to get access to reasonably priced therapies, and academia to become more successful in advancing towards the clinic innovative ideas. We, in ReMedys, strongly believe, that based on smart partnerships, we can build a paradigm shift in the R&D process, together with all those, who are eager to bring therapeutic solutions to patients with high unmet need. Here we present our effort to reposition a drug for the treatment of amyotrophic lateral sclerosis.

Fanconi Anemia: from Gene Discovery to Gene Therapy

AUTHORS: **SURRALLES JORDI**, jordi.surralles@uab.es, Spain;

KEYWORDS: Fanconi anemia, Gene therapy, whole exome sequencing, Gene discovery, DNA repair

BACKGROUND: Fanconi anemia (FA) is a rare genetic disease characterized by progressive anemia, malformations, chromosome fragility, hypersensitivity to DNA interstrand cross linkers (ICL) and cancer predisposition. The only cure of the hematological disease is bone marrow transplantation using an HLA compatible donor. Those families with unavailable donor rely on preimplantation genetic diagnosis with selection of an HLA related embryo and in the future implementation of advanced gene and cell therapies. In this context, we previously generated disease-free hematopoietic progenitors from the skin of FA patients (Raya et al., Nature, 2009) and we are running a phase I/II gene therapy clinical trial using a lentiviral vector carrying the FA gene FANCA designated as orphan drug by the European Medicines Agency. All these novel therapeutic applications to human health are further complicated by the fact that at least 16 FA genes, some of them involved in breast cancer susceptibility in otherwise unaffected mutation carriers. Therefore, the discovery of novel FA genes is important not only for the affected patients but also for the general population and for the future implementation of advanced gene/cell therapies.
METHODS: 110 FA patients were genetically studied by retroviral subtyping and mutational screening and those unassigned patients were subjected to whole exome sequencing. The candidate gene was functionally studied at the gene and protein level.
RESULTS: A novel FA gene (ERCC4/FANCQ) encoding the DNA repair nuclease XPF was discovered. Since this gene causes not only FA but also Xeroderma pigmentosum, Cockayne syndrome and XFE-type progeroid syndrome, three clinical conditions characterized by defects in nucleotide excision repair (NER) of UV-light induced DNA damage, we probed that mutations leading to FA specifically disrupt ICL but not NER due to abnormal nuclease activity of the mutant protein.
CONCLUSION: ERCC4/FANCQ mutations cause four rare diseases depending on the resulting balance between ICL repair and NER deficiencies, highlighting the complex interplay between genotype and phenotype in human health and disease.

PROGRAM PAGE 23

Cell Penetrating Peptide-Peptide Nucleic Acid (Cpp-Pna) Conjugates for Inflammatory Bowel Disease Therapy

AUTHORS: **LEE SOO HYEON**, soo-hyeon.lee@pharma.ethz.ch, ETH, Switzerland; **MOROZ ELENA**, elena.moroz@pharma.ethz.ch, ETH Zürich, Switzerland; **CASTAGNER BASTIEN**, bastien.castagner@pharma.ethz.ch, ETH Zürich, Switzerland; **LEROUX JEAN-CHRISTOPHE**, christophe.leroux@pharma.ethz.ch, ETH Zürich, Switzerland

KEYWORDS: gene therapy, oral delivery, peptide nucleic acid, cell penetrating peptide, inflammatory bowel disease

Inflammatory bowel disease (IBD) is a group of chronic inflammatory disorders of the colon and small intestine that could greatly benefit from antisense gene therapies [1]. As a target tissue, colon is one of the most accessible sites via oral administration, in comparison to other tissues. Oral delivery to the colon has several advantages, such as higher dose tolerance, patient's convenience, and minimal systemic exposure. However the harsh conditions in the gastrointestinal tract, e.g., pH and digestive enzymes, should be considered in the design of an efficient oral delivery system [2]. For this reason, we selected peptide nucleic acids (PNAs) as a nucleic acid drug, to eventually modulate the abnormal expression levels of problematic genes in the colon mucosa. PNAs are oligonucleotide analogues in which the sugar-phosphate backbone has been replaced by peptide backbone formed from N-(2-aminoethyl)-glycine units linked by amide bonds. PNAs are chemically stable and resistant against enzymatic digestion but cannot penetrate easily through the cell membrane due to their high molecular weight. Cell-penetrating peptides (CPPs) form a class of peptides that have the ability of carrying a large diversity of cargos into cells, including macromolecules (e.g., proteins and nucleic acids) [3]. We conjugated a model luciferase-targeting PNA to 15 different CPPs in order to increase cellular uptake and antisense activity [4]. The transfection efficiency of the conjugates was evaluated on colon adenocarcinoma cells (HT-29) stably expressing luciferase by measuring the expression of the latter. We identified the most potent CPP-PNA that displayed a sequence-specific and dose-dependent luciferase inhibition at concentrations that were not cytotoxic. Furthermore, this CPP was conjugated to a PNA sequence targeting ICAM-1 (Intercellular Adhesion Molecule-1) mRNA as a model gene for the IBD therapy. After transfection with CPP-PNA conjugates in HT-29 cells, ICAM-1 level were down regulated as assessed by western blot analysis. These bio-reactive CPP-PNA conjugates with well-defined structure will be further modified for colon-specific delivery. This work was financially supported by the Gebert Rüf Stiftung (GRS-041/11).

References:

[1] Wu F, et al. Gastroenterology. 2008;135:1624-35.
[2] Friend DR. Adv Drug Deliv Rev. 2005;57:247-65.
[3] Lee SH, Castagner B, Leroux JC, Eur J Pharm Biopharm. 2013;85:5-11.
[4] Rogers FA, et al. Mol. Ther. 2012;20(1):109-18.

Optimization of RPE65-Gene Transfer Using a Lentiviral Vector for LCA Treatment.

AUTHORS: **KOSTIC CORINNE**, corinne.kostic@fa2.ch, University of Lausanne, Jules-Gonin Eye Hospital, Switzerland; **CRIPPA SYLVAIN**, sylvaincrippa@fa2.ch, University of Lausanne, Jules-Gonin Eye Hospital, Switzerland; **PIGNAT VÉRÈNE**, verene.pignat@fa2.ch, University of Lausanne, Jules-Gonin Eye Hospital, Switzerland; **MARTIN SAMIA**, samia@genethon.fr, Genethon, France; **ARSENIJEVIC YVAN**, yvan.arsenijevic@fa2.ch, Switzerland

KEYWORDS: Gene Therapy, Eye, Lentiviral vector, retinal pigment epithelium

Ocular diseases are promising candidates for gene therapy thanks to the identification of a growing number of genes causing visual impairment as well as to the particularity of the eye as an accessible organ easy to monitor. The existence of many animal models for inherited ocular diseases also accelerated the application of gene transfer into the eye. The main illustration of this phenomenon is the clinical trials for RPE65-affected patients that are proposed now using AAV vectors. After evidence of the absence of adverse effects following AAV-RPE65 injection in the subretinal space of patients, younger affected patients were treated to determine if such approach can improve vision. Despite an amelioration of visual sensitivity there has been so far no change in ERG results and no stop of the retinal degeneration. Optimization of RPE65 gene replacement strategy is thus now required.
An alternative vector presently used in ex vivo clinical trials for hematopoietic cell transduction, the lentiviral vector, demonstrated high efficiency for retinal pigment epithelium transduction in different mouse models. In particular, we demonstrated that a lentiviral vector encoding RPE65 cDNA is able to rescue 100 % of cones when injected in an appropriate therapeutic window in RPE65-deficient mouse models. Moreover, in mice bearing the human missense mutation R91W which induces a milder phenotype than in RPE65 knockout mice, with notably, a delay in the loss of cone photoreceptors, the treatment at an adult age allowed to revitalize cones. In parallel, we identified and characterized patients with RPE65 defects.
Thus, considering our studies and the long-term expression described in the literature using lentiviral vectors in non-human primates, we started the process to validate this vector for a human application. We first transferred our therapeutic cassette into a lentiviral backbone certified for patient use. We also observed in mice that viral vector production using an ion exchange column improves the efficiency of transduction. We therefore produced a large batch of vector following protocols similar to clinical batch quality in order to fully evaluate the efficacy in mice and the tolerance in pig of this vector. These future experiments using large animals are now needed to validate correct gene transfer and expression of the RPE65 gene as well as tolerance of the vector after subretinal injection before envisaging a clinical trial application.

PROGRAM PAGE 23

Reducing Dynamin 2 Rescues a Severe Congenital Myopathy in Mice

AUTHORS: **COWLING BELINDA**, belinda@igbmc.fr, IGBMC, France; **CHEVREMONT THIERRY**, thierry.chevremont@outlook.com, IGBMC, France; **PROKIC IVANA**, Ivana@igbmc.fr, IGBMC, France; **KRETZ CHRISTINE**, cricri@igbmc.fr, IGBMC, France; **FERRY ARNAUD**, arnaud.ferry@upmc.fr, UMRS974, Université Pierre et Marie Curie-Paris., France; **COIRAULT CATHERINE**, C.coirault@institut-myologie.org, UMRS974, Université Pierre et Marie Curie-Paris., France; **LAUGEL VINCENT**, Vincent.LAUGEL@chru-strasbourg.fr, Hautepierre University Hospital, France; **ROMERO NORMA**, nb.romero@institut-myologie.org, Institut de Myologie, France; **LAPORTE JOCELYN**, jocelyn@igbmc.fr, IGBMC, France

KEYWORDS: centronuclear myopathy, dynamin, myotubularin, genetic rescue, animal model

Centronuclear myopathies (CNM) are congenital disorders associated with muscle weakness and abnormally located nuclei in skeletal muscle. An autosomal dominant form of CNM results from mutations in the gene encoding dynamin 2 (DNM2), and loss-of-function mutations in the gene encoding myotubularin (MTM1) result in X-linked centronuclear myopathy (XLCNM), which promotes severe neonatal hypotonia and early death. Currently, no effective treatments exist for XLCNM.
The main goal of this study was to validate a novel rescue approach for XLCNM. Recent data suggested some CNM-causing DNM2 mutations increase the dynamin oligomer stability and GTPase activity. Also, we and others showed that overexpression of wildtype DNM2 in skeletal muscle cause a CNM-like phenotype. We hypothesize myotubularin and dynamin 2 function in a common pathway, where either MTM1 loss-of-function or DNM2 gain-of-function lead to the CNM phenotype. To test this hypothesis, we reduced the expression of DNM2 in Mtm1-/y mice that reproduce a CNM phenotype with a progressive myopathy leading to death by about 12 weeks. Mtm1-/yDnm2+/- mice survived up to 2 years. Classical CNM histological features including fiber atrophy and nuclei mispositioning were prevented or strongly delayed and reduced, and muscle strength was increased. Downregulation of Dnm2 selectively in skeletal muscle during embryogenesis or in young mice after onset of the disease showed that the rescue is cell autonomous and that downregulation of Dnm2 can stop and potentially revert the progression of the phenotype.
In conclusion, we identified MTM1 and DNM2 are in a common pathway regulating muscle organization and force. We introduce the original concept of 'cross-therapy' where one form of the disease (XLCNM, MTM1) can be rescued by decreasing expression of another gene mutated in CNM (DNM2 in ADCNM). While DNM2 is a key mechanoenzyme for important cellular processes, its reduction is strongly beneficial for centronuclear myopathy and represents a novel potential therapeutic approach.

Activation of Nrf2 in Keratinocytes Causes Chloracne (MADISH)-like Skin Disease in Mice

AUTHORS: **SCHÄFER MATTHIAS**, matthias.schaefer@biol.ethz.ch, Switzerland; **WILLRODT ANN-HELEN**, ann-helen.willrodt@pharma.ethz.ch, ETH, Switzerland; **KURINNA SVITLANA**, svitlana.kurinna@biol.ethz.ch, ETH, Switzerland; **WERNER SABINE**, sabine.werner@biol.ethz.ch, ETH, Switzerland;

KEYWORDS: acne, sebaceous gland, Nrf2, oxidative stress, skin

The transcription factor Nrf2 is a key regulator of the cellular stress response through the regulation of antioxidant enzymes and cytoprotective proteins. Therefore, pharmacological activation of Nrf2 is considered as a promising strategy for skin protection and cancer prevention. However, little is as yet known about the function of Nrf2 in the skin and the consequences of Nrf2 activation. We show that prolonged Nrf2 activation in keratinocytes causes sebaceous gland enlargement and seborrhea in mice due to upregulation of the growth factor epigen (Epgn), which we identified as a novel Nrf2 target. This was accompanied by thickening and hyperkeratosis of hair follicle infundibuli. These abnormalities caused dilatation of infundibuli, hair loss and cyst development upon aging. Upregulation of Epgn, secretory leukocyte peptidase inhibitor (Slpi), and small proline rich protein 2d (Sprr2d) in hair follicles was identified as the likely cause of infundibular acanthosis, hyperkeratosis and cyst formation. These alterations were highly reminiscent to the phenotype of chloracne/"metabolizing acquired dioxin-induced skin hamartomas" (MADISH) patients. Indeed, SLPI, SPRR2 and EPGN were strongly expressed in cysts of MADISH patients and upregulated by dioxin in human keratinocytes in an NRF2-dependent manner. These results identify novel Nrf2 activities in the pilosebaceous unit and point to a role of NRF2 in MADISH pathogenesis.

Trafficking and Metabolism of Deoxysphingolipids and Their Implications in Pathophysiological Changes

AUTHORS: **ALECU IRINA**, irina.alecu@usz.ch, UniversityHospitalZurich, Switzerland; **HORNEMANN THORSTEN**, thorsten.hornemann@usz.ch, University Hospital Zurich, Switzerland

KEYWORDS: deoxysphingolipids, neuropathy, trafficking, metabolism

Serine palmitoyltransferase (SPT) catalyzes the first step in the de novo synthesis of sphingolipids, normally forming sphinganine from the condensation of serine and palmitoyl-CoA. SPT can also use alanine or glycine in this condensation reaction, which results in atypical 1-deoxysphingolipids (1-deoxySLs). Due to the missing C1 hydroxyl group, the 1-deoxySLs cannot be metabolized to complex sphingolipids nor degraded by the canonical catabolic pathways. Pathologically elevated 1-deoxySL levels are a hallmark of the inherited neuropathy HSAN I. Neither the metabolism nor the trafficking of 1-deoxySLs is thus far understood.To investigate the intracellular trafficking of 1-deoxySLs we analyzed the distribution of fluorescently labeled sphinganine (SA) and 1-deoxysphiganine (doxSA) by fluorescence microscopy in live and fixed cells. We analyzed the metabolism of the 1-deoxySLs by LC-MS.
As proof of principle we first investigated the metabolism and trafficking of commercially available NBD-labeled SA (NBD-SA). LC-MS analysis revealed that NBD-SA is metabolized to the further downstream metabolites NBD-ceramide and NBD-sphingosine within 15 minutes of being added to cells. Within a few minutes of adding the NBD-SA to cells, we observed the appearance of a fluorescence signal in ER-like structures around the nucleus. With passing time the signal partitioned into vesicle-like structures at the periphery of the cells. However, as it has been observed that NBD-lipids spontaneously transfer from exogenous sources into biological membranes, we wanted to use doxSA labeled with a fluorophore that did not alter its natural properties so much. We used 1-deoxySA labeled with nile red (NR-doxSA), a less polar fluorophore than NBD, and found that it is not metabolized and concentrates in the nucleus of the cells. This indicates that the addition of a Nile-red group interferes with the proper intracellular localization and metabolism of the lipid.
We are currently optimizing a new method using alkyne doxSA which is reacted with a flurophore after being internalized for which preliminary results have been promising. The doxSA labeled in this manner appears to enter cells and localize differently from SA labeled in the same manner.

A Silencing Resistant Lentiviral Gene Therapy (GT) Vector for p47phox-Deficient form of Chronic Granulomatous Disease (CGD)

AUTHORS: **SILER ULRICH**, ulrich.siler@kispi.uzh.ch, University Children´s Hospital Zürich, Switzerland; **HÄNSELER WALTHER**, hwalther@gmx.ch, University Children´s Hospital Zürich, Switzerland; **BRENDEL CHRISTIAN**, cbrendel@med.uni-frankfurt.de, Georg Speyer Resarch Institute, Germany; **KUZMENKO ELENA**, Elena.Kouzmenko@kispi.uzh.ch, University Children´s Hospital Zürich, Switzerland; **COWLEY SALLY A.**, sally.cowley@gmail.com, James Martin Stem Cell Facility, Sir William Dunn School of Pathology, University of Oxford, United Kingdom; **JAMES WILLIAM S.**,william.james@path.ox.ac.uk, James Martin Stem Cell Facility, Sir William Dunn School of Pathology, University of Oxford, United Kingdom; **THRASHER THRASHER**, a.thrasher@ucl.ac.uk, Molecular Immunology Unit and Centre for Immunodeficiencies, UCL Institute of Child Health, University College London, United Kingdom; **GREZ MANUEL**, Grez@em.uni-frankfurt.de, Georg Speyer Resarch Institute, Germany; **REICHENBACH JANINE**, janine.reichenbach@kispi.uzh.ch, University Children's Hospital Zürich, Switzerland

KEYWORDS: Chronic Granulomatous Disease, lentiviral vector, CGD, gene therapy

CGD comprises a group of primary immunodeficiencies caused by a defective NADPH oxidase. A first clinical gene therapy (GT) trial aiming to cure gp91phox-deficient CGD (X-CGD) brought proof-of-concept and revealed transactivation of oncogenes in HSCs and transgene silencing as primary causes of adverse events.
We generated a new lentiviral self-inactivating GT vectors encoding p47phox under control of the miR223 promoter. miR223 driven p47phox expression revealed almost exclusively myelospecific p47phox expression in p47phox-/- mice and reconstitution of phagocytic ROS production and E.coli killing activity in primary p47phox CGD patient derived cells. The vector was tested in a p47phox-/- patient derived iPSC cell line known for its high DNA methylation activity and in hematopoietic cells derived thereof. Unexpectedly, the miR223 promoter, methylated in iPSCs, was demethylated and activated upon monocytic differentiation. The identical pattern of demethylation upon phagocytic differentiation was observed for the natural cell intrinsic mircoRNA223 promoter. Therefore, we expect our new lentiviral miR223-p47phox GT vector to facilitate stable and highly myelospecific long term p47phox transgene expression in patients.

Further Molecular Characterization of a Novel Neurodegenerative Syndrome Associated to a Mutation in the Seipin/BSCL2Gene

AUTHORS: **ARAUJO-VILAR DAVID**, david.araujo@usc.es, Spain; **RUIZ-RIQUELME ALEJANDRO**, alejandroivan.ruiz@usc.es, Spain; **SANCHEZ-IGLESIAS SOFIA**, sofia.sanchez@usc.es, Spain; **REQUENA JESUS**, jesus.requena@usc.es, Spain

KEYWORDS: Neurodegeneration, BSCL2/seipin, Berardinelli-Seip syndrome, ER stress

Mutations in the Seipin/BSCL2 gene cause either type 2 congenital generalized lipodystrophy (BSCL) or dominant motor neuron diseases. However, we recently discovered a c.985C>T mutation in the BSCL2 gene that results in a novel fatal neurodegenerative syndrome (Celia encephalopathy). This mutation induces an alternative splicing which results in skipping of exon 7 and a reading frame shift (Guillen-Navarro et al. J Med Genet. 2013;50:401-9). Homozygous patients suffer from progressive encephalopathy since ages 2-3 years, with fatal outcome at ages 6-8 years; however, carriers for the c.985C>T mutation are asymptomatic, conflicting with the gain of toxic function attributed to the mutation. Our previous studies showed a partial nuclear localization of wt and exon 7 skipped seipin. This location might be related to the presence of intranuclear ubiquitin-positive inclusions in brain tissue from a homozygous patient (index case), which are likely to consist of misfolded, aggregated mutant seipin. Besides, ER stress in cells expressing exon 7 skipped seipin was also found.Here we report further molecular characterization of exon 7 skipped seipin. Using density gradient ultracentrifugation, we found that wt seipin oligomerizes forming tetramers according to calibration with a set of proteins of known MW. We also found that exon 7 skipped seipin forms much larger aggregates under similar conditions, corresponding to dodecamers. We hypothesized that wt and exon 7 skipped seipin might interact and form mixedoligomers. Given that levels of wt seipin expressed by heterozigous individuals are substantially higher than those of exon 7 skipped seipin, we reasoned that wt seipin might rescue the phenotype by recruiting exon 7 skipped seipin into mixed normal size oligomers, thus impeding their aggregation into larger, presumably toxic, oligomers. We therefore expressed wt and exon 7 skipped seipin at a 3:1 ratio in HeLa cells and performed density gradient ultracentrifugation of cell extracts. We found a change in the pattern of distribution of each of the seipin isoforms, with exon 7 skipped seipin emerging at earlier fractions. This result clearly indicates the interaction between both seipin isoforms through the formation of mixed oligomers. Together, our findings provide a clue about the origin of the intranuclear aggregates observed in neurons from the index case, and offer a possible explanation of the absence of phenotype in heterozygous mutation carriers. (Funded by Consellería de Industria (Xunta de Galicia) 10PXIB-208013PR and ISCIII-FEDER PI10/02873)

Diagnosis of Familial Dysautonomia in Europe-the Need for Increased Awareness

AUTHORS: **MAAYAN CHANNA**, cmaayan@hadassah.org.il, Israel; Holzer Naama, naamah@hadassah.org.il, Israel; **BELITSKY GALIT**, galitbz@hadassah.org.il, Israel; **JACOBS KAYLA**, ktjacobs12@gmail.com, Israel; **LEVZION-KORACH OSNAT**, osnat@hadassah.org.il, Israel

KEYWORDS: Familial dysautonomia, Undiagnosis

BACKGROUND: Familial Dysautonomia (FD) is a severe complicated autosomal recessive disorder affecting Ashkenazi Jews. The carrier frequency of the FD mutation in Ashkenazi Jews is 1:17 to 1:32 with a birth incidence of 1:3703. The diagnosis of FD requires awareness of typical clinical features (e.g. feeding difficulty, vomiting, aspiration pneumonia, blood pressure instability, hypotonia, absence of overflow tears) and since 2001 by genetic testing. It is estimated that in Europe 2012 there are 1,426,900 Ashkenazi Jews. There are only 31 diagnosed FD patients out of an estimated 246.6 patients (12.5 %).
METHODS: According to the FD frequencies, we calculated the estimated FD patients who were expected to be diagnosed. As it is not possible in a few countries to distinguish between Ashkenazi and Sephardic Jews, we have eliminated Spain, Portugal and France where Sephardic Jews are the majority. Mixed marriages also affect the statistics. Our predictions indicate that the there could be many patients who are not known.
RESULTS: Based on the number FD birth incidence, more affected FD patients should have been born table 1 (based on 2012 Web). Country Estimated Ashkenazi Jews Estimated FD patients born Known diagnosed FD patients. Russia, 4 patients diagnosed in Israel; Bosnia, Bulgaria, Croatia, Estonia, Finland, Ireland, Luxemburg, Lithuania, Macedonia, Norway, Poland, Portugal, Serbia, had less than 3703 Jewish population and were not included in the table. The accumulative number in these countries is 18,200 – with 4.9 estimated FD patients. Total estimated European FD patients are 242.6.

Country	Estimated Ashkenazi Jews	Estimated FD patients born	Known diagnosed FD patients
Austria	9000	2.4	1
Belgium	30000	8.1	0
Belarus	12000	3.2	0
Czech. Republic	3900	1	0
Denmark	6400	1.7	0
Germany	119000	32	2
Greece	4500	1.2	0
Hungary	48200	13	0
Italy	28000	7.6	0
Latvia	6200	1.7	0
Moldova	3900	1	0
Netherlands	29000	7.8	0
Russia	194000	52.4	7 (since 1990)
Switzerland	17500	4.7	0
Sweden	15000	4	0
Ukraine	67000	18	0
United Kingdom	291000	78.5	20
Turkey			1

CONCLUSION: The undiagnosed cases that migrated to Israel and the small number of documented FD cases, indicate fewer cases than estimated and suggest that FD may be misdiagnosed, unreported or both. An unknown number of affected fetuses may have been terminated. Assimilation of Jews might also decrease the number; however mixed origin can also result in birth of patients. Increased FD awareness and screening is needed.

Lamin B1 Modulates Cell Fate Commitment and Differentiation in Murine-Derived Neural Stem Cells

AUTHORS: **MAHAJANI SAMEEHAN**, sameehan.mahajani@iit.it, Italy; **GIACOMINI CATERINA**, caterina.giacomini@iit.it, Italy; **GASPARINI LAURA**, laura.gasparini@iit.it, Italy

KEYWORDS: Lamin B1, Neurogenesis, Neural Stem Cells, Autosomal Dominant Leukodystrophy, Nuclear Lamina

Lamin B1 (LMNB1) is a type V intermediate filament protein and is one of the major components of the nuclear lamina. It has been shown that LMNB1 acts as a modifier gene affecting the risk of Neural Tube Defects in mice and humans, in which synonymous and non-synonymous missense variants of LMNB1 resulting in protein loss-of-function have been observed. Consistently, it has been demonstrated that experimental ablation of LMNB1 deeply impairs neurogenesis during embryonic development in the mouse. However, how LMNB1 protein expression regulates neurogenesis at the cellular and molecular levels is still undetermined. Here, we investigate whether LMNB1 influences cell fate commitment and early neuronal differentiation in cultured Neural Stem Cells (NSCs) from the dorsal forebrain of E12 embryos of wild type (WT) and LMNB1-null mice. We find that NSC differentiation rate into neurons and astrocytes but not oligodendrocytes, is dependent on LMNB1 protein levels. In fact, LMNB1 deficiency significantly reduces the number of neurons and increases the number of astrocytes originating from NSCs, without altering oligodendrocyte numbers. Conversely, LMNB1 overexpression significantly increases the rate of NSC differentiation into neurons, but does not change the numbers of both astrocytes and oligodendrocytes. Apoptotic features are undetectable in NSC-derived cells, indicating that the observed changes are not due to altered cellular survival. Nuclear abnormalities (i.e. reduced nuclear area and circularity) are present only in LMNB1-deficient NSC-derived neurons, but not astrocytes and oligodendrocytes, nor LMNB1-overexpressing neurons. We also find that LMNB1 protein levels affect the differentiation of NSCs-derived neurons. In fact, both LMNB1-deficiency and overexpression significantly alter axonal length of NSCs-derived neurons, indicating that the protein levels of LMNB1 regulate axonal outgrowth.
These results indicate that LMNB1 plays a key role in cell fate commitment and differentiation during embryonic neurogenesis and that finely tuned levels of the protein are required to achieve proper morphological properties of NSCs-derived neurons.

Alterations of Lamin B1 Levels Affect Viability and Differentiation of Primary Murine Cortical Neurons.

AUTHORS: **GIACOMINI CATERINA**, caterina.giacomini@iit.it, Italy; **MAHAJANI SAMEEHAN**, sameehan.mahajani@iit.it, Italy; **CONTESTABILE ANDREA**, andre.contestabile@iit.it, Italy; **MAROTTA ROBERTO**, roberto.marotta@iit.it, Italy; **RUFFILLI ROBERTA**, roberta.ruffilli@iit.it, Italy; **GASPARINI LAURA**, laura.gasparini@iit.it, Italy

KEYWORDS: Lamin B1, primary cortical neurons, adult-onset autosomal dominant leukodystrophy nuclear lamina

Lamin B1 (LMNB1) is one of the major components of the nuclear lamina, a filamentous network underlying the inner nuclear envelope of eukaryotic cells. There is evidence that LMNB1 is essential during embryonic development of the mouse brain and plays a key role in maintaining brain function in humans during adulthood. In fact, it has been shown that neurogenesis and cortical development are severely impaired in LMNB1-deficient mice. Moreover, in humans, duplications of the LMNB1 gene on chromosome 5 are associated with adult-onset autosomal dominant leukodystrophy (ADLD), a rare demyelinating disease with neurodegenerative features. This suggests that the brain is particularly vulnerable to altered levels of LMNB1. Here, we investigate how altered protein levels of LMNB1 affect neuronal viability and morphology in vitro. We found that, in LMNB1-deficient primary cortical neurons, the nuclear area is reduced and nuclear pore complexes are delocalized. LMNB1 overexpression in neurons results in abnormal nuclei, with blebbings similar to those detected in primary human skin fibroblasts derived from ADLD patients. Abnormal LMNB1 levels also affect survival and differentiation of neurons. In fact, in cortical neurons, LMNB1 deficiency significantly increases the percentage of apoptotic nuclei. LMNB1 transient overexpression also induces apoptosis at early phases of neuronal differentiation, but not during late differentiation stages. LMNB1 protein levels also profoundly affect the morphology of surviving neurons. LMNB1-deficient neurons have reduced dendritic length and arborisation, while those overexpressing LMNB1 have reduced axonal outgrowth. Overall, our data indicate that altered LMNB1 expression levels deeply affect neuronal survival and morphology, with distinct outcomes at different timing of neuronal differentiation and maturation.

PROGRAM PAGE 24

Molecular Testing for Autosomal Dominant Hereditary Spastic Paraplegia in Polish Patients

AUTHORS: **ELERT-DOBKOWSKA EWELINA**, elerte@ipin.edu.pl, Institute of Psychiatry & Neurology, Poland; **KRYSA WIOLETTA**, krysa@ipin.edu.pl, Institute of Psychiatry & Neurology, Poland; **RAJKIEWICZ MARTA**, rajkiewi@ipin.edu.pl, Institute of Psychiatry & Neurology, Poland; **STEPNIAK IWONA**, stepniak.iwona@gmail.com, Institute of Psychiatry & Neurology, Poland; **RAKOWICZ MARIA**, rakowicz@ipin.edu.pl, Institute of Psychiatry & Neurology, Poland; **RUDZINSKA MONIKA**, rudzinsk@neuro.cm-uj.krakow.pl, Jagiellonian Univeristy Medical College, Poland; **PILCH JACEK**, japilch@poczta.onet.pl, Medical University of Silesia, Poland; **SOBANSKA ANNA**, asobanska@op.pl, Institute of Psychiatry & Neurology, Poland; **KUBALSKA JOLANTA**, kubalska@ipin.edu.pl, Institute of Psychiatry & Neurology, Poland; **KURDZIEL KATARZYNA**, katarzynakurdziel@gmail.com, St. Louis Provincial Specialized Children's Hospital, Poland; **ZAREMBA JACEK**, zaremba@ipin.edu.pl, Institute of Psychiatry & Neurology, Poland; **SULEK ANNA**, suleka@ipin.edu.pl, Institute of Psychiatry & Neurology, Poland

KEYWORDS: HSP, Hereditary Spastic Paraplegia, SPAST, ATL1, REEP1

Hereditary spastic paraplegias (HSPs) are a group of genetically and clinically heterogeneous conditions with progressive lower-extremity weakness and spasticity as the most prominent clinical features. Despite the broad range of clinical symptoms, HSP are characterized by genetic heterogeneity in terms of inheritance mode: autosomal dominant (AD), recessive (AR) and X-linked (XL) and number of corresponding loci. Up till now, among known 56 loci related with spastic paraplegia - SPG (spastic paraplegia gene), 36 genes have been identified. In the European population the HSP autosomal dominant forms appear predominantly and three the most common genetic types SPG3 (ATL1), SPG4 (SPAST) and SPG31 (REEP1) may account for up to 50 % of AD-HSP. Autosomal recessive and X-linked HSP are accounted as less frequent and rare. Moreover substantial number of patients comprise apparently sporadic cases. The clinical inclusion criteria for HSP molecular investigation were based on studies by: Dürr et al. (1996) and Fink (2006). Clinical assessment comprised Spastic Paraplegia Rating Scale – SPRS, Scale for assessment rating of ataxia 5th version – SARA, Inventory of Non-Ataxia symptoms 6th version – INAS and Mini-Mental State Examination – MMSE.
The group of 216 probands (85 familial cases with AD-HSP and 131 isolated cases) were screened for mutations in the ATL1, SPAST and REEP1 genes. Molecular analysis was performed using the multiplex ligation-dependent probe amplification (MLPA) and Sanger sequencing analysis. Molecular investigation in 216 index patients enabled us to identify the HSP causative mutations in 52 subjects. The MLPA screening revealed 12 microrearrangements in the SPAST gene in 15 families. Moreover, the 36 point mutations in the ATL1 (8 mutations), SPAST (25 mutations) and REEP1 (4 mutations), genes were detected. Out of all 52 identified molecular defects, 43 mutations were detected in AD-HSP familial cases, whereas 9 were found in the group of sporadic patients. Genetic investigation in 216 clinically suspected HSP patients was positive in 52 cases that accounted for 24 % of the studied subjects. Moreover, in the group of 85 familial cases, molecular testing for the three most frequent HSP types (SPG3, SPG4, SPG31) confirmed the clinical diagnosis in 43 subjects (50,6 %). Our study, similarly to other European populations, revealed that SPG4 is the most frequent genetic SPG type detected in AD-HSP families (38 %) as well as sporadic individuals (6 %).

Clinical and Molecular Studies on 87 Chinese Patients with Isolated Methylmalonic aciduria

AUTHORS: **YANG YANLING**, organic.acid@126.com, Peking University First Hospital

KEYWORDS: methylmalonic aciduria, organic acidurias, MUT, metabolic disease

STATEMENT OF PURPOSE: Methylmalonic aciduria (MMA) is a rare inherited metabolic disease. But it is the most common disorder of organic acidurias in Mainland China. In this study, the clinical and laboratory findings of 87 Chinese patients with isolated MMA were investigated.
CASES AND METHODS: From 2005 to 2013, 87 patients originating in 16 provinces or cities of Mainland China were diagnosed as isolated MMA in our hospital. They had clinical symptoms from the age of 2 hours to 7 years and diagnosed at the age of 5 days to 10 years. All patients had normal serum and urine total homocysteine.
RESULTS: 60 patients (68.9 %) had early-onset MMA before the age of one year, presented with feeding difficulty, vomiting, lethargy, seizures and mental retardation. 31 (35.6 %) of them showed symptoms in neonatal period. 11 cases (12.6 %) had late-onset MMA. They showed psychomotor deficits, seizures or multi-organ disorders from the age of 1 to 7 years. Out of 46 patients who accepted gene analysis, 42 mutations on MUT gene were found from 41 patients. 34 mutations were reported worldwide. Among 34 mutations reported, c.729-730insTT was the most frequent mutations. It was found in 13 alleles (15.9 %) of 11 patients (26.8 %). c.2080C>T was found in 5 alleles (7.3 %) of 5 patients (12.2 %). c.494A>G was found in 5 alleles (7.3 %) of 4 patients (9.8 %). 60 patients were treated by protein-restricted diet, special formula and L-carnitine. 5 patients died. Mild to severe psychomotor retardation was observed in 83 cases.
CONCLUSIONS: MMA due to mutase deficiency is the common type of isolated MMA in Chinese. The spectrum of mutations of MUT in Chinese patients with mutase deficiency is different from other populations. The clinical manifestation of the patients with isolated MMA is complex. Newborn screening, early diagnosis and adequate therapy are very important to improve the prognosis of the disease.

Perinatal Gene Therapy Rescues Acute Neonatal Lethal Neuronopathic Gaucher Disease in Mice

AUTHORS: **WADDINGTON SIMON**, s.waddington@ucl.ac.uk, University_College_London, United Kingdom; **RAHIM AHAD**, a.rahim@ucl.ac.uk, University_College_London, United Kingdom; **SUZY BUCKLEY**, suzy.buckley@ucl.ac.uk, University_College_London, United Kingdom; **HOWE STEVEN**, s.howe@ucl.ac.uk, United Kingdom

KEYWORDS: Gene Therapy, Gauchers Disease

AA Rahim1, DG Burke2, SM Buckley1, E Cullen2, K Mills2, E Sirka2, B Herbert3, S Karlsson4, DAHughes5, AB Mehta5, SJ Howe2, S Heales2, JD Cooper6, SH Cheng7, SN Waddington1
1 UCL Institute for Women´s Health, London. 2 UCL Institute of Child Health, London 3 Imperial College, London. 4 Lund University, Lund 5 The Royal Free Hospital, London 6 KCL Institute of Psychiatry, London 7 Genzyme Corporation, Boston

BACKGROUND: Type II Neuropathic Gaucher Disease (nGD) is caused by mutation of the glucocerebrosidase gene. Patients exhibit acute and aggressive neurodegeneration and die before two years of age; no treatment exists. A neonatal lethal mouse model of nGD exhibits neurodegeneration and dies before 14 days of age. We conducted a temporospatial analysis of disease progression in the brain. We used this data to measure the efficacy of gene therapy in utero and in neonatal mice.

METHODS: Brains from wild type, heterozygous and knockout nGD mice were collected at 1 day old (P1), P9 (pre-symptomatic) and P12 (symptomatic). Microglial activation, astrogliosis, lysosomal content and neurodegeneration were measured. For rescue of the model, adeno-associated virus serotype 9 carrying therapeutic glucocerebrosidase gene was administered to the brains of mice by intracranial injection at E15 gestation or on P1. Survival, behavior and indices of brain pathology were analysed.

RESULTS: Microglial activation and astrogliosis at P1 in the brain stem of KO mice was observed. Global and progressive spread of CNS pathology was evident at P9 and P12; the most affected regions were the brain stem, VPL/VPM and layer V of the cortex. This was accompanied by severe and rapid neurodegeneration. A single injection of AAV9 vector in utero dramatically ameliorated astrogliosis, microglial activation, lysosomal accumulation and neuronal loss and extended the lifespan of all treated KO mice by at least nine-fold (day 130, n=5, $p<0.005$). Nevertheless performance on rotarod and foot-fault tests was subnormal. Neonatal gene therapy was equally effective; treated knockouts were fertile and we have been able to maintain the mice as a colony of treated knockouts. As expected, visceral pathology remained uncorrected by the intracranial treatment.

CONCLUSION: Perinatal gene therapy is successful in profoundly ameliorating an early neonatal lethal mouse model of nGD. To date, this is the most severe model of a neurodegenerative lysosomal storage disorder to be rescued by gene therapy.

PROGRAM PAGE 24

Roles of Cell Cycle Proteins during Photoreceptor Degeneration

AUTHORS: **ARSENIJEVIC YVAN**, yvan.arsenijevic@fa2.ch, University of Lausanne, Jules-Gonin Eye Hospital, Switzerland; **SCHOUWEY KARINE**, karine.schouwey@gmail.com, University of Lausanne, Jules-Gonin Eye Hospital, Switzerland; **VAN LOHUIZEN MAARTEN**, m.v.lohuizen@nki.nl, The Netherlands Cancer Institute, Netherlands

KEYWORDS: neurodegeneration, retinitis pigmentosa, neuroprotection, regeneration, dedifferentiation

Several studies show the reactivation of cell cycle proteins in post-mitotic neurons during the process of cell death in different neurodegenerative diseases. We asked whether these proteins play a major role in retinal degeneration. We investigated the retina of Rd1 mice, a model of retinitis pigmentosa with rod function defects, to study photoreceptor loss.

At early stage of the disease, Rd1 mice displayed an increased expression of different cell cycle proteins, including Cdk4. Genetic and pharmacological interferences with cell cycle protein activities extended photoreceptor survival both in vitro and in vivo, the ablation of Bmi1, which controls the cell cycle, having the greatest effect by protecting around 70 % of the photoreceptors (Zencak et al., PNAS 2013).

We then investigated whether the dying cells attempt to divide or if the Bmi1 and the Cdks are involved in another process. We observed in the Rd1 mouse, that Bmi1 does not have an effect on p16 and p19 (use of TKO), on oxidative stress, nor on DNA repair. To synchronise cell death, we induced retinal degeneration in WT animals by chemicals and follow GFP-positive photoreceptors in retina explants by time-lapse recording and cell sorting. We observed that a subgroup of photoreceptors migrated towards the inner part of the retina, duplicated the DNA and attempted to dedifferentiate into progenitor cells attested by immunohistochemistry and RT-PCR techniques.

In conclusion, our data show for the first time a mechanism of retina degeneration involving a reactivation of cell cycle proteins that precedes photoreceptor death which attempts to divide. The dissection of such mechanisms may help to understand cues controlling cell regeneration versus cell death and these results already provide targets for therapy to slow down the degenerating process.

Biomarkers for Neurodegenerative Disorder, Friedreich's Ataxia

AUTHORS: **MOGANTY RAJESWARI**, rajeswari3011@hotmail.com, AllIndiaInstituteOfMedicalSciences, India

KEYWORDS: FRDA, mtDNA, plasma biomarkers, ataxia

PURPOSE: Exactly 150 years ago, Nikolaus Friedreich, described a new spinal disease for the first time which is now known as Friedreich's ataxia, (FRDA). FRDA, a rare and autosomal recessive degenerative disorder of nervous and muscles tissues affects children and manifests before puberty. Mitochondrial dysfunction is the primary causative factor for cellular death. For the first time, we made an attempt to search for blood plasma-based DNA for evaluating the molecular and pathological changes in FRDA patients.

METHODS: Clinically suspected patients for FRDA (58) from north India were evaluated by International Co-operative Ataxia Rating Scale followed by genetic analysis using Long Range PCR. Circulating cell-free DNA, (nuclear (n) and mitochondrial (mt) DNA) analysis of genetically confirmed FRDA patients (n=23), suspected patients (25) and age matched healthy controls (n=20) were performed along with oxidative stress assessment.(Ethical Committee Sanction: IEC/NP-311/2012/RP-24/2012).

RESULTS: Multiplex quantitative Real Time PCR analysis revealed significant up-regulation of nDNA (~2 fold, $p< 0.01$) and down-regulation mtDNA (~3.2 fold, $p<0.001$) in FRDA confirmed subjects in comparison with suspected and healthy subjects. Relative levels of mtDNA to nDNA in FRDA subjects was found to be reduced and significantly correlated with the age of onset ($p < 0.05$, R2 0.763). No significant correlation was obtained with plasma MtDA (oxidative stress parameter) levels.

CONCLUSION: This work opens up new avenues to find association between disease pathogenesis and plasma cell-free DNA in FRDA patients. This will help in developing a simple, biochemical analytic tool which will lead to early diagnosis/prognosis of FRDA. This work is funded by: Indian Council of Medical Research of India (5/4-5/85/Neuro-2012-NCD-I) Competing Interests: None.

Tissue Integrity and Laminopathic Phenotypes Correlate with Subnuclear Heterochromatin Positioning

AUTHORS: **MATTOUT ANNA**, anna.mattout@fmi.ch, Friedrich Miescher Institute for Biomedical Research, Switzerland; **GONZALEZ-SANDOVAL ADRIANA**, adriana.gonzales@fmi.ch, Friedrich Miescher Institute for Biomedical Research, Switzerland; **TOWBIN BENJAMIN**, benjamin.towbin@weizmann.ac.il, Weizmann Institute, Israel; **GRUENBAUM YOSSI**, gru@vms.huji.ac.il, The Hebrew University of Jerusalem, Israel; **GASSER SUSAN**, susan.gasser@fmi.ch, Friedrich Miescher Institute for Biomedical Research, Switzerland

KEYWORDS: Lamin, EDMD Y59C, Chromatin Organization, Muscular Dystrophy, Heterochromatin

We have previously shown that wild-type lamin helps organize the subnuclear position of heterochromatin, and that a point mutation in lamin, Y59C, which in humans leads to Emery-Dreifuss muscular dystrophy, impairs the proper muscle-specific redistribution of a heterochromatic array away from the nuclear periphery. We also found that this muscle-specific misorganization of heterochromatin correlated with transcriptional defects and with defective locomotion and muscle integrity (Mattout et al, Curr Biol, 2011). It has remained unclear, however, whether the chromatin misorganization was a cause or an effect of the observed physiological defects, nor was it clear whether either defect led directly to altered gene expression.

In order to clarify this, we took advantage of the cec-4 deletion mutant recently characterized in our laboratory, which specifically releases H3K9me-containing heterochromatin from the nuclear periphery (Gonzalez-Sanz et al., in preparation). This release occurs in embryos and does not necessarily provoke transcriptional reactivation. We combined this mutation with expression of the lamin Y59C mutant, in a strain bearing a muscle-specific reporter array, which is heterochromatic due to its large size. We find that combining the cec-4 deletion with the Y59C lamin mutation restores the proper positioning of the muscle-specific heterochromatic array in differentiated muscle cells. Interestingly, preliminary results suggest that the cec-4 mutation rescues the impaired locomotion phenotype of the Y59C lamin mutant.

Together, this data indicate that expression of mutant lamin proteins can lead to a spatial misorganization of heterochromatin, which in turn initiates a cascade of events, most probably through gene misregulation, that causes some of the pathologies of the wide range of lamin-related genetic diseases.

Genetic Analysis of CAPS and TRAPS in Russian Patients Affected with Systemic Juvenile Idiopathic Arthritis

AUTHORS: **NAMAZOVA-BARANOVA LEYLA**; docseasur@gmail.com, Russian Federation, Savostyanov Kirill; 7443333@gmail.com, Russian Federation; **ALEXEEVA EKATERINA**, el.mitenko@yandex.ru, Russian Federation; **PUSHKOV ALEXANDR**, pushkovgenetika@gmail.com, Russian Federation; **SLEPTSOVA TATYANA**, tatyanasl08@mail.ru, Russian Federation; **CHISTIAKOV DMITRY**, dimitry.chistiakov@lycos.com; Russian Federation; **SULEYMANOV ELKHAN**, docsuleymanov@gmail.com, Russian Federation; **BARANOV ALEKSANDR**, baranov@nczd.ru, Russian Federation

KEYWORDS: Autoinflammatory, TRAPS, CAPS, Systemic JIA, Mutations

BACKGROUND: Systemic juvenile idiopathic arthritis (JIA) is a rare subtype of JIA that can be classified as an autoinflammatory disease instead of an autoimmune disease.
METHODS: The study included 52 children (23 boys, 29 girls) at the age from 6 months to 17 years (8.2 (4.7; 11.5) with fever of unknown cause, after exclusion of infections, malignancy and autoimmune diseases. The median age at which symptoms began was 3.0 (1.5; 5.1) years, disease duration – 4.4 (1.0; 7.6) years. The commonest features were fever (100 %), arthritis or arthralgia (100 %), rash (96 %), hepato- and splenomegaly (96 %), lymphadenopathy (94 %), headache (62 %), abdominal pain (58 %) and eye manifestations (21 %). The patients were selected according to the clinical manifestations, with subsequent obligatory genetic counseling in the Division of Rheumatology of the Research Center for Children's Health. Patients' DNA was sequenced in all coding exons and intronic flanks of the TNFRSF1A and NLRP3 genes whose mutations cause autoinflammatory syndromes, TRAPS and CAPS, respectively.
RESULTS: In seven patients, we found etiological mutations in TNFRSF1A. Most patients (6) had a mutation c.362G>A (p.R92Q) located in exon 4 and associated with the mild progression of TRAPS. Interestingly, one patient was homozygous for p.R92Q while others were heterozygous. The 7th TRAPS patient had a novel frameshift mutation c.792delT (p.Lys265Serfs87) in exon 9 of TNFRSF1A. In two patients, mutations in NLRP3 were detected. The first CAPS patient had a NLRP3 mutation c.2113C>A (p.Gln705Lys) whereas the second contained a novel mutation c.2861C>T (p.Thr954Met).
CONCLUSIONS: Our analysis of obtained data revealed a 17,3 % incidence of CAPS and TRAPS in Russian systemic JIA patients.

RAD50 Phosphorylation Promotes ATR Downstream Signaling and DNA Restart Following Replication Stress

AUTHORS: **GATEI MAGTOUF**, magtouf6@qimr.edu.au, QIMR Berghofer Medical Research Institute, Radiation Biology and Oncology, Brisbane, QLD 4029, Australia; **AMANDA W KIJAS**, QIMR Berghofer Medical Research Institute, Radiation Biology and Oncology, Brisbane, QLD 4029, Australia; **MARTIN F LAVIN**, QIMR Berghofer Medical Research Institute, Radiation Biology and Oncology, Brisbane, QLD 4029, Australia and University of Queensland Centre for Clinical Research, Building 71/918, Royal Brisbane & Women's Hospital Campus, Herston, QLD 4029 , Australia

KEYWORDS: DNA damage, Rad50, DNA replication stress

BACKGROUND: To investigate the role of Rad50 in the cellular response to DNA damage following DNA replication fork stalling.
METHODS: Control (NFF) ATM null (AT5), ATR- Seckel and Rad50 deficient (F239) h-TERT immortalized fibroblasts were exposed to either 5 Gy of IR, 20 J/m2 of UV or 2 mM of HU and harvested after 15 min, 1 h or 2 h respectively. These cells were employed for immunoblotting, ATR kinase assay, G2/M checkpoint activation, Clonogenic survival and immunofluorescence analyses. Results: The Mre11/Rad50/NBN complex plays a key role in DNA damage signalling, cell cycle checkpoint control and DNA repair through ataxia telangiectasia mutated (ATM) and ataxia telangiectasia mutated and Rad3 related (ATR) activation in response to DNA damage. Hypomorphic mutations in these genes give rise to ataxia telangiectasia-related disorder (ATLD) Mre11 deficient, Nijmegen breakage syndrome (NBS) NBN deficient and Nijmegen breakage syndrome-like disorder (NBSLD) due to Rad50 deficiency (Waltes et al, 2009; Gatei et al 2011). These disorders are characterized by cellular radiosensitivity, cell cycle abnormalities, and a defective response to DNA damage. Although several families with ATLD and NBS have been identified, only two patients with Rad50 deficiency have been reported. We provide evidence here that Rad50 is required for ATR activation and Rad50 is phosphorylated by ATR at S635 following replication stress. This activation is required to phosphorylate Chk1 at S317 and a Rad50 S635G mutant failed to do so. This indicates that Rad50 acts upstream as an activator as well as downstream as an effecter for ATR in response to stalled replication forks. Interestingly, we find that Rad50 phosphorylation is essential for DNA replication restart and the mechanism involved is by promoting loading of cohesin at sites of DNA replication restart. We also demonstrate that replication stress-induced Rad50 phosphorylation is functionally significant for cell survival and cell cycle checkpoint activation. These results highlight the importance of Rad50 in the aspects of the DNA response to replication stress.
CONCLUSIONS: These results demonstrate that Rad50 mediates ATR-dependent substrate phosphorylation in response to replication stress. Furthermore, these data also indicate that Rad50 is phosphorylated at a single site (S635) to play the role in cell cycle checkpoint activation and DNA replication restart.

An Epidemiological Survey of Adults with Histiocytic Disorders in the Northeast Region of the UK

AUTHORS: **SALOTTI JANE**, jane.salotti@ncl.ac.uk, United Kingdom; **WOOD KATRINA**, Katrina.Wood@nuth.nhs.uk, United Kingdom; **BIGLEY VENETIA**, Venetia.bigley@ncl.ac.uk, United Kingdom; **COLLIN MATTHEW**, matthew.collin@ncl.ac.uk, United Kingdom; **WINDEBANK KEVIN**, kevin.windebank@ncl.ac.uk, United Kingdom

KEYWORDS: Histiocytoses, Adults, Epidemiology

BACKGROUND: Histiocytic disorders have clinical and pathological features of neoplasia and inflammation and may cause dysfunction of multiple organ systems. Adults may therefore present to many different clinical specialties. However, there is no national or international consensus on the best treatment and no open clinical trial or national registry. The scale of the problem in the UK is unknown. Some adults in the Northeast region attend a dedicated clinic in Newcastle with haematological, dermatological and paediatric (LCH expert) input but it is not known which other specialists are treating patients. This regional study will estimate the frequency of disease and assess the treatments and services patients are receiving. This may then lead to the establishment of a national registry for those with histiocytoses.
METHODS: Patients are being identified via pathology department databases by searching for appropriate Snomed codes (in brackets) for histiocytic diseases: Langerhans cell histiocytosis - LCH (M7791,M77800); Haemophagocytic lymphohistiocytosis - HLH (F42000); Rosai-Dorfman – R-D (M77940); Erdheim Chester - ECD (M77800); Juvenile xanthogranuloma -JX (M55380). Eligible patients are >=16 years old and diagnosed by biopsy from 2000-2012 with a histiocytic disease. For those eligible, questionnaires are mailed to the referring clinicians for information on patient presentation, treatment and services used. The study received appropriate research governance approvals. Results: A pilot study in one regional hospital (Newcastle) identified 67 adults, aged 16-81 years. However, 20 cases were found not to have a histiocytic disease and a further 17 were ineligible for other reasons. Of those with histiocytosis, 25 had LCH, 7 had JX, 4 had R-D disease and 1 had HLH. The M:F ratio was 1.5:1. Of those with LCH, the sites of disease were lung, bone, lymph, skin and genital mucosa. A further 28 cases have been identified at 2 of 8 other regional hospitals, including 18 cases of JX.
CONCLUSION: Snomed codes were found to include reactive types of histiocytosis as well as primary histiocytic disease. Therefore anonymised pathology reports are now being screened to exclude ineligible patients before contacting clinicians. Data collection is continuing at the other regional hospitals. As well as improving our knowledge, it is hoped that the results of the study will improve co-operation and planning for adults with histiocytoses both regionally and nationally.

Molecular Characterization of the Only Frequently Recurrent Mutation in Carbamoyl Phosphate Synthetase 1 (CPS1) Deficiency

AUTHORS: **HU LIYAN**, Liyan.hu@kispi.uzh.ch, Switzerland; **DIEZ-FERNANDEZ CARMEN**, cdiezf@gmail.com, Spain; **RÜFENACHT VÉRONIQUE**, Veronique.Ruefenacht@kispi.uzh.ch, Switzerland; **RUBIO VICENTE**, rubio@ibv.csic.es, Spain; **HÄBERLE JOHANNES**, Johannes.Haeberle@kispi.uzh.ch, Switzerland

KEYWORDS: urea cycle disorder, Carbamoyl phosphate synthetase 1 deficiency, hyperammonemia, recurrent mutation, baculovirus/insect cell expression system

BACKGROUND: Carbamoyl phosphate synthetase 1 deficiency (CPS1D), due to CPS1 mutations, is a rare autosomal-recessive urea cycle disorder causing hyperammonemia that can lead to death or severe neurological impairment. CPS1 catalyzes carbamoyl phosphate formation from ammonia, bicarbonate and two ATPs, and requires the essential allosteric activator N-acetyl-L-glutamate. Clinical mutations were found spreading over the entire CPS1 coding region, occurring mainly in single families, with little recurrence. We characterize here the only known frequently recurrent CPS1 mutation, p.Val1013del, found in patients of Turkish descent.
MATERIALS AND METHODS: p.Val1013del was found in eight unrelated Turkish CPS1D patients. Recombinant, His-tagged, CPS1, either wild-type (WT) or V1013del, was expressed using baculovirus/insect cells (confirmed by western blotting of virus-infected cell extracts). These CPS1 forms were purified to homogeneity. The global CPS1 reaction and the ATPase and ATP synthesis partial reactions that reflect, respectively, the bicarbonate and the carbamate phosphorylation steps, were assayed. Structural modelling was performed to rationalize the p.Val1013del effects.
RESULTS: CPS1 WT and V1013del mutant were expressed at comparable level and were purified to homogeneity (Coomassie-stained SDS-PAGE). The mutant exhibited no significant residual activities in the assays for the carbamoyl phosphate synthesis reaction or for the partial reactions. In the CPS1 structural model V1013 belongs to a highly hydrophobic β-strand at the middle of the central β sheet of the A subdomain of the carbamate phosphorylation domain (an ATP-grasp domain). It is close to the predicted carbamate tunnel that links both phosphorylation sites, being just 5 residues away from E1018, which is predicted to belong to the tunnel wall.
CONCLUSION: p.V1013del inactivates the enzyme but does not render the enzyme grossly unstable or insoluble. The deletion, by shortening the β-strand, could pull E1018 away from the carbamate tunnel, distorting this tunnel and possibly hampering the connection between both phosphorylation steps.

Mutation Analysis in 2 Swiss Families with Non-Syndromic Hereditary Hearing Impairment through Sequence Capture and Next-Generation-Sequencing

AUTHORS: **GÜRTLER NICOLAS**, nguertler@yahoo.com, Switzerland; **LUDIN KATJA**, katja.ludin@ksa.ch, Switzerland; **RÖTHLISBERGER BENNO**, benno.roethlisberger@ksa.ch, Switzerland

KEYWORDS: Hereditary Hearing Impairment, Next-generation-sequencing, Snesorineural hearing impairment

BACKGROUND: iHereditary non-syndromic hearing impairment is characterized by a high heterogeneity with dozens of genes and hundreds of different mutations. The search for mutations by classic sequencing method is time and labour intensive. New methods such as Next-Generation-Sequencing based on higher through-put and array technology offer a much higher yield.
The objective was to detect mutations by targeted genome capture in combination with next-generation sequencing in two Swiss families with hereditary non-syndromic hearing impairment. Hearing impairment in family A is sensorineural, postlingual and affects the high frequencies. Family B shows sensorineural, postlingual hearing impairment in the low frequency range.
METHODS: First, a possible larger pathogenic deletion was investigated with an exon focused high-density Roche NimbleGen CGH array. Second, a custom Sequence Capture 385K Human Array was designed and manufactured by Roche NimbleGen. The array included all known genes associated with hereditary hearing loss. After capturing the targeted regions the DNA was eluted, amplified and then sequenced on a Illumina MiSeq instrument. Variants were detected with the SEQNext Software (JSI Medical Systems) and possible pathogenic mutations were verified by Sanger Sequencing in the patient and further family members.
RESULTS: The mutation c.5383+5delGTGA in the TECTA-Gene was discovered in family A. The mutation was present in 8 affected and absent in 7 non-affected family members, consistent with segregation of hearing impairment. Family B harboured a novel mutation in the WFS1-gene: c.2614-2625delCATGGCGCCGTG (p.872-875delHGAV), which segregated with affected family members.
CONCLUSIONS: The search for mutations in hereditary hearing impairment can be facilitated by novel methods such as targeted genome capture in combination with next-generation sequencing.

High Rates of Medical Comorbidity in Narcolepsy: Findings from the Burden of Narcolepsy Disease (BOND) Study of 9,312 Patients in the United States

AUTHORS: **BLACK JED**, Jed.Black@jazzpharma.com, Stanford University Center for Sleep Research and Medicine, United States of America; **REAVEN NANCY**, nancy.reaven@strathealth.com, Strategic Health Resources, United States of America; **FUNK SUSAN**, susan.funk@kailos.com, Kailos Group, United States of America; **KAREN MCGAUGHEY**, kmcgaugh@calpoly.edu, Cal Poly Corporation, United States of America; **OHAYON MAURICE**, mohayon@stanford.edu, Stanford University Center for Sleep Research and Medicine, United States of America; **GUILLEMINAULT CHRISTIAN**, cguilleminault@stanford.edu, Stanford University Center for Sleep Research and Medicine, United States of America; **RUOFF CHAD**, cruoff@stanford.edu, Stanford University Center for Sleep Research and Medicine, United States of America

KEYWORDS: Narcolepsy, Burden of Illness, Medical Comorbidity

INTRODUCTION: While narcolepsy is known to be associated with medical comorbidities, the full scope of concomitant illness in this population has not been well characterized. The purpose of this analysis was to evaluate medical comorbidity patterns in patients with a narcolepsy diagnosis in the United States.
METHODS: Truven Health Analytics MarketScan® Research Databases were accessed to identify individuals >18 years of age with at least one diagnosis code for narcolepsy + cataplexy (ICD9 347.0, 347.00, 347.01, 347.1, 347.10 or 347.11) continuously insured between 2006 and 2010, and controls without narcolepsy matched 5:1 on age, gender, region, and payer. Extensive sub-analyses were conducted to confirm the validity of narcolepsy definitions. Narcolepsy and control subjects were compared for frequency of comorbid conditions, identified by the appearance of >1 diagnosis code(s) mapped to a Clinical Classification System (CCS) level 1 category any time during the study period, and on specific subcategories, including recognized narcolepsy comorbidities of obstructive sleep apnea (OSA) and depression.
RESULTS: The final population included 9,312 narcolepsy subjects and 46,559 controls (each group, average age of 46.1 years and 59% female). Compared with controls, narcolepsy patients had significantly higher frequencies of the following CCS categories: respiratory (90.9% vs 73.5%), musculoskeletal (89.5% vs 72.0%), endocrine (81.7% vs 63.8%), circulatory (80.9% vs 64.3%), genitourinary (77.5% vs 64.3%), digestive system (73.9% vs 52.5%), injury (72.1% vs 51.9%), infectious disease (67.8% vs 53.6%), skin (63.7% vs 49.3%), mental illness (62.3% vs 31.2%), neoplasms (55.7% vs 45.4%), blood diseases (30.7% vs 17.7%), and congenital anomalies (13.9% vs 6.9%) (all $p<0.0001$). High excess frequency was observed for OSA (51.4% vs 5.7%; OR 18.7; 95% CI 17.5, 20.0) and depressive disorders (35.8% vs 13.0%; OR 3.9; 95% CI 3.7, 4.1) ($p<0.0001$). No excess frequency was observed in conditions arising perinatally (1.7% vs 1.6%; $p=0.68$) or obstetrical conditions (11.3% vs 11.7%; $p=0.30$).
CONCLUSIONS: Narcolepsy is associated with a significant burden of medical comorbidity.

Comparison of Sureselect, Nimblegen and Nextera Capture Platforms for Whole Exome Sequencing

AUTHORS: **ZERJAVIC KATJA**, zerjavic@genetikzentrum.ch, Center for Cardiovascular Genetics and Gene Diagnostics, Switzerland; **MEIENBERG JANINE**, meienberg@genetikzentrum.ch, Foundation for People with Rare Diseases, Switzerland; **MATYAS GABOR**, matyas@genetikzentrum.ch, Switzerland

KEYWORDS: exome enrichment, next generation sequencing

BACKGROUND: Whole exome sequencing (WES) can be effective for identifying sequence variants. Here we present a comprehensive comparison of the most recent next generation sequencing (NGS) exome enrichment methods of three leading companies, Agilent (SureSelect), Roche (NimbleGen) and Illumina (Nextera), applied to 6 human DNA samples extracted from blood, saliva or cultured cells.

METHODS: Exome of each DNA sample was captured by the three enrichment methods and sequenced at 100x depth of coverage on the Illumina HiSeq 2000 platform in 4 different laboratories. In-house analysis of provided mapped sequencing data was performed. Of the more important features, read depth, % of coverage, GC bias, and number of detected single nucleotide variations (SNVs) and small indels have been estimated. In addition, to examine the methods' ability to identify SNVs and small indels, we analyzed 84 different heterozygous positions and 11 small indels previously detected by Sanger sequencing in our panel of eight genes associated with rare aortic diseases. For two DNAs, WES data were also compared to whole genome sequencing (WGS) data.

RESULTS: SureSelect and NimbleGen demonstrated much higher average read depth in their target region compared to Nextera. All three platforms covered more than 99 % of their target regions at 1x, however, considering at least 20 reads per nucleotide as our minimal quality standard, SureSelect covered the largest proportion of its targeted bases. When comparing the enrichment platforms to the RefSeq database, SureSelect and NimbleGen again showed the highest average read depth. No significant difference in coverage of the database among the three methods was observed. NimbleGen and SureSelect detected the highest number of SNVs and small indels. However, all 84 SNVs identified by Sanger sequencing were accurately called by all three methods at ≥20x. Much less consistent was the detection of small indels, where a substantial difference among the platforms and the sequencing providers was observed. In addition, all three methods showed high GC bias which was not seen in WGS.

CONCLUSIONS: Our analysis indicated a considerable variability among the exome enrichment methods, DNA sequencing laboratories, and even among the DNA samples. However, regarding the selected features of the capture platforms, this study suggested that both SureSelect and NimbleGen performed better than Nextera.

The Swiss Foundation for Research on Muscle Diseases

AUTHORS: **WILLMANN RAFFAELLA**, raffaella.willmann@fsrmm.ch, Swiss Foundation for Research on Muscle Disease,; Switzerland; **ROGNON JACQUES**(main author), jacques.rognon@fsrmm.ch, Swiss Foundation for Research on Muscle Disease, Switzerland

KEYWORDS: research, neuromuscular, myopathy

Rare diseases are those diseases which do not attract interest from the pharmaceutical industry because the potential market is too small, and which are not the object of research programs because of the lack of data. However, research into rare diseases is an unmet need as many patients are left without effective treatment. The costly clinical trials for rare diseases are hampered by the fact that patients who meet inclusion criteria are limited in number. Therefore especially in the field of rare diseases, strong and reliable data from the preclinical research are particularly important in order not to waste resources and hopes.

The Swiss Foundation for Research on Muscle Diseases recognized these needs 28 years ago, as research for neuromuscular disorders was underrepresented in Switzerland. Two main pillars were identified to overcome this situation: the support of excellent research projects and the facilitation of exchange and collaboration through national and international scientific meetings. Almost three decades later, Switzerland is best positioned in the international neuromuscular community and is contributing to first therapeutic developments for patients with muscle disorders.

Non-Coding Pah Gene Alterations Act as New Transcription Regulators

AUTHORS: **STOJILJKOVIC MAJA**, maja.stojiljkovic@imgge.bg.ac.rs, Institute of Molecular Genetics and Genetic Engineering; University of Belgrade, Yugoslavia; **KLAASSEN KRISTEL**, kristel.klaassen@yahoo.com, Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Yugoslavia; **ZUKIC BRANKA**, branka.zukic@imgge.bg.ac.rs, Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Yugoslavia; **UGRIN MILENA**, milenaradmilovic@gmail.com, Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Yugoslavia; **SPASOVSKI VESNA**, vesna_spasovski@yahoo.com, Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Yugoslavia; **KOTUR NIKOLA**, nikola0104@gmail.com, Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Yugoslavia; **NOVCIC NIKOLA**, novcicnikola@gmail.com, Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Yugoslavia; **NIKCEVIC GORDANA**, gordnik@imgge.bg.ac.rs, Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Yugoslavia; **PAVLOVIC SONJA**, sonya@sezampro.rs, Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Yugoslavia

KEYWORDS: phenylketonuria, phenylalanine hydroxylase, transcription, genotype-phenotype correlation, non-coding alterations

Phenylketonuria (PKU) is a rare metabolic disease caused by mutations in phenylalanine hydroxylase gene (PAH). PAH gene mutations that abolish structure and function of PAH are main determinant of PKU phenotype. However, phenotype could not be always predicted precisely. Previously, we found a transcription enhancer in PAH intron 8 that could affect genotype-phenotype correlation. In this study, we functionally analyzed additional non-coding PAH gene alterations to propose new transcription regulatory elements.

In silico prediction for transcription factor binding sites pointed to a population-specific promoter alteration (PAH: c.-170delC) and VNTR alterations (VNTR3, VNTR7 and VNTR8) in 3′ region, that have never been analyzed before. We transiently transfected HepG2 cell line with various CAT reporter constructs (derived from pBLCAT5 plasmid) to determine the effect of a PAH gene non-coding sequence on transcription. Subsequently, we performed EMSA supershift assays to identify interactions between selected non-coding sequences and transcription factors present in HepG2 nuclear extract.

We found that a construct, lacking in silico predicted binding site (c.-170delC) from promoter, had the same transcription activity as the basal one detected for control pBLCAT5. On the other hand, a construct with predicted binding site had a 50 % reduction of CAT activity in comparison to pBLCAT5. EMSA supershift showed binding of a KLF1 transcription factor to the analyzed promoter sequence. Furthermore, CAT assays showed that all three VNTR types have strong and mutually equal silencing effect on transcription activity. We detected around 60 % reduction of reporter activity in comparison to pBLCAT5. In EMSA supershift, we analyzed interaction of a 90bp long VNTR3 (most frequently found in Serbia, ~80 %) and a 30bp long individual repeats with different transcription factors. We found that full structure of VNTR3 is needed to obtain binding of C/EBPalfa.

Our study pointed to two new elements in promoter and 3′ region of PAH gene that could act as transcription silencers and thus influence genotype-based prediction of PKU severity. Given that these non-coding alterations are population specific, further validation of their relevance should be studied in different populations. New transcription regulators in non-coding regions, like these ones, will contribute to better understanding of PKU phenotype complexity and may become important for optimization of PKU treatment.

Card15, Il-6 And Tnf-α Gene Variants in Association with Crohn's Disease in Serbian Population

AUTHORS: **NIKCEVIC GORDANA**, gordnik@imgge.bg.ac.rs, Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Yugoslavia; **STANKOVIC BILJANA**, bi.stankovic@gmail.com, Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Yugoslavia; **DRAGASEVIC SANJA**, dragasevicsanja@yahoo.com, Clinical Center of Serbia, Belgrade, Serbia, Yugoslavia; **KOTUR NIKOLA**, nikola0104@gmail.com, Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Yugoslavia; **POPOVIC DRAGAN**, drendo@beotel.rs, Clinical Center of Serbia, Belgrade, Serbia, Yugoslavia; **SOKIC-MILUTINOVIC ALEKSANDRA**, asokicmilutinovic@gmail.com, Clinical Center of Serbia, Belgrade, Serbia, Yugoslavia; **LUKIC SNEZANA**, lukic.snezana@gmail.com, Clinical Center of Serbia, Belgrade, Serbia, Yugoslavia; **ALEMPIJEVIC TAMARA**, altam@eunet.rs, Clinical Center of Serbia, Belgrade, Serbia, Yugoslavia; **SRZENTIC SANJA**, sanjasrz@gmail.com, Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Yugoslavia; **ZUKIC BRANKA**, branka.petrucev@gmail.com, Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Yugoslavia; **KRSTIC MIODRAG**, misa@tehnicom.net, Clinical Center of Serbia, Belgrade, Serbia, Yugoslavia; **MILOSAVLJEVIC TOMICA**, tommilos@hotmail.com, Clinical Center of Serbia, Belgrade, Serbia, Yugoslavia; **PAVLOVIC SONJA**, sonya@sezampro.rs, Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Yugoslavia;

KEYWORDS: : Crohn's disease, CARD15, TNF-α, IL-6, prediction of disease development

STATEMENT OF PURPOSE: Crohn's disease (CD) is a rare, chronic inflammatory disorder of the gut. Several genes have been related to the development of CD, among which CARD15 showed the strongest association. Also, association between TNF-α and IL-6 promoter variants and CD were demonstrated, but have not been universally replicated. The objective of this study was to investigate association of CARD15 gene variants, TNF-α and IL-6 promoter variants with the disease occurrence and clinical features in Serbian CD patient cohort. Furthermore, we aimed to design probabilistic model for prediction of CD development.

METHODS: We genotyped 68 patients with CD and 69 healthy controls for three common CARD15 variants (R702W, G908R, Leu1007insC), TNF-α (-308G/A) and IL-6 (-174G/C) promoter variants by PCR-RFLP. Patients with CD were divided into different categories following Montreal classification guideline, according to age onset, localization and behavior of the disease. Data were analyzed using the Pearson chi-squared test or Fisher's exact test, when appropriate. For prediction of disease development, a Bayesian network model was designed and applied.

SUMMARY OF RESULTS: CARD15 variants were found to be significantly more frequent in CD patients (22 %) than in healthy control group (5.8 %) and therefore demonstrated association with the disease (p=0.007). These variants showed statistically significant association with ileal type of the disease (p=0.05), but no association was detected with age of CD onset and patterns of behavior. TNF-α-308G/A promoter variants were not associated with CD occurrence. Yet, TNF-α-308G variant showed association with early onset of CD (p=0.05). We found a decrease in frequency of carriers homozygous for IL-6 -174G variant in CD group in comparison with control group (36.7 % and 52.2 %, respectively), not statistically significant but with distinctive trend (p=0.07). Further, significant decrease of IL-6 -174G homozygous carriers was observed in group with ileal type of disease (p=0.025). Data for CARD15 (R702W, G908R, Leu1007insC), TNF-α (-308G/A) and IL-6 (-174G/C) gene variants were also used to compute the probability of disease occurrence. Results showed that the development of CD could be predicted with 62 % accuracy when these gene variants were taken into account. Our study revealed association of CARD15, TNF-α and IL-6 gene variants with the development and clinical features of Crohn's disease in Serbian patient cohort.

ABSTRACT n° A051_2014

Transcription of Tpmt Gene is Increased during 6-Mp Therapy in Childhood Acute Lymphoblastic Leukemia Patients

AUTHORS: **ZUKIC BRANKA**, branka.zukic@imgge.bg.ac.rs, Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Yugoslavia; **KOTUR NIKOLA**, nikola0104@gmail.com, Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Yugoslavia; **STANKOVIC BILJANA**, bi.stankovic@gmail.com, Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Yugoslavia; **DOKMANOVIC LIDIJA**, lidija.dokmanovic@udk.bg.ac.rs, University Children's Hospital, Medical Faculty, University of Belgrade, Belgrade, Serbia, Yugoslavia; **JANIC DRAGANA**, dragana.janic@udk.bg.ac.rs, University Children's Hospital, Medical Faculty, University of Belgrade, Belgrade, Serbia, Yugoslavia; **KRSTOVSKI NADA**, nada.krstovski@udk.g.ac.rs, University Children's Hospital, Medical Faculty, University of Belgrade, Belgrade, Serbia, Yugoslavia; **STOJILJKOVIC MAJA**, maja.stojiljkovic@imgge.bg.ac.rs, Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Yugoslavia; **KLAASSEN KRISTEL**, kriste.klaassen@yahoo.com, Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Yugoslavia; **UGRIN MILENA**, milenaradmilovic@gmail.com, Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Yugoslavia; **TOSIC NATASA**, nmtosic@sezampro.rs, Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Yugoslavia; **NIKCEVIC GORDANA**, gordnik@imgge.bg.ac.rs, Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Yugoslavia; **PAVLOVIC SONJA**, sonya@sezampro.rs, Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Yugoslavia

KEYWORDS: Six-mercaptopurine (6-MP) thiopurine S-methyltransferase (TPMT) acute lymphoblastic leukemia (ALL), pharmacogenetics

Six-mercaptopurine (6-MP) is a drug used in treatment of childhood acute lymphoblastic leukemia (ALL). Efficacy and toxicity of the drug is dependent on thiopurine S-methyltransferase (TPMT) activity. Gene variants in coding region of TPMT gene are pharmacogenetic markers, recognized by relevant authorities, used for 6-MP therapy individualization. In our previous study, we showed that variable number of tandem repeats (VNTR) in promoter region of TPMT gene could be a novel pharmacogenetic marker. We also showed that regulatory proteins bind differentially depending on VNTR motives and 6-MP treatment. Furthermore, our functional assays in vitro demonstrated that TPMT promoter activity depended on the architecture of VNTRs and 6-MP treatment. The aim of this study was to investigate the influence of 6-MP therapy on human TPMT gene transcription, mediated by the different VNTR architecture in the TPMT gene promoter region. Also, our goal was to explain the finding from our previous study that patients treated with initially lower doses of 6-MP in accordance to their TPMT genotype could after a while reach full 6-MP doses without developing toxicity. Blood samples of 25 childhood ALL patients were collected before and during 6-MP therapy at University Children's Hospital, Belgrade. Genotyping of VNTR region in promoter of TPMT gene was done by direct sequencing. Level of TPMT gene expression was measured before and during the therapy for each patient using qRT-PCR assay. Wilcoxon signed-rank test was applied for statistical analysis. Study of TPMT gene expression in childhood ALL patients before and during 6-MP therapy, revealed that 6-MP has a positive effect on transcription of TPMT gene. The range of increase in the level of transcription was from 150 to 790 %. Median increase was 390 %.

LIST OF PARTICIPANTS

LIST OF PARTICIPANTS

Enas	**Abdalla**			Egypt
Chris	**Adams**		Cydon Development Inc.	United States
Karen	**Aiach**	25, 30, 74	Lysogene	France
Mansoureh	**Akouchekian**	106	Iran University of Medical Sciences	Iran
Irina	**Alecu**		University Hospital Zurich	Switzerland
Safianou	**Amadou**			Togo
Madjid	**Amer Ali**		Novartis	Switzerland
Gerhild	**Angyalosi**		Novartis Pharma AG	Switzerland
Stylianos E.	**Antonarakis**	21	University of Geneva - Faculty of Medicine - GEDEV	Switzerland
George	**Apostol**		Novartis Pharma AG	Switzerland
David	**Araujo-Vilar**	132	University of Santiago de Compostela-IDIS	Spain
Jonathan	**Arm**		Novartis	Switzerland
Aurelia	**Arry**		Novartis	Switzerland
Yvan	**Arsenijevic**	104,127,139	Jules-Gonin Eye Hospital University of Lausanne	Switzerland
Reza	**Asadollahi**		University of Zurich, Institute of Medical Genetics	Switzerland
Aida	**Baban**		Novartis	Switzerland
Yann	**Barrandon**	19, 32, 75	CHUV, Dept. Experimental Surgery	Switzerland
Rita	**Barresi**	107	Muscle Immunoanalysis Unit, Dental Hospital	United Kingdom
Julia	**Barske**		Kidness for Kids	Germany
Francesca	**Barzaghi**			Italy
Fabio	**Baschiera**		Novartis	Switzerland
Matthias	**Baumgartner**	26, 31	Universitäts-Kinderspital Zürich, Abteilung für Stoffwechselkrankheiten	Switzerland
Anita	**Becker-Heck**		Novartis	Switzerland
Panagiotis	**Beretsos**		Novartis	Switzerland
Anke	**Berger**		Novartis Pharma AG	Switzerland
Juliane	**Bernholz**		Novartis	Switzerland
Harald	**Berninger**		Takara Bio Europe	France
Yves	**Berthiaume**		Institut de recherches cliniques de Montréal	Canada
Isabelle	**Besson Faure**		AFM TELETHON	France
Joerg	**Betschinger**		FMI	Switzerland
Bhupinder	**Bhullar**		Novartis	Switzerland
Miriam	**Bibel**		Novartis Campus	Switzerland
Jed	**Black**	147	Jazz Pharmaceuticals	United States
Heiko	**Bode**		University Hospital Zurich	Switzerland
Lilian	**Bomme Ousager**		Department of Clinical Genetics, Odense University Hospital	Denmark
Luisa	**Bonafé**		CHUV	Switzerland
Gisèle	**Bonne**	24, 34, 76	Institut de Myologie Inserm	France
Olivier	**Braissant**		Biomedicine, University Hospital of Lausanne (CHUV)	Switzerland
André	**Brändli**			Switzerland
Eva	**Brauchle**	102	Frauenhofer Institute for Interfacial Engineering and Biotechnology	Germany
Andreas	**Brecht**		Actelion Pharmaceuticals Ltd	Switzerland
Kym	**Brünggel**		EPFL	Switzerland
Andreas	**Buhr**		Novartis Campus	Switzerland
Nicolas	**Charlet Berguerand**		NPSuisse	Switzerland
Salah-Dine	**Chibout**		Novartis	Switzerland

Laurie	**Chicha**		University of Basel, Pharmazentrum	Switzerland
Swen	**Chichon**		NPSuisse	Switzerland
Chiara	**Ciriminna Swan**		BLACKSWAN Foundation	Switzerland
Roger G.	**Clerc**		Friedrich Miescher Institute for Biomedical Reserach	Switzerland
Giulio	**Cossu**	19, 36, 77	University College London	UK
Sylvain	**Cottens**		Novartis	Switzerland
Belinda	**Cowling**	128	CERBM - IGBMC	France
Jérôme	**Daeppen**		University of Bern	Switzerland
Sonia	**Davila**		Genome Institut	Singapore
Sarah	**Decembrini**	19, 104	University of Lausanne	Switzerland
Elena	**Degl'innocenti**		Novartis	Switzerland
Ivanka	**Dimova**			Bulgaria
Ted	**Dryja**	21, 37, 78	Massachusetts Eye and Ear Infirmary, Novartis Institutes for Biochemical Research	United States
Emmanuel	**Dulac**		Novartis	France
Philipp	**Egger**		Gebert Rüf Stiftung	Switzerland
Simone	**Eisenbeis**	102, 107, 108	Universitäts-Frauenklinik	Germany
Ewelina	**Elert-Dobkowska**	136	Institute of Psychiatry and Neurology	Poland
Orly	**Elpeleg**	22, 38, 79	Hadassah, Hebrew University Medical Center	Israel
Michael	**Elser**		Takara Bio Europe	France
Alicia	**Esteban**		Novartis	Switzerland
Christina	**Fagerberg**		Department of Clinical Genetics, Odense University Hospital	Denmark
Maria	**Fagerquist**		Novartis	Switzerland
Rocco	**Falchetto**		Novartis	Switzerland
Eric	**Fischer**		Friedrich Miescher Institute for Biomedical Research	Switzerland
Barna	**Fodor**		Novartis	Switzerland
Siv	**Fokstuen**		University of Geneva, Service de médecine génétique; centre médical universitaire	Switzerland
Vincent	**Forster**		ETH Zurich	Switzerland
Georgios	**Foteinos**		Novartis	Switzerland
Giancarlo	**Francese**		Novartis	Switzerland
Barbara	**Frisch**		Novartis	Switzerland
Davide	**Gabellini**	21, 39, 80	Division of Regenerative Medicine San Raffaele Scientific Institute	Italy
Michela	**Galeazzi**			Italy
Laura	**Gasparini**	134, 135	Fondazione Istituto Italiano Di Tecnologia	Italy
Fabrizio	**Gasparini**		Novartis Institutes for BioMedical Research	Switzerland
Susan	**Gasser**	2, 20, 141	Friedrich Miescher Institute for Biomedical Research	Switzerland
Max	**Gassmann**		University of Zurich, Institute of Veterinary Physiology	Switzerland
Magtouf	**Gatei**	143	QIMR Berghofer	Australia
Pascale	**Gaudet**	113	Swiss Institute of Bioinformatics	Switzerland
Ortrud	**Gerstner**		Novartis	Germany
Caterina	**Giacomini**	24, 134, 135	Fondazione Istituto Italiano Di Tecnologia - Via Morego 30	Italy
Cecilia	**Giunta**	115	University Children's Hospital Zurich	Switzerland
Pierre-Olivier	**Goineau**		ERYtech Pharma	France
Robert D.	**Goldman**	24, 40, 81	Northwestern University	United States
Adriana	**Gonzalez**		Friedrich Miescher Institute	Switzerland

Philippe	**Gorry**	25, 41, 82	Université of Montesquieu Bordeaux IV	France
Diana	**Graus Porta**		Novartis	Switzerland
Stephen (Steve) C.	**Groft**	20,42	National Center for Advancing Translational Sciences, NIH	Switzerland
Nicolas	**Gürtler**	146	Universitässpital Basel	Switzerland
Sabine	**Guth**		Novartis	Switzerland
Kimberley	**Hammond**		Novartis	Switzerland
Ibrahim	**Hamouda**			Egypt
Khalil	**Hamzi**			Morocco
Stephen	**Helliwell**		Novartis	Switzerland
Caroline	**Henggeler**		Foundation for People with Rare Diseases	Switzerland
Yann	**Hérault**		igbmc	France
Viktoria	**Hermann**		Novartis	Switzerland
Lysann	**Hesske**		Novartis	Switzerland
Susan	**Hill**		Alexion Pharmaceuticals	Switzerland
Daniel	**Hillier**		Friedrich Miescher Institute	Switzerland
Gabriele	**Hintzen**		Novartis Campus	Switzerland
Michael	**Hofmann**		Centogene	Germany
Francesco	**Hofmann**		Novartis	Switzerland
Thorsten	**Hornemann**	26, 43, 117	UniversitätsSpital Zürich, Institut für klinische Chemie	Switzerland
Steven	**Howe**	123, 138	UCL Institute of Child Health	United Kingdom
Liyan	**Hu**		University Hospital Zurich	Switzerland
Jeffrey	**Hubbell**	26, 44	EPFL	Switzerland
Mia	**Huber**		NPSuisse	Switzerland
Marjo	**Hytönen**	105	Helsinki University	Finland
Omer	**Iqbal**	120	Loyola University Health System	United States
Pavithra	**Iyer**	103	University of Lausanne, Laboratory of Molecular Biotechnology (LBTM)	Switzerland
Marisa	**Jaconi**	19	University of Geneva	Switzerland
Cecile	**Janssens**	22, 45, 83	Erasmus University Medical Center	Netherlands
Xavier	**Jaumont**		Novartis	Switzerland
Keith	**Johnson**		Novartis	Switzerland
Pascal	**Joset**		University Hospital Zurich	Switzerland
Daria	**Julkowska**		Fondation maladies rares	France
Uwe	**Junker**		Novartis	Switzerland
Kostas	**Kaloulis**	124	Remedys	Switzerland
Michael	**Kammüller**		Novartis	Switzerland
Saskia	**Karg**		Universitäts-Kinderspital Zürich	Switzerland
Nicolas	**Katsanis**	21, 46, 84	Duke University	United Kingdom
Petra	**Keil**		Novartis	Switzerland
Jeremy	**Keusch**		Friedrich Miescher Institute for Biomedical Research	Switzerland
Bernd	**Kinzel**		Novartis	Switzerland
Ursula	**Knauf**		Novartis	Switzerland
Michaela	**Kneissel**		Novartis	Switzerland
Philip	**Knuckles**	112	Friedrich Miescher Institute	Switzerland
Michel	**Koenig**	28, 47	NPSuisse	Switzerland
Stefan	**Kolb**		Actelion Pharmaceuticals Ltd	Switzerland
Gbone	**Komi Honam**			Togo

Corinne	**Kostic**	23, 127	University of Lausanne	Switzerland
John	**Kovarik**		Novartis Pharma	Switzerland
Carina	**Kraupa**		Novartis	Switzerland
Jan	**Kraus**	122	University of Colorado Denver	United States
Wioletta	**Krysa**	136	Institute of Psychiatry and Neurology	Poland
Michael	**Lai**		Novartis Pharma AG	Switzerland
Petra	**Laux**		Novartis	Switzerland
Yann	**Le Cam**	4, 20, 48	Eurordis	Switzerland
David	**Lee**	20, 49	Novartis Institutes for Biomedical Research	Switzerland
Soo Hyeon	**Lee**	126	ETH Zürich	Switzerland
Jean-Christophe	**Leroux**	126	ETH Zürich	Switzerland
Ephrat	**Levy-Lahad**	22, 50, 85	Shaare Zedek Medical Center	Israel
Uschi	**Lindert**	115	Kinderspital	Switzerland
Xinyu	**Liu**		Friedrich Miescher Institute for Biomedical Research	Switzerland
Dennis	**Lo**	22, 51, 86	Li Ka Shing Institute of Health Sciences	Hong Kong
Alberto	**Loche**		Friedrich Miescher Institute	Switzerland
Hannes	**Lohi**	105, 109		Finland
Vito	**Lonoce**		ORION Clinical Services	United Kingdom
Stanislas	**Lyonnet**	21, 52, 87	Université Paris Descartes	France
Channa	**Maayan**	133	Hadassah Medical Center	Israel
Aengus	**Mac Sweeney**		Novartis Campus	Switzerland
Wifried	**Maerz**		synlab Services GmbH synlab Akademie	Germany
Sameehan	**Mahajani**	134, 135	Fondazione Istituto Italiano di Tecnologia	Italy
Yael	**Mamane**			Canada
Andreas	**Massouras**			Switzerland
Tafheem	**Masudi**		Friedrich Miescher Institute	Switzerland
Patrick	**Matthias**		Friedrich Miescher Institute	Switzerland
Gabriele	**Matthias**		Friedrich Miescher Institute	Switzerland
Anna	**Mattout**	141	Friedrich Miescher Institute	Switzerland
Gabor	**Matyas**	119, 148	Center for Cardiovascular Genetics and Gene Diagnostics, c/o Foundation for People with Rare Diseases	Switzerland
Fraser	**Mcblane**		Novartis	Switzerland
Colin	**McKerlie**	23, 53, 88	University of Toronto, Dept. of Lab Medicine & Pathobiology	Canada
Terry	**Meehan**	21, 110	EMBL-EBI	United Kingdom
Gilan	**Megeed**			United States
Janine	**Meienberg**	119, 148	Center for Cardiovascular Genetics and Gene Diagnostics	Switzerland
Olivier	**Menzel**	1, 2, 162	BLACKSWAN Foundation	Switzerland
Doron	**Merkler**		University of Geneva	Switzerland
Friedrich	**Metzger**		F. Hoffmann-La Roche Ltd, Pharma Research & Early Development Neuroscience	Switzerland
Claas	**Meyer**		F. Hoffman-La Roche AG	Switzerland
Giulia Claudia	**Minetti**		Novartis	Switzerland
Hiroshi	**Mizushima**			Japan
Rajeswari	**Moganty**	140	Dept of Biochemistry, New Delhi	India
Jonathan	**Moggs**		Novartis	Switzerland
Denis	**Monard**	24	Friedrich Miescher Institute for Biomedical Research	Switzerland
Elena	**Moroz**	126	ETH Zürich	Switzerland

Michael	**Morris**	2, 22	synlab Suisse	Switzerland
Juergen F. K.	**Mueller**		University of Basel Department of Chemistry	Switzerland
Patrick	**Mueller**		Novartis Pharma AG	Switzerland
Roman	**Muff**	111	Klinik Balgrist	Switzerland
Mark	**Nash**		Novartis	Switzerland
Alexander	**Navarini**		University Hospital Zurich	Switzerland
Albert	**Neutzner**		University of Basel	Germany
Dunja	**Niedrist**		Universität Zürich, Institut für medizinische Genetik	Switzerland
Gordana	**Nikcevic**	150,151,152	Institute of Molecular Genetics and Genetic Engineering, University of Belgrade	Serbia and Montenegro
Jean-Marc	**Nuoffer**		Inselspital UKC	Switzerland
Petr	**Obrdlik**		Novartis	Switzerland
Victoria	**Ohla**	121		Germany
David	**Palacios**		Novartis	Switzerland
Shaloo	**Pandhi**		Novartis	Switzerland
Ségolène	**Perin**		Kurma Life Science Partners	France
Marc	**Peschanski**	19, 54, 89	I-STEM	Switzerland
Thomas	**Pietzonka**		Novartis	Switzerland
Brietta	**Pike**		Karger	Switzerland
Barbara	**Plecko**	26, 55	Universitäts-Kinderspital Zürich, Neuropädiatrie	Switzerland
Roland	**Pochet**		Université Libre de Bruxelles	Belgium
Christoph	**Poincilit**	28	NPSuisse	Switzerland
David	**Prefontaine**		Novartis	Canada
Anne	**Puel**	22, 56, 90	Université Paris Descartes Laboratoire de Génétique Humaine des Maladies Infectieuses	France
Alexander	**Pushkov**			Russia
Alexander	**Pushkov**	142	National Research Center	Russia
Thomas	**Radimerski**		Novartis	Switzerland
Katharina	**Rall**		Womens university Hospital	Germany
Pedro	**Ramos**		Novartis	Switzerland
Lakshminarayan	**Ranganath**	23, 57, 91	Alkaptonuria Centre Liverpool, Royal Liverpool University Hospital	United Kingdom
Anita	**Rauch**	26, 58	Universität Zürich, Institut für Medizinische Genetik	Switzerland
Alecs	**Recher**		Unviersity of Luzern	Switzerland
Janine	**Reichenbach**	26, 59, 131	University Children´s Hospital Zurich	Switzerland
Juergen	**Reinhardt**		Novartis	Switzerland
Axel	**Rethwilm**		Unviersity of Wuerzburg	Germany
Alexandre	**Reymond**	21, 60, 92	University of Lausanne	Switzerland
Jan	**Richter**		Novartis Campus	Switzerland
Alain	**Rinaldi**		MedExpansion	Switzerland
Marie-Emmanuelle	**Riviere**		Novartis Pharma AG	Switzerland
Carlo	**Rivolta**		UNIL - Dept. of Medical Genetics	Switzerland
Fernando	**Romero**		Novartis AG	Switzerland
Francesco	**Roselli**		Friedrich Miescher Institute	Switzerland
Botond	**Roska**		Friedrich Miescher Institute for Biomedical Research	Switzerland
Asta	**Roslaya**		Novartis	Russia
Marc-David	**Ruepp**		University of Bern	Switzerland

Heiko	**Runz**	28, 62	NPSuisse	Switzerland
James	**Rush**		Novartis	Switzerland
José-Alain	**Sahel**	24, 63, 93	Pierre and Marie Curie University Medical School, Paris, Ophtalmology	France
Leonardo	**Sahelijo**		Alexion Pharmaceuticals	United States
Andreas	**Sailer**		Novartis	Switzerland
Pierre	**Saint-Mezard**		Novartis	Switzerland
Elisabeth	**Saller**		Institut für medizinische & molekulare Diagnostik	Switzerland
Jane	**Salotti**	144	Institute of Health&Society	United Kingdom
Francisca	**Sanchez-Jimenez**		University of Malaga	Switzerland
Matthias	**Schäfer**	23, 129	ETH Zürich	Switzerland
Marco	**Schapira**		University of Geneva	Switzerland
Lisa	**Schleicher**		Takara Bio Europe	France
Thomas	**Schlitt**		Novartis	Switzerland
Niko	**Schmiedeberg**		Novartis Campus	Switzerland
Daniel	**Schümperli**		Institute of Cell Biology, University of Bern	Switzerland
Michael	**Seewald**		Novartis	Switzerland
Jeffrey	**Shaw**		Geneva Business Center	Switzerland
Margarita	**Shchedrova**		Novartis	Russia
Ana	**Siegmann Hrus**		Novartis	Switzerland
Ulrich	**Siler**	131	University Children´s Hospital Zurich	France
Michael	**Sinnreich**	23, 64, 94	Departement of Biomedicine University of Basel	Switzerland
Nick	**Sireau**	25, 65, 95	AKU Society	United Kingdom
Lotta	**Sjögreen**		Mun-H-Center Odontologen	Sweden
Frank	**Staedtler**		Novartis	Switzerland
Colin L.	**Stewart**	24, 66, 96	Singapore Biopolis, Institute of Medical Biology	Singapore
Maja	**Stojiljkovic**	150, 152	Institute of Molecular Genetics and Genetic Engineering, University of Belgrade	Serbia and Montenegro
Jürg	**Streuli**		University Hospital Zurich	Switzerland
Alessandra	**Strom**		CHUV	Switzerland
Elkhan	**Suleymanov**	142		Russia
Marshall	**Summar**	25, 67, 97	Children´s National Medical Center	United States
Andrea	**Superti-Furga**	2	University of Lausanne	Switzerland
Thomas	**Suply**		Novartis Institutes for Biomedical Research	Switzerland
Saranya	**Suriyanarayanan**			Switzerland
Jordi	**Surrallés**	23, 125	Department of Genetics and Microbiology, Universitat Autonoma de Barcelona	Spain
Franziska	**Suter**		Karger	Switzerland
Marc	**Tardieu**	23, 68, 98	University Paris South, Research Laboratory INSERM	France
Diethilde	**Theil**		Novartis	Switzerland
Elisabetta	**Traggiai**		Novartis	Switzerland
Joerg	**Trappe**		Novartis	Switzerland
Estelle	**Trifilieff**		Novartis	Switzerland
Didier	**Trono**	4, 26, 69	Ecole Polytechnique Fédérale de Lausanne	Switzerland
Chiaki	**Tsubouchi**		Novartis	Switzerland
Alan	**Tyndall**	19, 70, 99	University of Basel	Switzerland
Sadeq	**Vallian**		University of Isfahan	Iran

LIST OF PARTICIPANTS

Gisou	**Van Der Goot**	26, 71	Ecole Polytechnique Fédérale de Lausanne	Switzerland
Marlies	**Van Hoef**		Transplantcreations	Switzerland
Luc	**Van Rompaey**		Galapagos	Belgium
Rodrigo	**Villasenor-Molino**		Friedrich Miescher Institute	Switzerland
Marlies	**Van Hoef**			Switzerland
Thomas	**Von Känel**		Medizinische Genetik	Switzerland
Pascale	**Vonmont**	1, 2	Gebert Rüf Stiftung	Switzerland
Miriam	**Votteler**	102	University of Tuebingen	Germany
Simon	**Waddington**	24, 138	University College	United Kingdom
Adam	**Wanner**		Alpaone	United States
Georges	**Weissgerber**		Novartis	France
Hans	**Widmer**		Novartis Institutes for BioMedical Research	Switzerland
Raffaella	**Willmann**	149		Switzerland
Ralph	**Woessner**		Novartis	Switzerland
Babette	**Wolf**		Novartis	Switzerland
Stefan	**Wurzer**		Novartis Campus	Switzerland
Yanling	**Yang**	137	Department of Pediatrics, Peking University First Hospital	China
Katja	**Zerjavic**	148	Center for Cardiovascular Genetics and Gene Diagnostics	Switzerland
Assem	**Zhakupova**	118	University Hospital Zurich	Switzerland
Elena	**Zhuravleva**		Novartis	Switzerland
Martine	**Zimmermann**	25, 72, 100	Alexion Pharma International Sarl	Switzerland
Branka	**Zukic**	150 – 152	University of Belgrade, Institute of Molecular Genetics and Genetic Engineering	Serbia and Montenegro

IMPRESSUM

BLACKSWAN Foundation, Gebert Rüf Stiftung; Graphic design: a+; Print: Druckerei Krebs AG, Basel

SUPPORTERS AND SPONSORS

EURORDIS Rare Diseases Europe

E-Rare

PRORARIS

Alliance Maladies Rares – Suisse
Allianz Seltener Krankheiten – Schweiz
Alleanza Malattie Rare – Svizzera

MAIN SPONSOR

NOVARTIS

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 characterization 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 suffers 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 recognized international experts is responsible for deciding, which projects the foundation finances.

MISSIONS

- 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.

facebook.com/Blackswan.Foundation
twitter.com/BLACKSWANFound
blackswanfoundation.ch

The charter of Gebert Rüf Stiftung, founded in 1997, states its purpose as "promoting Switzerland as a place to live and do business". The foundation has an annual grant budget of some 15 million Swiss francs and 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. Gebert Rüf Stiftung is a grant-making foundation actively shaping and enabling. On the one hand, it supports high-quality innovative projects, on the other, 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 Rüf 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 initiatives.

CURRENT GRANT-MAKING STRATEGY

Gebert Rüf Stiftung's active areas of activity place its 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), public understanding of science (Scientainment), Science & Design, foundation governance 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 diseases. The programme is aimed at bridging the worlds of basic and clinical research: Projects with new approaches or technologies that focus on a clinical or diagnostic application. 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 lead to drugs and diagnostic tests that could benefit patients. The focus must be on innovation, feasibility and effectiveness, while maintaining 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 was established in 2009 as a five-year area of activity. The 2014 call ist the 6th and last of this programme.

grstiftung.ch

RE(ACT) 2014
RARE DISEASES

STAY IN CONTACT WITH US

#REACTCongress
#REACTCommunity
facebook.com/REACT.community.official
twitter.com/react_community

INITIATED BY

BLACKSWAN FOUNDATION

GEBERT RÜF STIFTUNG
WISSENSCHAFT.BEWEGEN

MAIN SPONSOR

NOVARTIS