

#### **RE(ACT)** CONGRESS 2018 INTERNATIONAL CONGRESS OF RESEARCH ON RARE AND ORPHAN DISEASES MARCH 2018

## TABLE OF CONTENTS

WELCOME MESSAGE	_ 7
KEY FACTS	_ 8
TIME TABLE	_ 10
FULL PROGRAM	_ 11
SPEAKERS' BIOGRAPHIES	_ 14
SPEAKERS' ABSTRACTS	_ 30
ABSTRACTS	_ 62
LIST OF PARTICIPANTS	_ 82
SUPPORTERS	_ 87

## The RE(ACT) Community We are the RAREvolutionary People



## **EXPERIENCE**

the experience has been made simpler and stickier. Four easy steps let stakeholders support the research

#### 1. Sign-up:

possibility to create a patient, a researcher or a supporter profile



#### Follow one or more diseases: possibility to follow and share one or more diseases

FOUNDATION

which has involved an international network of actors including

Make a donation: opportunity to donate in just one ćlick

3.

#### 4. Submit your scientific project:

possibility for researchers to submit their projects to the RE(ACT) Scientific Committee and start a crowdfunding campaign

## RE(ACT) r e S

The RE (ACT) Congress - International Congress on Research of Rare and Orphan Diseases - is the event conceived and organized by BLACKSWAN the MEETING is a moment of knowledge sharing, study and development on scientific research related to rare diseases.

The RE (ACT) Congress takes place every 2 YEARS each time in a different city.



The next congress will be held in **Bologna**, from 7<sup>th</sup> to 10<sup>th</sup> March 2018.





patient organizations



patients

#### **CONTACT** දුමුදු

To connect with the RE(ACT) Community, please visit react-community.org or contact the Team for more information:

contact@react-community.org

You can follow us on:

REACT.community.official

@react\_community

# STAND UP FOR SCIENTIFIC RESEARCH

# **#RAREvolution**

#### WELCOME

Dear Colleagues,

Welcome to the fourth «International Congress on Research of Rare and Orphan diseases», RE(ACT) Congress 2018. It is a pleasure to host you here in Bologna, the home to numerous prestigious cultural, economic and political institutions as well as one of the most impressive trade fair districts in Europe.

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. The overall aim of this congress is not only to bring together researchers and their knowledge but also to promote research on rare and orphan diseases among the general public, industry and policy makers. new and promising therapies and treatments must be rapidly delivered to patients all around the world. To ensure exchange of information and collaboration on a continuous basis after the congress we created the online RE(ACT) Community (react-community.org). Its mission is to facilitate scientific cooperation, but also to increase knowledge sharing and promote research projects through crowdfunding. The RE(ACT) Community also aims at promoting opportunities to optimize synergies between stakeholders, from patient organizations to academic institutions, centers of expertise, health industry, regulators and policy makers.

We are pleased about your active participation to the debates over the coming days and on behalf of the organizers we hope you will enjoy your time in Bologna.

Dr. Olivier Menzel BLACKSWAN Foundation

Murch

Dr. Daria Julkowska E-RARE

O. Jullions he

## **KEY FACTS**

#### Scientific program committee and advisory board

Jacques Beckmann, CH - Nicolas Katsanis, USA - Maria Paola Landini, IT - Alex MacKenzie, CAN - Lucia Monaco, IT - Michael Morris, CH - Luca Sangiorgi, IT - Domenica Taruscio, IT

#### Venue

The RE(ACT) Congress 2018 is held in the Rizzoli Institute – Istituto di ricerca Codivilla Putti. Founded in 1896, the Rizzoli Orthopaedic Institute from the very beginning was interlocked with the progress of orthopaedics and traumatology in Italy and worldwide, especially thanks to the first directors, Alessandro Codivilla and Vittorio Putti.

The historical aspect though is also due to the location and the complex that houses the Rizzoli Hospital: the Monastery of San Michele in Bosco. The history of this monumental complex dates back at least to the XIVth century. This section gives a idea of the events (stories of kings, popes, scholars and famous artists) that characterized it. The historical, monumental and artistic value of San Michele in Bosco made it a natural candidate for the Genus Bononiae – Musei nella Città, the project for the Town museums funded by the Cassa di Risparmio in Bologna Foundation. To redevelop the monumental complex and to restore its connection with the Town, the green area that surrounds the hospital – a real park – was refurbished with challenging project.

#### **Congress Initiator**

BLACKSWAN Foundation Chemin de la Riaz 11 CH-1418 Vuarrens blackswanfoundation.ch

#### **Congress Organizers**

BLACKSWAN Foundation E-Rare

#### **Professional Congress Organizer**

Amiconi Consulting is an internationally recognized Company, which, thanks to its experience, professionalism and dynamism, is equipped to find efficient and innovative solutions for the organization of Conventions, Meetings, Incentive Travel Programs, Tours, Seminars, Meetings, Product Launches and Events. The Company performs at the regional, national and international level, provides a wide range of services from general advice to highly focused solutions.

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

#### Important information for speakers

We kindly ask the speakers to submit their presentation to the people in charge of the technic at least two hours before their talk.

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

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

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

To facilitate allocation, please create a respective folder on your storage medium including your presentation (e.g. RE(ACT) 2018\_Speaker's name\_Session).

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

#### Important information for abstract presenters

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

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

- Posters may be set up on 7<sup>th</sup> March from 8am.
- Posters should be removed on 9<sup>th</sup> March from 5pm.
- Poster which have not been removed after this time will be discarded. Please note that the posters and others material will not be sent to you after the conference.

#### Posters

Please be present in front of your poster during the poster sessions dedicated to your topic.

#### **Disclaimer:**

Biographies and abstracts are printed as received by the authors.

#### TIME TABLE

#### **TUESDAY, MARCH 6th**

2018 E-RARE, Membership meeting (closed), all day 9 to 17

#### WEDNESDAY, MARCH 7th

Special morning sessions 9 to 12:

- Parallel session: Undiagnosed Diseases Network International (UDNI)
- Parallel session: European Reference Networks (ERNs), where we stand?

**A.** Session, Afternoon 14 to 17 **"Opportunities in rare diseases around the world"** POSTER SESSION A 17 to 18 Public Opening Ceremony 18 to 20

#### **THURSDAY, MARCH 8th**

**B.** Session, Morning 9 to 12M **"NGS and undiagnosed rare diseases"** Lunch 12 to 13 POSTER SESSION B & C 13 to 14

**C.** Session, Afternoon, 14 to 17 **"Pathophysiology"** POSTER SESSION B & C 17 to 18

#### FRIDAY, MARCH 9th

**D.** Session, Morning 9 to 12 **"Gene and cell therapy"** Lunch 12 to 13 POSTER SESSION D & E 13 to 14

**E.** Session, Afternoon 13 to 17 **"Neurological diseases"** POSTER SESSION D & E 17 to 18 Social event: Delegates' dinner/party

#### SATURDAY, MARCH 10th

Rare Disease Day Emilia Romagna

## **FULL PROGRAM**

#### TUESDAY, MARCH 6th

E-RARE Monitoring meeting, by invitation only, all day 9 to 17

#### WEDNESDAY, MARCH 7th

Special morning sessions 9 to 12 open to all:

**Parallel session 1:** Undiagnosed Diseases Network International (UDNI) – Chair Domenica Taruscio

Panellists:

- <u>Helene Cederroth, SE</u> "The Undiagnosed"
- William Gahl, USA "The NIH Undiagnosed Diseases Program and Network"
- <u>Steve Groft, USA</u>"Undiagnosed Diseases: Meeting the Needs of the Rare Diseases Community"
- <u>Domenica Taruscio, IT</u>, Undiagnosed Rare Diseases: a bilateral project between Italy (Istituto Superiore di Sanità) and USA (NIH)
- Josef Penninger, AT "Haploid stem cells"
- Alessandra Ferlini, IT, Undiagnosed and not diagnosed: a genetic view
- Paraskevas Patropoulos, IT

**Parallel session 2:** European Reference Networks (ERNs), where we stand? – Chair Luca Sangiorgi

Panellists:

- Maurizio Scarpa, DE; European Reference Networks
- Holm Grassner, DE; European Reference Network ERN-RND
- Luca Sangiorgi, IT; BOND European Reference Networks
- Daria Julkowska, FR; E-RARE and Europe Joint Program

A. Session, Afternoon 14 to 17 "Opportunities in rare diseases around the world"

• <u>Maurizio Scarpa, DE</u>: European References Networks (ERNs): "The European Reference Network Program and the MetabERN (ERN for Rare Hereditary metabolic Diseases)"

• <u>Hugh Dawkins, AU</u>: IRDiRC and RD Connect "Opportunities in rare diseases around the world"

• <u>Daria Julkowska, FR</u>: E-Rare and the European Joint Programme on Rare Diseases "The coordination of rare diseases research in Europe – The European Joint Programme on Rare Diseases"

• Olivier Menzel, CH: RE(ACT) Community

• <u>Gabriela Costa Cardoso, BR</u> (Abstract n° A005) "Genetically Isolated Populations in Brazil"

POSTER SESSION A 17 to 18

#### Public Opening Ceremony 18 to 20

Welcome message

Professor <u>Silvio Garattini</u>, IT, pioneer in rare disease research, professor in chemotherapy and pharmacology and director of the Mario Negri Institute for Pharmacological Research. "Rare diseases and orphan drugs"

Professor <u>Harvey F. Lodish</u>, USA, professor at the Massachusetts Institute of Technology (MIT), Founding Member of the Whitehead Institute for Biomedical Research and lead author of the textbook Molecular Cell Biology. "Academic Entrepreneurs, New Technologies, and Building Companies to Treat Rare Diseases"

#### THURSDAY, MARCH 8th

B. Session, Morning 9 to 12 "NGS and undiagnosed rare diseases"

• <u>Xavier Estivill, ES</u> "Large-scale sequencing of inbreed populations and the compendium of mutations causing rare disorders"

• Marco Gattorno, IT "Impact on NGS in daily practice in autoinf ammatory diseases"

• <u>Vincenzo Nigro, IT</u>"Next NGS approaches to the unsolved: Telethon Undiagnosed Program"

• Lisenka Vissers, NL "The circle of NGS innovation: from research to diagnostics and back"

• <u>Annalisa Santucci, IT</u> (Abstract n° C005) "An integrated interactive ecosystem for alkaptonuria: a tool for physicians and researchers"

• John Dawson, UK (Abstract n° B003) "RD-Connect: data sharing and analysis for rare disease research within the integrated platform and through GA4GH Beacon and Matchmaker Exchange"

Lunch 12 to 13

POSTER SESSION B & C 13 to 14

C. Session, Afternoon, 14 to 17 "Pathophysiology"

• <u>Gregor Andelfinger, CA</u>"CAID syndrome: in search of a druggable molecular signature for a novel rare disease"

• <u>Nicolas Lévy, FR</u> "Pathophysiology and Therapeutic developments in Progeroid Syndromes"

• Kristina Hettne, NL "Multi-omics analysis powered by massive data integration"

• <u>Roman Chrast, SE</u> "The role of endoplasmic reticulum-mitochondria crosstalk in axonal maintenance"

• <u>Michela Soardi Pathophysiology, IT</u> (Abstract n° C002) "Novel zebrafish models of sarcoglycanopathy"

#### FRIDAY, MARCH 9th

D. Session, Morning 9 to 12 "Gene and cell therapy"

- Peter Lenting, FR "Small Antibody Fragments as Alternative Tools in Haemophilia Care"
- Luigi Naldini, IT

• Josef M. Penninger, AT "Haploid stem cells – from discovery to a library of repairable mutations for reproducible research"

• Tatiana Petrova, CH "Dissecting the biology of lymphedema-distichiasis"

Lunch 12 to 13

POSTER SESSION D & E 13 to 14

E. Session, Afternoon 14 to 17 "Neurological diseases"

• <u>Donald W. Cleveland, USA</u> "Gene silencing therapy for human neurodegenerative disease"

• <u>Antonio Federico, IT</u> "The lesson of Rare Neurologic Diseases to clinical neurologists and neuroscientists for understanding normal and pathological nervous system functions"

• Jesus Requena, ES "In search of a therapy for Creutzfeldt-Jakob disease: identification of chemical chaperones that stabilize the prion protein PrP"

• Edward Wild, UK "Progress in Huntington's disease: drugs, biomarkers and community"

#### SATURDAY, MARCH 10th

Rare Disease Day Emilia Romagna

## **SPEAKERS' BIOGRAPHIES**

## ANDELFINGER GREGOR

Gregor Andelfinger received his MD from the University of Ulm (Germany) and his pediatric specialty at the University of Geneva. After his pediatric cardiology fellowship, he trained in Cardiovascular Genetics at the Cincinnati Children's Hospital and Molecular Cardiovascular Biology at the IRCM, Montréal. Since 2006, he has established the first Canadian biobank specifically geared towards the investigation of the genetics of congenital heart disease in a province-wide effort. His main interest is to characterize the genetic architecture underlying Mendelian and complex traits in congenital heart disease. His laboratory uses state-of-the-art technologies for gene discovery and genotype-phenotype correlation. The focus of the study funded by Génome Québec will lie on diseases of the aortic valve as well as a common complex lesion called tetralogy of Fallot. For both lesions, current medical and surgical therapies can provide adequate relief of symptoms, but insight into disease pathogenesis is very limited. Another line of investigation will aim to reproduce such phenotypes in animal models. Also, the study will address the question how to relate genetic data stemming from interrogation of the entire genome back to patients and their families.

## **ANTONIO FEDERICO**

Full professor of Neurology and Director Unit Clinical Neurology and Neurometabolic Diseases, Medical School, University of Siena, Siena, Italy Chairman of the Scientific Committee of the European Academy of Neurology President of Neuromediterraneum Forum Italian delegate at World Federation of Neurology and at European Union of Specialist (Neurology Section) Past-President of Italian Society of Neurology Editor in Chief of Neurological Sciences, Springer Verlag

Author of more 400 articles in the main neurological Journals

## **CEDERROTH HELENE**

President of Wilhelm Foundation and board member of Undiagnosed Diseases Network International. In 90s the vice president of Epilepsy organization in Stockholm and vice president of HSO in Stockholm (an umbrella organization for the 27 most common diseases).

Helene is devoted the Undiagnosed Diseases and especially to help children around the world with an Undiagnosed Disease to a diagnosis. She and her husband were parents of four children. In three years their three youngest children past away. They died in an age of 16, 10 and six years from an undiagnosed disease that no one thought was genetic or fatal.

Helene and her husband funded Wilhelm Foundation with the goal that the specialists would collaborate to solve the unsolved undiagnosed diseases. The first major goal was a world congress to try to get the specialists to cooperate and solve some of the mysterious undiagnosed diseases.

Together with Dr Gahl NIH and Dr Taruscio ISS the Wilhelm Foundation arranged the first world congress in Italy. Wilhelm Foundation have since then co-arranged four more congresses together with Dr Gahl and a local specialist in five different countries.

At the first and second international congress for undiagnosed diseases the Undiagnosed

Diseases Network International was formed and is now a growing network. Helene and her husband has co-arranged five international congresses on rare and undiagnosed Diseases and arranged three training school for parents to undiagnosed children in Sweden. Helene gives presentations about the Undiagnosed Diseases and the patients, not only in Sweden but also abroad.

Helene and her husband is one of the recipients of the Black Pearl Awards 2018 The EU-RORDIS Volunteer Award.

Co-author of Undiagnosed Diseases Network International (UDNI) White paper for global actions to meet patient needs published in Molecular Genetics and Metabolism 116 (2015) Co-author EURORDIS International Joint Recommendations To Address Specific Needs of Undiagnosed Rare Disease Patients (2016)

## **CHRAST ROMAN**

Dr. Roman Chrast received his PhD in 2000 from the University of Geneva, Switzerland where he worked in the laboratory of Dr. S.E. Antonarakis on the molecular characterization of trisomy 21. He did his postdoctoral work at the Salk Institute, California, USA in the laboratory of Dr. G. Lemke, concentrating on the transcriptional characterization of myelinating glial cells. In 2005, he became a Swiss National Science Foundation professor in a newly established Department of Medical Genetics at the University of Lausanne, Switzerland where he started working on Charcot-Marie-Tooth diseases. In 2014 he was selected for the Swedish Strategic Research Area Neuroscience (StratNeuro) program award and became senior researcher at the Department of Neuroscience and Department of Clinical Neuroscience at Karolinska Institutet, Stockholm, Sweden.

Roman's laboratory is using two parallel and complementary strategies to understand and potentially prevent disease-induced changes leading to peripheral neuropathies. The first approach is based on genetics. This work is done in close collaboration with clinicians and aims at the identification of genes that are mutated in various forms of Charcot-Marie-Tooth disease. Once the mutated gene is identified, a combination of in vitro and in vivo approaches are used in order to establish a model of the disease that will help to uncover the underlying pathophysiological mechanisms. The second strategy is based on a detailed characterization of the key mechanisms involved in the biology of glial and neuronal cells with a particular accent on the mechanisms implicated in metabolic interactions between these two cellular partners. The insights gained through this characterization are important not only for the understanding of the biology of neurons and glia, but also to help discover new therapeutical targets that can be explored in a larger context of neuronation.

## CLEVELAND DON W.

Dr. Don Cleveland has made field leading contributions in cancer genetics and neurosciences. He is currently Professor and Chair of the Department of Cellular and Molecular Medicine at the University of California at San Diego, as well as a member of the Ludwig Institute for Cancer Research. He has been elected to the National Academy of Sciences, the National Academy's Institute of Medicine, the American Academy of Arts and Sciences, and the American Association for the Advancement of Science. A recipient of three NIH Merit Awards, he has also won the Wings Over Wall Street MDA Outstanding Scientist award and The Sheila Essey Prize from the ALS Association and American Academy of Neurology and the Judd award from Memorial Sloan-Kettering Cancer Center. Cleveland initially identified tau, the protein which accumulates aberrantly in Alzheimer's disease and which is the protein whose misfolding underlies chronic traumatic brain injury (now receiving international attention from its impact in athletics, especially American football). He uncovered the mechanisms underlying the major genetic forms of Amyotrophic Lateral Sclerosis (ALS) and demonstrated that disease involves neurons and their non-neuronal neighbors. He has developed gene silencing therapy for neurodegenerative diseases using designer DNA "antisense oligonucleotide (ASO)" drugs. Clinical trials with these ASOs have been initiated for multiple neurodegenerative diseases, including for ALS and Huntington's diseases.

#### **DAWKINS HUGH**

Hugh is the Director of the Office of Population Health Genomics (OPHG), Department of Health Government of Western Australia.

Hugh leads the development of policies, plans and the translation of genomics knowledge into health services to minimise the impact of genetic and rare diseases within Western Australia. He provides advice and recommendations on issues relating to genetic diagnosis, screening programs and precision public health through the translation of new knowledge to transform public health services. OPHG is responsible for implementing the Western Australian Rare Diseases Strategic Framework. OPHG is working with Aboriginal Health Council of Western Australia (AHCWA), Aboriginal Health Directorate Government of WA, and relevant Aboriginal Medical Services and stakeholders to improve access and optimise Aboriginal experiences in the WA Health system. OPHG is also currently leading the development of a national framework for newborn bloodspot screening; and the development of a whole-of –government National Genomics Policy Framework. At a health translation policy level he is responsible for implementing, with the Genetic Services of WA and Path-West Laboratory Services, the genetic and undiagnosed disease service which includes integrating enabling phenotyping tools; and developing a national approach to the incorporation of massively parallel sequencing into clinical diagnostic services.

Prof. Dawkins is the Australian member on the International Rare Disease Research Consortium (IRDiRC), and currently serves as Vice Chair of the Consortium Assembly and co-chair of the IRDiRC Funders Constitute Committee. IRDiRC is coordinating efforts to align global funders to improve diagnostics and access to therapies for rare diseases. He is also the Australian member on the Orphanet Executive Management Committee.

From a rare diseases research perspective he is leading the Australian partnership in a European Commission FP7 programs, RD-CONNECT; concerted action project RARE-Best-Practice; and EC Joint Action program RD-ACTION. Hugh has been instrumental in building national rare disease registries in Australia with the aim of linking up to global networks of national registries through his role, including Past Chair, TREAT NMD Global Data Oversight Committee (TGDOC) and as an Executive Committee Member of TREAT-NMD. Dr Dawkins is Chair of the National Australian Neuromuscular Diseases Registry Advisory Group. He has over 130 peer-review publications.

## **ESTIVILL XAVIER**

Xavier Estivill is Senior Investigator and Chair of the Genetics Program in the Experimental Genetics Division of Sidra Medical and Research Centre. He graduated in Medicine, specialised in Haematology, and doctorate in Medicine by the Autonomous University of Barcelona and in Philosophy by the University of London. Between 2002 and 2015 he was Senior Group Leader and Director of the Genes and Disease Program at the Centre Genomic Regulation, Associate Professor at Pompeu Fabra University, and Director of the Genomics Unit at Dexeus Woman's Health in Barcelona. Previously, he was Visiting Scientist at the Hospital for Sick Children in Toronto, and directed the Genetics Service of the Clinic Hospital and the Genetics Centre of the Cancer Research Institute in Barcelona.

The research of his group has provided molecular understanding of many human genetic disorders, including cystic fibrosis, neurofibromatosis, hereditary deafness and Down syndrome. Recent achievements have been the identification of genetic variants associated with psoriasis and psychiatric diseases, the description of toxicity of CAG RNAs in Huntington's disease, and the identification of novel small RNA molecules in the human genome. He has published over 600 research papers, has received numerous awards, and sits on the board of several human genetics journals and scientific advisory boards, including the World Anti-Doping Ethics Panel, International Rare Disorders Research Consortium and the International Cancer Genomics Consortium.

Xavier Estivill is interested in applying genomic-centric approaches to reveal the genetic basis of complex and rare diseases, and to promote translational genomic approaches based on the multilayer characterization of the individual's genome and deep phenotypic characterization of disease. He co-coordinates the germline mutations group of the International Cancer Genomics Consortium on PanCancer analysis, involving the evaluation of sequence data of thousands of patients with cancer, and participates in projects to understand the genetic component of human diseases.

## **FERLINI ALESSANDRA**

Associate Professor at the University of Ferrara/Italy, born in 1958 in Bologna (I), married, one son. She graduated in medicine and surgery at the University of Bologna in 1983. She specialized in Neurology (1988) and Medical Genetics (1993) at the Universities of Bologna and Ferrara. In 2002 she achieved a PhD in Genetics at the Imperial College School of Medicine in London (UK). She is Director of both Unit (Hospital) and Section (University) of Medical Genetics. As part of her professional career she has accomplished profound research experience at the Universities of Bologna, Padova, Milan and Modena. In 1995 she moved to London where she worked as Senior Research Officer at the Hammersmith Hospital, Neuromuscular Unit, Department of Paediatrics, under the supervision of Prof. F. Muntoni. In June 1999 she returned to Italy.

She is member of the American Society of Human Genetics, the American Society of Cell and Gene Therapy, the European Society of Human Genetics, the World Muscle Society, the Italian Society of Human Genetics and the Italian Association of Myology. She is also Associate Editor of the journal Neuromuscular Disorders.

**Research Activities** 

For many years already her special interest and major research effort is concentrated on dystrophinopathies and hereditary neuromuscular pathologies. Distrophinopathies are he-

reditary diseases caused by heterogeneous mutations in the dystrophin gene. Aim of the actually conducted research is to identify the processes which determine the regulation of expression of this specific gene, particularly referring to the process of splicing and its modulation. Her research team is studying in vitro and in vivo systems to modulate mutations of the gene with antisense oligonucleotides while using new systems of release (nanomaterials). Furthermore the team is in charge with the definition of the RNA profile of various hereditary pathologies and the identification of molecular markers both in humans and in animal models. She is also member of several European research groups that in particular are studying new therapeutic approaches of dystrophinopathies and other neuromuscular pathologies as well as innovative aspects of molecular diagnostics with focus on high throughput techniques and next generation sequencing. She is provided with all ethical aspects referring to medical genetics and the therapy of genetic diseases. She is member of the Project Ethical Committee of the TREAT-NMD NoE, of group of genetic quality control at the Institute of Health (Italy), and of the key group of Medical Genetic Coordination of the Regione Emilia-Romagna (Italy).

## **GAHL WILLIAM**

Dr. William A. Gahl earned his B.S. in biology from the Massachusetts Institute of Technology in 1972 and his M.D. and Ph.D. from the University of Wisconsin. He served as pediatric resident and chief resident at the University of Wisconsin hospitals from 1976-80. In 1984, he completed clinical genetics and clinical biochemical genetics fellowships at the NIH's Interinstitute Medical Genetics Training Program, which he directed from 1989 to 1994. Dr. Gahl elucidated the basic defects in cystinosis and Salla disease and helped bring cysteamine to new drug approval by the Food and Drug Administration as the treatment for cystinosis. His group described the natural history of Lowe syndrome, alkaptonuria, autosomal recessive polycystic kidney disease, Chediak-Higashi disease, GNE myopathy, and Hermansky-Pudlak syndrome (HPS), and his lab discovered the genetic bases of gray platelet syndrome, Hartnup disease, arterial calcification due to deficiency of CD73, 3-methylglutaconic aciduria type III, 3 types of HPS, and neutropenia due to VPS45 deficiency. Gahl has published more than 400 peer-reviewed papers and trained over 40 biochemical geneticists. He established American Board of Medical Specialties certification for medical biochemical genetics. He served on the board of directors of the ABMG and American Society of Human Genetics, as president of the Society for Inherited Metabolic Disorders, and was elected to the American Society for Clinical Investigation and the Association of American Physicians. Dr. Gahl received the Dr. Nathan Davis Award for Outstanding Government Service from the AMA, the Service to America Medal in Science and the Environment, the RareVoice Award for a Government Agency Leader, the March of Dimes Pruzansky Lecture Award, and numerous other awards.

## **GARATTINI SILVIO**

Silvio Garattini was born in Bergamo (Italy) on 12 November 1928. He earned a diploma in Chemistry, then a degree in Medicine and was appointed lecturer in Chemotherapy and Pharmacology. Founder in 1961 and director since then of the Istituto di Ricerche Farmacologiche Mario Negri that now has three locations (Milan, Bergamo and Ranica) and about

750 people work there. He was a founder of the European Organisation for Research and Treatment of Cancer (EORTC). He has been recipient of many awards and honours for his research activity.

He has been member of different national and international Committees. Now he is member of Consiglio Superiore di Sanità and Comitato Nazionale per la Bioetica.

## **GATTORNO MARCO**

Pediatric Rheumatologists, working at "G. Gaslini" Institute for Children in Genoa, Italy. His main scientific interests involve the study of the pathogenic mechanisms of the rheumatic conditions in children and the clinical and pathogenic characterization of the monogenic autoinf ammatory diseases. He is author of 185 full-papers on international journals (total IF 1254, H-index 47), of many book chapters (i.e. "The Immune System and the Inf ammatory Response" in the Textbook of Pediatric Rheumatology; JT Cassidy et al. eds; 5th, 6th and 7th Edition). He is the Editor of the book "Familial Mediterranean Fever" (Springer).

He received the 1998 and 1999 Pediatric Rheumatology Abstract Awards at the 62nd and 63rd Congress of the American College of Rheumatology and the Kourir Award 13th Congress of Pediatric Rheumatology European Society, Amsterdam, June 2006

He is the past-Chairman of the Working Party for Autoinf ammatory diseases of the Pediatric Rheumatology European Society (PRES).

From July 2008 he is the Principal Investigator of the "Eurofever" Project (UE – Executive Agency for Health and Consumers).

From May 2016 is the Principal Investigator of the E-rare project INSAID (E-Rare JTC 2015-pp-156).

From May 2017 is the President of the International Society of Systemic Autoinf ammatory Diseases (ISSAID)

## **GRAESSNER HOLM**

Holm Graessner is Executive Director of the Rare Disease Centre, since 2010, at the University and University Hospital Tübingen, Germany.

He is Coordinator of the European Reference Network for Rare Neurological Diseases (ERN-RND).

Together with Olaf Riess, he coordinates the H2020 Solve-RD project on "Solving the unsolved rare diseases".

He received his PhD "Summa cum laude" in 2004 and, then, he obtained his MBA degree in 2008.

From 2003 until now, he has been coordinating and managing more than 10 EU funded collaborative projects. The main focus of these projects are rare and neurological diseases, among them EUROSCA, MEFOPA, SENSE-PARK, MULTISYN, NEUROMICS and PROOF.

He has been co-leading one of the four working groups of the German Action Plan for Rare Diseases.

Since 2017, in his function as the coordinator of ERN-RND, he is a member of the Rare Disease Task Force of the European Academy of Neurology. In the Coordinator's Group of the European Reference Networks, he leads the cross-border healthcare working group.

## **GROFT STEPHEN C.**

Assisted in establishing the Office of Orphan Products Development at FDA in 1982, served as the Executive Director of the National Commission on Orphan Diseases from 1987-1989, and served as the Director of NIH's Office of Rare Diseases Research from 1993-2014 stimulating rare diseases research and developing information for patients, families, health care providers, academic/foundation research investigators, the biopharmaceutical industry, and the public about rare diseases, ongoing and completed research and clinical trials, and patient advocacy groups. Stimulated the development of the Genetic and Rare Diseases Information Center, the International Rare Diseases Research Consortium, the International Conference on Rare Diseases and Orphan Drugs, the Rare Diseases Clinical Research Network, assisted in the development of the Undiagnosed Diseases Program at NIH and the global Undiagnosed Diseases Network International, and developed common data elements for patient registries. ORDR co-sponsored over 1,300 scientific conferences to assist in identifying research priorities and developing research agendas for the investigation of rare diseases.

## **HETTNE KRISTINA**

Kristina Hettne (1978), PhD, is a senior researcher at the Leiden University Medical Center in Leiden, The Netherlands.

She obtained her master in computer science from Skövde University in Sweden in 2003 and shortly thereafter joined the computational toxicology group at AstraZeneca R&D in Mölndal, Sweden as a research scientist. In 2006, she moved to the Netherlands to pursue her PhD degree in bioinformatics of toxicogenomics, which she obtained from the University of Maastricht in 2012. Her seminal paper in 2009 on text mining for chemical entities using a dictionary of integrated resources is considered a reference resource in the broad field of text mining. In 2011 she joined the BioSemantics group at the Leiden University Medical Center as postdoctoral researcher, in which she since 2015 leads the research on knowledge discovery applications.

During her time at the Leiden University Medical Center she has developed resources and methods for in-silico knowledge discovery in the biomedical domain, integrated prior knowledge from literature with statistical pathway analysis methods to analyze and integrate -omics data, and contributed to setting standards for providing resources and methods to the research community in a Findable, Accessible, Interoperable and Re-useable (FAIR) way. Her current research interest are in-silico prediction of biomedical relations, multi-omics analysis, and drug discovery.

## IATROPOULOS PARASKEVAS

Paraskevas latropoulos is working at the Mario Negri Institute (Bergamo, Italy) as senior researcher, since 2008. He graduated in Medicine and Surgery, and then obtained the board certification for the specialization in Medical Genetics at the University of Brescia (Italy). He obtained the PhD title in Life and Biomolecular Sciences at the Open University (UK). During his studies at the University of Brescia he investigated for the presence of genetic risk factors in schizophrenia. In the last 10 years, dr. latropoulos is mainly working in the genomics and transcriptomics of rare kidney diseases. He is specialized in next-generation sequencing and is applying biostatistic and bioinformatic techniques to identify the genetic basis and the pathogenetic mechanisms of these diseases. He is author of several articles treating rare diseases, mainly focused in focal segmental glomerulosclerosis, steroid-resistant nephrotic syndrome, membranoproliferative glomerulonephritis and C3 glomerulopathies. He has been invited lecturer in several sceitnific and divulagative events regarding rare diseases, kidney diseases, next-generations sequencing and bioinformatics. He leaded or participated at the identification of two genes associated with steroid-resistant nephrotic syndrome. He has also performed bioinformatic analyses to study RNA expression in stem cells. In his last study, which was awarded at the 16th European Meeting on Complement in Human Disease in Copenhagen, by applying advanced biostatistics he integrated genetic histopathologic biochemical and clinical data in membranoproliferative glomerulonephritis and C3 glomerulopathies and identified disease subtypes characterized by different pathogenesis and phenotypes.

#### JULKOWSKA DARIA

Daria Julkowska is a Scientific Coordinator at the French National Research Agency (ANR) where she is responsible for the management of several European and international funding programmes. Among others, since 2010 she is involved in E-Rare, the ERA-Net for Research programmes on rare diseases, where for the first two years she occupied the position of the project manager to finally (April 2013) take over the coordination of the programme. As the coordinator she developed and put into action a set of collaborations facilitating rare diseases research, including the partnerships with European Research Infrastructures and Patients' Organizations. She has an extensive knowledge and understanding of European funding schemes and programmes. Since February 2017 she serves as the chair of the Funders Constituent Committee of IRDiRC. She is the future coordinator of the European Joint Programme on Rare Diseases that brings together research and funding stakeholders from Europe and beyond and is currently developed under the direction of the Thematic Institute for Genetics, Genomics & Bioinformatics of INSERM.

Of Polish origin, Dr. Julkowska obtained her international PhD in molecular biology at the University of Paris XI, France and University of Gdansk, Poland in 2005. She pursued her scientific vocation by the post-doctoral experience in cellular biology, at Institut Pasteur, Paris and extensive training in communication and European Union counselling. She also holds MSc in Management of Research from the University of Paris Dauphine (FR).

## **LENTING PETER**

Peter Lenting obtained his PhD with honours at the medical faculty of the University of Amsterdam, the Netherlands in 1996. He was appointed associate-professor of haematology at the University Medical Center in Utrecht, the Netherlands in 2000. Between 2007 and 2009, he held a position of Director of Protein Discovery at Crucell Holland (Leiden, the Netherlands). In March 2009, he joined Inserm as Director of Research. His research activities are mainly focussed on the Factor VIII/von Willebrand factor (FVIII/VWF) complex and the related disorders haemophilia A and von Willebrand disease. He was elected member of the council of the International Society of Thrombosis and Haemostasis (ISTH) in 2012, and chairs the ISTH-WHO-liaison committee. He is also an elected member of the council of the French Group for Thrombosis & Haemostasis (2017), and is member of the Scientific advisory board of the French Association for Haemophilia patients. In 2009, Dr. Lenting received the Prix Danièle Hermann (Foundation for Cardio-vascular Research, Institut de France) for his research activities.

## LEVY NICOLAS

Professor Nicolas Lévy leads the Department of Medical Genetics and the Inserm UMR\_S 910 research lab in Marseille. He is responsible for numerous projects on rare diseases and has a special interest in neuromuscular disorders and premature ageing. As a clinician and researcher engaged primarily in translational medicine in rare diseases, he is also the principal investigator for the EU trial in Progeria conducted in Marseille and is involved in other therapeutic studies.

Nicolas was appointed Director of the French Institute for Rare Diseases (GIS-Institut des maladies rares) in 2009 and in 2012 became the Scientific Director of the French Rare Disease Foundation (Fondation Maladies Rares). In 2013 he was awarded the Grand Prix Robert-Debré 2012 for clinical research by the Association Robert Debré for medical research (ARDRM).

Nicolas's activity is primarily focused on the genetics and cell biology of neuromuscular disorders (NMDs). At both a diagnostic and research level, his laboratory has set up specific protocols towards exploring genes involved in peripheral neuropathies and limb girdle muscular dystrophies together with the exploration of numerous other NMDs including Duchenne and Becker muscular dystrophy, facioscapulohumeral muscular dystrophy, GNE myopathy, calpainopathies and laminopathies. This activity has allowed the identification of large cohorts of patients perfectly characterized at the molecular level who may therefore be eligible for future innovative therapeutic trials. In particular, they have the largest known cohort of patients affected with dysferlin deficiency and have set up targeted therapeutic approaches according to their mutation types.

## LODISH HARVEY F.

Dr. Lodish is a Founding Member of the Whitehead Institute for Biomedical Research and Professor of Biology and Professor of Biological Engineering at the Massachusetts Institute of Technology.

He is a Member of the National Academy of Sciences, a Fellow of the American Association for the Advancement of Science, a Fellow of the American Academy of Arts and Sciences, a Fellow of the American Academy of Microbiology, and an Associate (Foreign) Member of the European Molecular Biology Organization.

Current efforts of his research group focus on identifying genes and extracellular signals that regulate red blood cell development, and elucidating the roles of many long noncoding RNAs (IncRNAs) that are essential for the differentiation and function of erythroid and myeloid cells, and others essential for formation of white and brown adipose cells.

Most recently his laboratory developed culture systems for generating mature human red

blood cells from hematopoietic stem cells. With Flagship Pioneering he founded Rubius Therapeutics, a company that uses gene- and enzyme- modified red blood cells as vehicles for the long- term introduction of many novel therapeutics, immunomodulatory agents, and diagnostic imaging probes into the human body.

Dr. Lodish is a member of the Board of Trustees of Boston Children's Hospital, where he is Chair of the Board of Trustees Research Committee. From 2008 to 2016 he was the Founding Chair of the Scientific Advisory Board of the Massachusetts Life Sciences Center, the group charged with oversight of the state's 10- year billion investment in the life sciences. He was a founder and scientific advisory board member of several companies including Genzyme, Inc., Arris Pharmaceuticals, Inc, and Millennium Pharmaceuticals, Inc., and has served on the scientific advisory boards of numerous biopharmaceutical companies.

Dr. Lodish is the lead author of the textbook Molecular Cell Biology; the eighth edition was published in April 2016; the book has been translated into 12 languages. During the 2004 calendar year Dr. Lodish served as President of the American Society for Cell Biology.

#### **MENZEL OLIVIER**

Dr Olivier Menzel graduated (B.Sc.) from the University of Geneva where he obtained a Master of Medical Genetics (M.Sc.) in 2001 and a PhD in 2006 from the University of Lausanne and EPFL at the Swiss Institute for Experimental Cancer Research (ISREC). For seven years he directed the laboratory of pediatric surgery at the University Hospital of Geneva. In parallel he created the BLACKSWAN Foundation, a Swiss foundation to support research on rare and orphan diseases, organized international scientific conferences (RE(ACT) Congress) and launched an online platform for sharing scientific knowledge and crowdfunding (RE(ACT) Community). For two years he was a director of a company specialized in the identification, acquisition, development, marketing and sale of research programs for rare and orphan diseases. In 2013 he obtained an Executive MBA from the HEC of Lausanne with a specialization in Management Healthcare. For 2 years he was a director at the second largest group of private clinics in Switzerland, Swiss Medical Network. Now he is Managing Director at Think Rare Sàrl and fully involved in the BLACKSWAN Foundation activities.

## NALDINI LUIGI

Luigi Naldini received his M.D. from the University of Torino, Italy in 1983 and his Ph.D. from the University of Rome in 1987, carried out post-doctoral work in the U.S.A. with Yossi Schlessinger (1987-89), was visiting scientist with Inder Verma and Didier Trono at the Salk Institute (1994-96), subsequently had independent appointments at Cell Genesys, California (1996-98) and the University of Torino prior to moving to Milan in 2002, where he is currently the Director of the San Raffaele Telethon Institute for Gene Therapy, Director of the Division of Regenerative Medicine, Stem Cells and Gene Therapy, and Professor at the San Raffaele University. In his early career, he identified the ligand for the Met receptor with Hepatocyte Growth Factor. For the last 20 years, Luigi Naldini has pioneered the development and applications of lentiviral vectors for gene transfer, which have become one of the most widely used tool in biomedical research and, upon recently entering clinical testing, are providing a long-sought hope of cure for several currently untreatable and oth-

erwise deadly human diseases. Throughout this time, he has continued to investigate new strategies to overcome the major hurdles to safe and effective gene transfer, bringing about innovative solutions that not only are being translated into new therapeutic strategies for genetic disease and cancer but have also allowed novel insights into hematopoietic stem cell function, induction of immunological tolerance and tumor angiogenesis. Luigi Naldini has been President of the European Society of Gene and Cell Therapy (ESGCT, 2012-2014), Member of the Board of Directors (2005-2008) and the Advisory Council (2008-2012) of the American Society of Gene and Cell Therapy (ASGCT), has served on several Scientific Committees of the ASGCT, ESCGT, American Association of Cancer Research (AACR), International Society for Stem Cell Research (ISSCR), International Society of Cell Therapy (ISCT). He is member of EMBO, the European Molecular Biology Organization, since 2008 and was awarded the Outstanding Achievement Award from ASGCT in 2014.

In 2015 He was appointed member of the Human Gene Editing Study Committee by the National Academies of Sciences and of Medicine of the USA; in 2016 He was appointed member of the National Advisory Committee on Biosafety, Biotechnology and Life Sciences (2016-2020) and of the Advisory Committee to the Italian Ministry of Health.

#### **NIGRO VINCENZO**

Full professor of Medical Genetics at the Department of "Precision Medicine" of the "University "Luigi Vanvitelli" of Naples, Italy " and Associate Investigator of the Telethon Institute of Genetics and Medicine (TIGEM). Born in Naples July 28, 1960, graduated in Medicine. University Researcher from 1992 to 2000, associate professor from 2000 to 2006 and full professor of general pathology from 2006 to 2010. In 1982-1990 he was at the Institute of General Pathology and Oncology, as a student and then with a fellowship of the Italian cancer research association (AIRC), aimed to the study of the mechanism of action of the estrogen receptor. From 1989 to 1994, he was at the International Institute of Genetics and Biophysics (IIGB), CNR, Naples with Edoardo Boncinelli (developmental biology, identification of transcription factors that regulate embryogenesis and the formation of brain). Since 1992, his research team is involved in the study of muscular dystrophies. He published >160 articles in peer reviewed journals. Among the most significant results, the identification of delta-sarcoglycan and mutations that cause limb-girdle muscular dystrophy (LGMD2F), the identification of the gene that causes the cardiomyopathy of the BIO14.6 hamster, a leading experimental model. In addition, he identified the causes of other Mendelian disorders, such as FG syndrome 4, LGMD1F, etc. He directs the laboratory of Medical Genetics. He leads research projects on the gene therapy of delta-sarcoglycanopathy and on the identification and classification of novel causes of genetic myopathies using next generation sequencing. He developed specific strategies for detecting mutations in neuromuscular disorders, lysosomal storage disorders, neufibromatosis, kidney disorders, etc. He is coordinator of the Tigem-University Next Generation Sequencing facilities, and co-coordinator of the Telethon Undiagnosed Program that provides diagnosis of new and unrecognized genetic disorders based on NGS.

## **PENNINGER JOSEF**

Josef Penninger, MD was formerly a lead researcher at the Amgen Research Institute in Toronto. In 2002 he accepted the appointment as founding director of the newly established Institute of Molecular Biotechnology (IMBA) of the Austrian Academy of Sciences in Vienna, Austria. Major achievements include pioneering insights into the molecular basis of osteoporosis and breast cancer, as well as the study of metastatic spread. His group has also developed the first haploid embryonic stem cells for functional genetics. He has authored and co-authored more than 580 scientific papers. Josef Penninger's major awards include the Descartes Prize, the Wittgenstein Prize of the Austrian Federal Government, the Ernst Jung Prize for medical excellence, an AAAS Award the Innovator Award from Era of Hope/DOD and a second ERC Advanced grant.

## **PETROVA TATIANA**

Tatiana Petrova received her M.Sc in chemistry from Moscow State University and a Ph.D. in biochemistry from the University of Geneva. She did a post-doctoral work at Northwestern University in Chicago, and then moved to a second postdoctoral position at the University of Helsinki, Finland. In 2004 she became a group leader at Molecular Cancer Biology Program at the University of Helsinki, and in 2008 joined University of Lausanne as Swiss National Foundation professor. Her main research interests are the molecular mechanisms of lymphatic and blood vascular growth and remodeling.

## **REQUENA JESÚS R.**

Jesús R. Reguena is Associate Professor at the University of Santiago de Compostela, Spain, where he leads a research group focused on prions and prion diseases at the CIMUS Biomedical Research Institute. He obtained his Ph.D. in Biochemistry at the University of Santiago de Compostela, and subsequently carried out postdoctoral research at the University of South Carolina, and the Laboratory of Protein Biochemistry at the National Heart Lung and Blood Institute at Bethesda, USA. Dr. Requena has been interested for many years in the structure of the PrPSc prion, the causal agent of the fatal neurodegenerative ailment Creutzfeldt-Jakob disease. In collaboration with Holger Wille and Howard Young, from the University of Alberta, Canada, he has recently elucidated the general architecture of this enigmatic infectious and pathogenic protein, which consists of a 4-rung -solenoid. This knowledge allows for the first time an understanding of the mechanism by which PrPSc prions propagate. More recently Dr. Requena has opened a research line on therapy of prion diseases, and he currently leads a multinational eRare-funded project aimed at finding chemical chaperones that, stabilizing the normally folded precursor of PrPSc, this is, PrPC, might prevent their conversion to the PrPSc form. Dr. Requena is the author of more than 60 peer-reviewed papers, coordinated the FP7, EC-funded project "Priority" and will host the 2018 international prion meeting in Santiago de Compostela.

## SANGIORGI LUCA

Dr Luca Sangiorgi helds a Medical degree from the University of Bologna, a PhD in Clinical Genetics at "La Sapienza" University of Rome and a Master Degree in Research Promotion and Governance in Hospital Trusts and Local Health Units at the University of Modena and Reggio Emilia.

He has been Visiting Scientist at the Molecular Oncology Section, Paediatric Branch of the National Cancer Institute in Maryland (USA).

He is coordinator of the Rizzoli Rare Disease Center and responsible of four National Registers of Rare Disease (Multiple Hereditary Exostoses, Osteogenesis Imperfecta, Ehrler Danlos and Ollier Disease). He also coordinates the Emilia Romagna Region Hub and Spoke Network on Rare Bone Disorders.

Italian representative in the Assembly of Member States (AoM) of BBMRI (Biobanking and Biomolecular Resources Research Infrastructure) since 2013, he is currently acting as Chair of the AoM and Coordinator of the BBMRI Rare Disease Interest Group.

Since December 2014 he is acting as Alternate of the Representative of Italian Government for the Committee for Advanced Therapies (CAT) of the European Medicine Agency (EMA).

Since March 2017 he is the coordinator of BOND ERN that includes 38 Centres of Excellence for the treatment of Rare Bone Disorders in 10 EU Member States.

As member of many different medical and scientific societies, he has been appointed President of Connective Tissue Oncology Society and International Skeletal Dysplasia Society.

## SCARPA MAURIZIO

Director Centre for Rare Diseases Helios Dr. Horst Schmidt Kliniken GmbH Wiesbaden, Germany.

Coordinator European Reference Network For Hereditary Metabolic Diseases, MetabERN Chair, ERN Coordinators Group

Maurizio Scarpa, MD PhD, paediatrician, is the Director of the Centre for Rare Diseases at the Helios Dr Horst Schmidt Kliniken GmbH in Wiesbaden, Germany. He is Professor of Paediatrics at the Dept. for the Woman and Child Health, University of Padova, Italy, and the Co-Founder of the Brains For Brain Foundation, together with Prof. David Begley, Kings College of London, London, UK.

Prof. Scarpa earned his medical degree, doctorate and residency in Paediatrics at the University of Padova in Italy. He completed a postdoctoral fellowship in molecular biology and gene expression at the European Molecular Biology Laboratory (EMBL) in Heidelberg, Germany, and in genetics and gene therapy at the Howard Hughes Medical Institute, Institute for Molecular Genetics, at Baylor College of Medicine in Houston, Texas, USA.

He has been the Director of the PhD Course on Genetics and Biochemistry at the Dept. for the Woman and Child Health at the University of Padova, Italy.

He served as vice-Dean for the International Affairs at the University of Padova and Director of the International Affairs Office at the Faculty of Medicine of the University of Padova, Italy. He is the Coordinator of the European DGSANTE Project, INNERMED.

Prof. Scarpa has extensive expertise as a basic scientist in genetics and biotechnology, as well as a clinician in the diagnosis and treatment of paediatric rare disorders, neurometabolic diseases in particular. He is especially interested in developing innovative health

#### 27 SPEAKERS' BIOGRAPHIES

approaches for the diagnosis and the treatment of metabolic inherited diseases, to this aim he is also collaborating with the major Biotech Companies as external independent expert.

Prof. Scarpa's teaching and educational interests aim, among other, at the development of a MD/PhD European Program on Inherited Metabolic Diseases.

Prof. Scarpa is the Coordinator of the European Reference Network for Hereditary Metabolic Diseases, MetabERN, formed by 69HCPs in 18 EU countries and treating 43000 metabolic patients, and he is the Chair of the ERN Coordinators Working Group.

Prof. Scarpa is author of about 140 international peer reviewed clinical and scientific papers, book chapters and reviews.

## TARUSCIO DOMENICA

Domenica Taruscio is the Director of the National Centre for Rare Diseases at the Italian National Institute of Health (Istituto Superiore di Sanità – ISS, Rome, Italy)

Director of research on rare diseases at the Italian National Institute of Health

She performed her medical degree (Summa cum laude) and specialization in histopathology at Bologna University; post-doctoral studies in human genetics at Yale University (CT-USA); master in bioethics (Sapienza University, Rome).

Author of more than 150 scientific peer-reviewed publications

Co-Chair of the Interdisciplinary Scientific Committee of IRDiRC

Co-founder of the Undiagnosed Diseases Network International (UDNI)

Scientific leader of the bilateral agreement on rare diseases between ISS-Italy and NIH-USA (since 2003 up to now)

Past President of ICORD – International Conference on Rare Diseases & Orphan Drugs (2010-2012) and currently ICORD Board Member

She is or has been member of several International (e.g. COMP-EMA, EUCERD) and National Committee (National Plan for Rare Diseases; Italian National Body for European Reference Networks; National Program on Expanded Newborn Screening)

Scientific coordinator of several EU projects (among them: NEPHIRD, EUROPLAN, EPIRARE, RARE-Bestpractices); WP Leader (RD-Connect Registry WP; Advance-HTA, BURQ-OL, E-RARE, EUROCAT Joint Action; EUCERD Joint Action, RD-Action).

Principal Investigator of the bilateral project Italy (ISS)-USA (NIH) "Undiagnosed rare diseases (2015-2018)

Director of the International School on Rare Disease and Orphan Drug Registries

## **VISSERS LISENKA**

Lisenka Vissers (1980), PhD, is a principal investigator at the Radboud university medical centre in Nijmegen, the Netherlands. She obtained her medical biology degree from the Radboud University Nijmegen in 2002, and obtained her PhD on molecular karyotyping by microarray-based comparative genomic hybridization in clinical care in 2007. In 2010, she was the first to apply trio-based whole exome sequencing to identify de novo mutations underlying sporadic intellectual disability, which created a paradigm shift in the field of medical genomics. From 2014 onwards, she was appointed head of Translational Genomics where she is responsible for clinical diagnostic innovation using genomic strategies.

She has been a member of teams which identified the genes underlying several human malformation syndromes, such as CHARGE syndrome and Koolen-de Vries syndrome, and amongst the first to use whole genome sequencing to identify major causes of severe intellectual disability. Her current interests are assessing clinical utility of novel diagnostic assays for routine clinical practice, identifying novel disease genes using genomics data, and improving interpretation of (de novo) non-coding mutations in disease phenotypes.

## WILD EDWARD

I'm a Consultant Neurologist at the National Hospital for Neurology and Neurosurgery in London's Queen Square. I run clinics in general neurology, neurogenetic movement disorders and Huntington's disease.

I'm an MRC Clinician Scientist at UCL Institute of Neurology, and a Principal Investigator at UCL Huntington's Disease Centre. My clinical research aims to accelerate the development of new therapies to make a real difference for people impacted by Huntington's disease.

I studied medicine at Christ's College, Cambridge University, and have worked in neurology since 2005. My PhD research at UCL Institute of Neurology won the 2009 Queen Square Prize in Neurology.

I believe that scientists have a duty to make their work accessible and understandable to the people who need it most. In 2010, I co-founded HDBuzz, an online source of reliable, impartial, easy-to-understand information about HD research. HDBuzz is now the world's foremost HD research news source. In recognition of this, I was awarded the 2012 Michael Wright Community Leadership Award by the Huntington Society of Canada and the 2014 Research Award by the Huntington's Disease Society of America.

I have authored 6 book chapters and over 50 peer-reviewed publications. I serve on the medical advisory panel of the Huntington's Disease Association, the Editorial Boards of Journal of Huntington's Disease and PLoS Currents: Huntington's Disease and the steering committee to the UK All-Party Parliamentary Group on Huntington's disease. I am the Lead Facilitator of the European Huntington's Disease Network's Biomarkers Working Group and an emeritus member of the Network's Scientific and Bioethical Advisory Committee.

## **SPEAKERS' ABSTRACTS**

#### **SPONSORS**

Silver sponsor

## **Cydan: Orphan Drug Accelerator**

Accelerating Rare Genetic Disease Therapies



Bronze sponsor



#### UNDIAGNOSED RARE DISEASES: A BILATERAL PROJECT BETWEEN ITALY (ISTITUTO SUPERIORE DI SANITÀ) AND USA (NIH)

UNDIAGNOSED DISEASES NETWORK INTERNATIONAL (UDNI)

Domenica Taruscio, Marco Salvatore, Maria Chiara De Stefano, Giovanna Floridia, Federica Censi

National Centre for Rare Diseases, Istituto Superiore di Sanità

The "Undiagnosed Rare Diseases: a joint Italy - USA project", is a pilot research funded by Italian Ministry of Foreign Affairs and International Cooperation, aiming to define a diagnosis for undiagnosed patients as well as to identify and characterize new rare diseases. The project is coordinated by the National Centre for Rare Diseases (Istituto Superiore di Sanità) and involves 6 Italian clinical Centres (Tor Vergata University, Rome; L'Aguila University; Mario Negri Institute for Pharmacological Research Clinical, Milan; Turin University; Ferrara University; Rare Diseases Centre Udine); the USA partner is the National Human Genome Research Institute, NIH (Dr. W.A. Gahl). A National database, collecting genetic and phenotypic data of undiagnosed patients, has been established from the Italian Network for rare diseases, using common standard and terminology for the classification (HPO, Human Phenotype Ontology). The database is progressively developing and interoperable at International level. Cases are included within the following specific topics: Intellectual disabilities syndromes, Connective tissue vascular disorders, Motor neurons syndromes, Multiple abnormalities syndromes and Nephropathies. The database patients are already extensively examined, so that obvious diagnoses are excluded, and deep sequencing (WES/ WGS of family and trios) is performed in selected cases. To facilitate data sharing and matching at international level, some cases have been entered in PhenomeCentral Platform. In particular, a specific Phenome Central work group has been set up, named "UDN ISS Italy" and managed by National Centre for Rare Diseases. Each case deposited on PhenomeCentral by "UDN ISS Italy" is shared with UDNI Work Group, in order to ensure the fully accessibility of the case information to UDNI members.

domenica.taruscio@iss.it

#### UNDIAGNOSED DISEASES NETWORK INTERNATIONAL (UDNI): AN INTERNATIONAL INITIATIVE TO FOSTER THE TRANSLATION OF RESEARCH INTO MEDICAL PRACTICE

UNDIAGNOSED DISEASES NETWORK INTERNATIONAL (UDNI)

Domenica Taruscio1, Stephen C. Groft2

1National Centre for Rare Diseases, Istituto Superiore di Sanità, Roma, Italy; 2 Stephen C. Groft, Pharm.D. Senior Advisor to Director National Center for Advancing Translational Sciences, NIH USA

Undiagnosed diseases are a global health issue, calling for an international scientific and healthcare effort. The Undiagnosed Diseases Network International (UDNI) established since 2015 modeled in part after the NIH UDP, include scientists, clinicians and patient representatives. The main aim is to provide diagnoses for individuals who had long sought one without success. Therefore, the Network involves centers with internationally recognized expertise, and its scientific resources and know-how aim to fill the knowledge gaps that impede diagnosis. Consequently, the UDNI fosters the translation of research into medical practice.

UDNI (http://www.udninternational.org) i. includes experts from many Countries and continents (Australia, Canada, Europe, USA, etc.) and it is rapidly expanding; ii. has published a consensus framework of principles, best practices and governance; iii) organizes International Conferences since 2015. Active patient involvement is important; therefore, the Patient Advisory Group is playing an increasing role in UDNI activities.

During the Meeting, speakers will present experiences and programs in different Countries (e.g. in USA, Italy, Austria), including SOLVE-RD, a new EU funded project.

domenica.taruscio@iss.it

#### THE UNDIAGNOSED UNDIAGNOSED DISEASES NETWORK INTERNATIONAL (UDNI)

#### Helene Cederroth, Wilhelm Foundation · Sandbacken · 18697 Brottby · Sweden

Even today 2018 there is still a lot of diseases that are undiagnosed. It is very difficult for the society to understand that the specialists can't solve these diseases. When you talk to people about undiagnosed diseases almost every conversation ends with the guestion "what's the name of the disease". It's not because they aren't paying attention, but they ask because it's impossible for most of us to believe that undiagnosed diseases still exist. One of Wilhelm Foundation's missions is to raise awareness around the world about the undiagnosed diseases and undiagnosed children. The undiagnosed diseases are divided into three groups. The first group; is all the undiagnosed patients that suffer from a disease that isn't diagnosed yet. The second group; is the patients who are misdiagnosed. The third group: the patients who suffer from an undiagnosed disease that not is discovered vet. Wilhelm Foundation's goal is that all children and youth with undiagnosed diseases should get a diagnosis. The funders of Wilhelm Foundation are not specialists, they are two parents who lost their three youngest children who all suffered from an undiagnosed disease. The parents decided that they had to do something to help all the undiagnosed children and youth in the world. One way Wilhelm Foundation is trying to help the undiagnosed is to support the specialists who work to solve the undiagnosed diseases that aren't discovered yet. The foundation has co-arranged world congresses for the undiagnosed diseases. Wilhelm Foundation together with NIH's Common Fund supports a worldwide network - Undiagnosed Diseases Network International which was funded at the first and second International conference on rare and Undiagnosed Diseases. The Wilhelm Foundation concentrate on the undiagnosed diseases that not discovered yet. When the specialists solve more diseases hopefully there will be less misdiagnosed, and the journey of diagnosis will not take several years as it does for some undiagnosed patients today. The funders are running the foundation and have a lot of experience of undiagnosed diseases since they meet a lot a of parents with undiagnosed children. Wilhelm Foundation have started a parent group. Parents around the world contact Wilhelm Foundation for help and advice.

helene@wilhelmfoundation.org

#### THE NIH UNDIAGNOSED DISEASES PROGRAM AND NETWORK

UNDIAGNOSED DISEASES NETWORK INTERNATIONAL (UDNI)

William A. Gahl1,2 1NIH Undiagnosed Diseases Program, Common Fund, Office of the Director, NIH 20ffice of the Clinical Director, National Human Genome Research Institute, NIH, Bethesda, Maryland USA 20892

The National Institutes of Health Undiagnosed Diseases Program (UDP) has two primary goals, i.e., to help patients who had long sought a diagnosis finally attain one, and to advance medical knowledge by the discovery of new biochemical, cellular, and physiological pathways. Intensive phenotyping is essential for these processes, and SNP analysis and family exome sequencing have contributed significantly. More than 1100 patients have been evaluated by the UDP during a 5-day inpatient admission to the NIH Clinical Center, with some diagnosis made in approximately 25%; most of the diagnoses are rare or extremely rare genetic disorders. In addition, new gene variants have been associated with novel phenotypes, and basic research studies have made the case for causality. Examples include vascular calcification defects due to NT5E mutations, spinocerebellar ataxia and hereditary spastic paraplegia due to AFG3L2 mutations, and Congenital Disorder of Glycosylation IIb due to biallelic mutations in the gene encoding glucosidase I. The success of the UDP has resulted in expansion to an Undiagnosed Diseases Network (UDN) consisting of 6 additional clinical sites, a Coordinating Center, two Sequencing Cores, a Model Organisms Screening Core, a Metabolomics Core, and a Biorepository. Functional studies are also performed via granting mechanisms, all through the NIH's Common Fund in the Office of the Director. The Network operates under a single IRB with Reliance Agreements and a protocol and consent that allow for sharing of phenotypic and sequence data. The UDP/UDN is currently collaborating with rare disease groups throughout the world to create an International Undiagnosed Diseases Network featuring sharing of both exomic and phenotypic data.

gahlw@mail.nih.gov

# UNDIAGNOSED DISEASES: MEETING THE NEEDS OF THE RARE DISEASES COMMUNITY

UNDIAGNOSED DISEASES NETWORK INTERNATIONAL (UDNI)

Stephen C. Groft, Pharm.D. Senior Advisor to Director National Center for Advancing Translational Sciences, NIH USA

Obtaining the correct diagnosis for patients with common and rare diseases can be one of the most challenging and frustrating tasks for patients and physicians. Estimates have been made that approximately 6% inquiries received by the Genetic and Rare Diseases Information Center supported by NIH related to undiagnosed diseases. What started as a demonstration or pilot project in 2008 at the Clinical Center of the National Institutes of Health (NIH) by the National Human Genome Research Institute and the Office of Rare Diseases Research has now gained international prominence leading to the development of the Undiagnosed Diseases Network International. The discussion will provide the historical perspective of implementing the Undiagnosed Diseases Program(UDP) at the NIH and highlight the emphasis that occurred in the USA with the establishment of the Undiagnosed Diseases Network and is now experiencing a rapid global expansion. There are many rare and common diseases associated with genotype and phenotype variability not easily recognized and diagnosed. Each year many new diseases are identified in the process of establishing the correct diagnosis. Obtaining the diagnosis is the first important step in leading to treatment and care. After the name of a diseases is identified, several options are available to the patient and the physician providing care for the patient. The second step leads to obtaining information about the disease and possible available treatments. The third step is the desire to connect with patient advocacy groups, individual patients and their families and learning life skills or coping mechanisms of living with the disease on a day to day basis. The last step is for many patients and clinicians to seek out other clinicians with extensive experience who are very knowledgeable about a recently diagnosed disease. Frequently these clinicians and research investigators are conducting clinical trials or contributing to patient registries. These efforts frequently seek research participants for longitudinal studies, natural history studies, or clinical trials. It is important to recognize that patients who are willing participants in many research initiatives do so to expand the knowledgebase for their disease for their own benefit and that of all patients with the disease and for future patients. Opportunities are available for all clinicians to participate in the recently developed undiagnosed disease networks by gathering and sharing patient data with others interested in the diagnosis and care of patients with undiagnosed diseases. All clinician participants are asked to follow the manual of operations, data sharing and use agreements among UDN sites and sharing de-identified data outside of the UDN/ UDNI members, adhering to single IRB model, and sharing of sequencing and phenotypic data. With expansion of activities in the Undiagnosed Diseases Network International (UDNI), more areas of scientific and social interest reveal themselves as opportunities for collaborative research projects in both rare and common diseases.

stephen.groft@nih.gov
#### UNDIAGNOSED AND NOT DIAGNOSED: A GENETIC VIEW

UNDIAGNOSED DISEASES NETWORK INTERNATIONAL (UDNI)

Alessandra Ferlini, Unit of Medical Genetics, University of Ferrara, Italy

Undiagnosed diseases (UDN) are defined as "longstanding medical condition that eludes diagnosis by a referring physician can be considered undiagnosed and may be of interest to this clinical research program" (UDN International). Indeed the UDN definition is wide and includes different medical conditions. Indeed, the concept of diagnosis can be related to the phenotype (clinical features) and genotype (genetic profile).

Following the advent of next generation sequences (NGS) techniques, a huge number of novel genes underlining known or unknown phenotypes, or/and novel phenotypes due to mutations in known genes have emerged. The gene discovery task is high demanding, and, although at least 2000 new genes were identified in the last 10 years (www.irdirc. org), still roughly 40% of patients analyzed by NGS (whole exome sequencing or WES and whole genome sequencing or WGS) remained orphan of a genetic diagnosis.

This means that these new methods have incomplete accuracy, and various mutation types (as dynamic mutation or copy number variations) escape their detection ability.

The phenotype discovery task seems easier and feasible since it consists of assigning know gene mutations to novel phenotypes. However, depending on the method used to pick up these variations, in many cases, mutations in known genes are not accurately identified in patients.

Therefore we may consider two different categories of UDNs, underlining different detection strategies.

UDN due to novel genes, never discovered associated with rare diseases. In this case an in depth whole genome analysis, often facilitated by familial analysis or based on newly developed algorithms to interpret the genome output could be used. A particular attention in these cases should be paid to epigenetics causes, currently unexplored, copy number variations identification, as well as innovative in vitro models to functional validate the genome variations.

Known gene mutations to expand the phenotypic spectrum. In this UDN type, effort should be put in extensively exploring all mutation types in known genes, reaching accuracy close to 95%, as for a diagnostic test. This implies the design of exhaustive gene panels or clinical exomes/genomes or RNA profiles, which can identify all mutation types. This may require more bioinformatics skill and novel methods. RNAseq is a promising tool to be utilized. Some examples of UDN patients representative of known or novel gene mutations will be described.

In conclusion, depending on the UDN category, the approach to identify the genetic cause of UDN might vary. Diagnostic pipelines should be designed to optimize the detection rate based on versatile molecular genetic strategies.

f a@unife.it

#### THE EUROPEAN REFERENCE NETWORK PROGRAM AND THE METABERN (ERN FOR RARE HEREDITARY METABOLIC DISEASES)

EUROPEAN REFERENCE NETWORKS (ERNS), WHERE WE STAND?

Maurizio Scarpa, Helios, Dr. Horst Schmidt Kliniken, Wiesbaden Germany, Coordinator, on behalf of the MetabERN Members

The European Reference Network for Hereditary Metabolic Diseases (MetabERN) responds to the European Commission call to establish European Reference Networks (ERNs) following the Directive on patients' rights in cross-border healthcare. MetabERN represents the first most comprehensive, panmetabolic, pan-european, patient-orientated platform ever conceived worldwide, aimed to transform how care is provided to patients with inherited metabolic diseases (IMDs) in Europe. MetabERN represents 69 founding nationally certified Healthcare Providers from 18 European countries, 44 Patients Organisations and is endorsed by the Society for the Inborn Errors of Metabolism (SSIEM).

MetabERN involves 1681 experts, of which about 52% are specialized medical doctors (particularly pediatrician, geneticist, neurologist and metabolic physicians).

42.427 are the patients managed by the MetabERN, 68% of which represented by pediatric patients. More than a half of the patients are affected by lysosomal disorders or aminoacid and organic acids related disorders diseases (23% and 39% respectively).

All Inherited Metabolic Diseases (IMDs), with no exclusion, are of interest for the MetabERN, independently from their prevalence, frequency and existing previous interest for research or therapy development.

Considering the complexity of the IMDs field as a whole, the group of more than 700 ultra rare metabolic diseases are structured in 7 subnetworks:

- 1. Aminoacid and organic acids related disorders,
- 2. Disorders of pyruvate metabolism, Krebs cycle defects, mitochondrial oxidative phosphorylation disorders, disorders of thiamine transport/metabolism,
- 3. Carbohydrate, fatty acid oxidation and ketone bodies disorders,
- 4. Lysosomal disorders,
- 5. Peroxisomal and lipid related disorders,
- 6. Congenital disorders of glycosylation and disorders of intracellular trafficking,
- 7. Disorders of Neuromodulators and Small Molecules.

In disease-specific networks professionals and patient associations will collaborate to transversal programs common to all the subnetworks. Patient organizations will work in close collaboration with Healthcare Professionals to map and understand patients' needs and identify solutions.

#### MetabERN aims to:

- Accommodate and interconnect expertise,
- Harmonise data collection,
- Establish approaches to optimise prevention, diagnostics, management and treatment,
- Develop and implement guidelines,
- Stimulate cross-border research and innovative treatments,
- Develop training and education opportunities,
- Interact with patients.

MetabERN will facilitate and harmonize patients' access to diagnosis and best treatment and design a collaborative governmental structure with patients, academia, politics, insurance companies and industry.

Maurizio.scarpa@metab.ern-net.eu

# ERN BASED DIAGNOSTIC RESEARCH. SOLVE-RD: SOLVING THE UNSOLVED RARE DISEASES.

EUROPEAN REFERENCE NETWORKS (ERNS), WHERE WE STAND?

Holm Graessner, Centre for Rare Diseases Tübingen, Germany

European Reference Networks (ERN) mainly focus on care of rare disease (RD) patients. However, ERN essentially bridge over to research. To obtain a molecularly confirmed diagnosis remains one of the largest challenges for RD patients. To jointly tackle this challenge a core group of four ERNs has motivated, designed and put together the Solve-RD project which is the first ERN based H2020 funded research project. Solve-RD brings together 21 partners from 10 countries and which will be running from 2018 to 2022. The main ambitions of the Solve-RD project are (i) to solve large numbers of RD, for which a molecular cause is not know yet, by sophisticated combined Omics approaches, and (ii) to improve diagnostics of RD patients through a "genetic knowledge web". Solve-RD will pursue a clear visionary and integrated "beyond the exome" approach. To tackle diseases which are unsolved by applying cutting edge strategies, Solve-RD has thus formed a consortium that comprises (i) leading clinicians, geneticists and translational researchers of these ERNs, (ii) RD research and diagnostic infrastructures, (iii) patient organisations, as well as (iv) leading experts in the field of -omics technologies, bioinformatics and knowledge management. Solve-RD will deliver 7 main implementation steps: (i) Collect Phenotypes, (ii) New phenotype patterns, (iii) Re-analyse exomes / genomes, (iv) Novel molecular strategies, (v) Functional analysis, (iv) Clinical utility and (vii) Towards therapy. For analysis Solve-RD will apply data driven and expert driven approaches. We anticipate to increase diagnostic yield from 19.000 unsolved exomes/genomes by about 3-5%. Cohort specific innovative -omis strategies will be pursud, also addressing cost-effective issues. Analysis of more than 800 patients with highly peculiar (ultra-rare) phenotypes will highly increase the chance to find novel disease genes and novel disease mechanisms. We anticipate to solve more than 2.000 cases. Finding further matching patients will be secured by newly developed matchmaking approaches and by screening using MIPs technology in the more than 20.000 unclassified patients of the ERNs. For the first time in Europe we will also implement a novel brokerage structure connecting clinicians, gene discoverer and basic researcher to guickly verify novel genes and disease mechanisms.

Holm.Graessner@med.uni-tuebingen.de

### BOND ERN MISSION, VISION AND INITIAL STRATEGIC PLAN

EUROPEAN REFERENCE NETWORKS (ERNS), WHERE WE STAND?

# Luca Sangiorgi, BOND European Reference Networks & Istituto Ortopedico Rizzoli, Bologna, Italy

The main ambition of the BOND ERN is to implement measures that facilitate multidisciplinary, holistic, continuous, patient-centred and participative care provision to people living with rare bone diseases (RBD), supporting them in the full realisation of their fundamental human rights. In particular, BOND ERN aim to ensure that people living with a RBD are afforded the same standards of care and support as the ones available to other citizens with similar requirements. To meet this goal, BOND ERN gathers European professionals highly specialized in the field of RBD for both scientific research and multidisciplinary care to increase knowledge on RDs, to improve healthcare quality and patient safety, to increase access to ultra specialized medical expertise and accessible information beyond national borders, in accordance with Directive 2011/24/EU.

ERN BOND aspiration is to support patients affected by rare bone diseases and their families, to increase their capacity to undertake a participative role in care provision, to set priorities and to participate in decisions regarding their care plan and their life project, in accordance with EUCERD recommendations (2013).

BOND ERN aims to assess patients and families accessibility to and appropriateness of healthcare and social services. At the same time, the Network seeks to evaluate healthcare, social effectiveness, cost-effectiveness of actions implemented, measuring their impact on the quality of life of people living with RD.

#### Vision

BOND will bring rapid interchange of information, skills and practice to shorten time to diagnosis, and treatment. BOND will develop, with PAGs, evidence/consensus-based guidelines to improve agreed outcomes in the 3 exemplar conditions, OI, XLH and ACH.

BOND HCPs will share clinical/phenotypic data within existing databases by developing tools to interrogate and combine data from these to create epidemiological surveillance registries, allowing improved understanding of interventions and co-morbidities at an individual level, and enabling refinement and standardization of diagnostic algorithms, management guidelines and outcomes. BOND will enable skill development through eHealth and Telemedicine platforms, alongside working visits, training courses and dissemination activities. BOND will work with PAGs in all activities to ensure patient-focused developments, with patient-reported outcome and experience measures to be adopted as specific outcomes against which to assess BOND performance in improving healthcare.

BOND will be instrumental for collaboration across Europe for clinical trials with novel orphan drugs, coordinated supportive care measures and translation of current research into patient benefit, alongside development of new approaches such as targeted (epi)genome editing that may be of great potential especially for the rare bone diseases. We anticipate interaction with and provision of expert advice to regulators and commissioners of care to define appropriate patient-centered outcomes for CTIMPS.

We expect that reduced time to diagnosis with fewer inappropriate tests, more accurate diagnosis and new viable treatments will be available within the 2-3 years and that the visibility of expert teams will be a magnet for attracting complex cases with improved communication allowing many more to receive their care locally with support from their expert centre HCP.

BOND will target less developed affiliate partners where the gap between existing provision and that aspired to through BOND is largest, meeting the target of improving healthcare in ALL Members, whether in BOND or not.

BOND will bring rapid interchange of information, skills and practice to shorten time to diagnosis, and treatment. BOND will develop, with PAGs, evidence/consensus-based guidelines to improve agreed outcomes in the 3 exemplar conditions, OI, XLH and ACH.

BOND HCPs will share clinical/phenotypic data within existing databases by developing tools to interrogate and combine data from these to create epidemiological surveillance registries, allowing improved understanding of interventions and co-morbidities at an individual level, and enabling refinement and standardization of diagnostic algorithms, management guidelines and outcomes. BOND will enable skill development through eHealth and Telemedicine platforms, alongside working visits, training courses and dissemination activities. BOND will work with PAGs in all activities to ensure patient-focused developments, with patient-reported outcome and experience measures to be adopted as specific outcomes against which to assess BOND performance in improving healthcare.

BOND will be instrumental for collaboration across Europe for clinical trials with novel orphan drugs, coordinated supportive care measures and translation of current research into patient benefit, alongside development of new approaches such as targeted (epi)genome editing that may be of great potential especially for the rare bone diseases. We anticipate interaction with and provision of expert advice to regulators and commissioners of care to define appropriate patient-centered outcomes for CTIMPs.

We expect that reduced time to diagnosis with fewer inappropriate tests, more accurate diagnosis and new viable treatments will be available within the 2-3 years and that the visibility of expert teams will be a magnet for attracting complex cases with improved communication allowing many more to receive their care locally with support from their expert HCP.

BOND will target less developed affiliate partners where the gap between existing provision and that aspired to through BOND is largest, meeting the target of improving healthcare in ALL Members, whether in BOND or not.

#### Strategic Plan

The ERN BOND brings together all rare diseases, essentially congenital, chronic and of genetic origin, that affect cartilage, bones and dentin. This considerable group of diseases present a significant variation in clinical outcomes and limited research program are currently available to clarify their physiopathological bases.

This large field may be shared in two main categories, skeletal dysplasia and metabolic bone diseases. These 2 categories themselves are subdivided in several thematic and sub thematic groups. The nosology and classification of genetic skeletal dysplasia delineated in 2015 more than 430 various rare disorders, (Bonafe et al. Am J Med Genet Part A, 2015) and more than fifty specific metabolic bone diseases, due to a disorder of mineralized tissues with bone involvement, but without official classification. Some disorders, such as osteogenesis imperfecta (OI) or Morquio disease belong to these two categories of disorders. Never the less, the principles of diagnosis, management and follow up are quite overlapping, giving a greater coherence and consistency for categorization.

The impossibility to consider all these diseases led our group to choose 11 main thematic groups, and, among these groups, to emphasize 3 major diseases that will be prioritized, serving as a starter/template for the 2 first years: Achondroplasia, Osteogenesis Imperfecta and X-linked hypophosphatemia. The rationale for choosing these leading diseases is based on 5 central arguments: 1/ disease frequency 2/ gravity of some devastating disorders, requiring an urgent improvement in early diagnosis and management 3/ difficulty and complexity of the diagnosis, requiring a dissemination of the diagnostic expertise and modern tools; 4/ difficulty and complexity in the treatment and management art, requiring also to ensure a better diffusion of symptomatic treatment or surgical techniques; 5/ current emergence of new drugs from basic research through translational research, or through biopharmaceutics research and development collaborations. Among the eleven main groups, nine are determined according to clinicalradiological symptoms entraining the diagnosis approach: 1/ short stature (disproportionate or not in mild forms), 2/ increased bone fragility, 3/ increased bone density, 4/ abnormal development of skeletal component, 5/ spondyloepi-(meta)-diaphyseal dysplasia, 6/ acromelic dysplasia, 7/ multiple dislocations 8/ dysostosis. Two are determined by following the physiopathological pathway, namely ciliopathies with major skeletal involvement and X-linked hypophosphatemia. Although prioritization of some diseases is mandatory for the implementation of BOND, it will of course be important to keep a larger view, and progressively to open the field to other ultrarare/"forgotten" other bone diseases. BOND ERN will establish European specific pathways, research programmers, and specific outcomes for patients in order to realize a European Health System.

To facilitate the organization of scientific activities and the management of the Network, in coherence with Annex 5 "BOND ERN Network Application Form", the Scientific activity of BOND ERN is structured in Working Groups (WG). Each WG will be headed and coordinated by an experienced principal investigator as WG Leader. They are responsible for the management of their WG scientific activities (see Chart 1 and 2).

luca.sangiorgi@ior.it

### OPPORTUNITIES IN RARE DISEASES AROUND THE WORLD

OPPORTUNITIES IN RARE DISEASES AROUND THE WORLD

Hugh Dawkins, Director, Office of Population Health Genomics, Public and Aboriginal Health Division, Department of Health Government of Western Australia

Public health relies on technologies to produce and analyse data, as well as effectively develop and implement policies and practices. An example is the public health practice of epidemiology, which relies on computational technology to monitor the health status of populations, identify disadvantaged or at risk population groups and thereby inform health policy and priority setting. These data and analytics are essential to driving health improvement across whole populations and targeting disadvantaged or at risk populations. Critical to achieving health improvements for the underserved population of people living with rare diseases is an early accurate diagnosis that can then lead to best medical care. In turn this requires that public health embrace new and existing technologies. In the rare diseases field, where the vast majority of diseases are caused by destructive but previously difficult to identify protein-coding gene mutations, the reduction in cost of genetic testing and advances in the clinical use of genome sequencing, data science and imaging are converging to provide more precise understandings of the 'person-time-place' triad. That is: who is affected (people); when the disease is occurring (time); and where the disease is occurring (place). Consequently we are witnessing a paradigm shift in public health policy and practice towards 'precision public health'. This is particularly important for people living with rare diseases and as with many fields of discovery, rare diseases are driving new knowledge generation and helping to inform health system change.

In this presentation, short vignettes will be used to illustrate how a new and emerging 'precision public health' paradigm is beginning to improve the experiences of patients living with rare diseases, their caregivers and families as they navigate the health system.

The conclusion to be drawn from this presentation is that the future of clinical genomics is already with us. It has been, and continues to be, driven by the needs of people living with rare diseases who seek a diagnosis so they might equitably access and experience the best care in our health systems. Most poignantly genomic public health should not be driven by technology; it is about individual and family needs, and the population health imperatives of early and accurate diagnosis, which is the portal to best practice care. Through the sharing of knowledge across global partnerships and networks, public health policies are being enacted that benefit people living with rare diseases, which at a very personal and local level is transforming health services and optimizing care pathways.

Hugh.Dawkins@health.wa.gov.au

#### THE COORDINATION OF RARE DISEASES RESEARCH IN EUROPE – THE EUROPEAN JOINT PROGRAMME ON RARE DISEASES.

OPPORTUNITIES IN RARE DISEASES AROUND THE WORLD

Daria Julkowska, E-Rare and the European Joint Programme on Rare Diseases. Agence Nationale de la Recherche – ANR; Health & Biology Department, Paris, France

RD research in Europe can be improved to overcome fragmentation, leading to efficacious use of data and resources, faster scientific progress and increase of competitiveness, and most importantly to decrease unnecessary hardship and prolonged suffering of RD patients.

In the specific context of the introduction of omics into care practice on one hand and of the ongoing structuration of RD care centers in European Reference Networks on the other hand, it appears crucial and timely to maximize the potential of already funded tools, projects and programmes by supporting them further, scaling them up, linking them together, and most importantly, adapting them to the needs of end-users through implementation tests in real settings. Such a concerted effort is necessary to develop a sustainable ecosystem allowing a virtuous circle between RD care, research and medical innovation.

The European Joint Programme Cofund is an instrument allowing high-level strategic organization and performance of research activities in an organized and transversal manner. Participation of Programme Owners (ministries) and Programme Managers (Research Funding and Research Performing organizations) accompanied by other relevant stakeholders like EU infrastructures, European Reference Networks, patients' organizations, regulatory bodies and private sector will ensure the necessary level of integration and unique strategy to efficiently tackle societal challenges. The ambition of the European Joint Programme for RD is to establish an urgently needed comprehensive strategy covering research, tools and clinics leading to optimization and exploitation of results, faster drug discovery at reduced costs, improved patients' care as well as giving Europe a leading role in the field of RD in the coming years. To achieve this goal, the European Joint Programme on RD will take the advantage of and integrate already existing programmes, tools and resources to further improve the integration, the efficacy, the production and the social impact of research on RD through the development, demonstration and promotion of Europe-wide and even world-wide sharing of research and clinical data, materials, processes, knowledge and know-how

Daria.JULKOWSKA@agencerecherche.fr

#### **#RAREVOLUTION: THE USE OF DIGITAL COMMUNICATION TO SUPPORT RARE DISEASE RESEARCH**

OPPORTUNITIES IN RARE DISEASES AROUND THE WORLD

Olivier Menzel, BLACKSWAN Foundation, Chemin de la Riaz 11, CH-1418 Vuarrens

The Internet and the use of social media have significantly changed the way rare diseases are diagnosed, studied, and treated. The web also helped people with rare diseases connect to others with the same condition and access information and support. The BLACK-SWAN Foundation has put at the heart of the #RAREvolution program the use of digital communication to empower the community of researchers working on rare diseases and to support them in connecting, learning and funding their projects as well as increasing awareness and advocacy for rare disease research.

The creation of the RE(ACT) Community in 2014 is part of this approach. The online platform is a tool at the service of researchers that facilitates international cooperation, knowledge sharing and the active participation of patients to research. The RE(ACT) Community is a virtual place where researchers can meet and share their knowledge at the same time as raising funds for their projects starting a crowdfunding campaign on the platform. Patients can share their health experience with researchers and provide important information to increase the scientific understanding of a disease.

The BLACKSWAN Foundation is also contributing through the #RAREvolution program to increasing awareness and advocacy at global level.

We are the RAREvolutionary people: Standup for scientific research

olivier.menzel@blackswanfoundation.ch

# **RARE DISEASES AND ORPHAN DRUGS**

OPENING CEREMONY

Silvio Garattini IRCCS Istituto di Ricerche Farmacologiche Mario Negri

Rare diseases have always been neglected considering the small number of patients involved. However, in 1983 the US Government introduced a law to stimulate the availability of therapies for rare diseases. The law incentivates the approval of so-called orphan drugs recognizing that all patients have the right to obtain efficacious and safe interventions. During the same period of time the Istituto di Ricerche Farmacologiche "Mario Negri" started a pioneer campaign to sensitize the public on this topic and to realize a structure (Centro di Ricerche Cliniche per le Malattie Rare "Aldo e Cele Daccò") devoted to provide information on rare diseases to patients, families and doctors. Furthermore, the Center has available facilities for clinical research integrating the pre-clinical research on orphan drugs already performed at "Mario Negri". Finally, in the year 2000, the European Commission approved to work on orphan drugs. After 18 years there is an opportunity to evaluate the results obtained. Even if the law has been very useful, it may be useful to discuss how it may be improved. Furthermore, the evaluation of the orphan drugs available reveals in several cases important pitfalls in terms of efficacy and safety. The paucity of research financing has determined an important gap between the number of drugs potentially "designed" as orphan drugs and the number of drugs approved for the market. Finally, the high cost of orphan drugs hampers the possibility of cure for many patients affected by rare diseases.

silvio.garattini@marionegri.it

#### ACADEMIC ENTREPRENEURS, NEW TECHNOLOGIES, AND BUILDING COMPANIES TO TREAT RARE DISEASES OPENING CEREMONY

Harvey F. Lodish Whitehead Institute for Biomedical Research, Massachusetts Institute of Technology, Boston Children's Hospital

Current research is enhancing our understanding of the genetic, molecular, and cellular bases of many rare human diseases. Translating these discoveries into actual drugs and diagnostics requires establishment of for-profit companies and often depends on entrepreneurial academic researchers as well as patient and disease based organizations. New types of therapeutics are entering clinical practice, including cell therapies such as replacement cells (e.g. insulin-producing islets) and engineered cells such as CAR-T cells. Gene therapies, including nucleic acid-based drugs and viral mediated gene transfer, are progressing rapidly. Together, these provide opportunities for understanding and treating heretofore-untreatable diseases. I will begin by describing my own experiences in helping start Genzyme and Millennium, focusing on the development of an enzyme replacement therapy for Gaucher Disease. More recently I was the scientific founder of Rubius, a Flagship Pioneering company that uses gene- modified red blood cells, produced in culture, to treat many diseases. I will focus on Rubius' first product, a therapy for phenylketonuria (PKU), as well as work from my own laboratory on the use of modified red cells to treat autoimmune disorders. I will discuss several companies that have become successful by developing drugs to treat specific rare diseases. Several have developed nucleic acid- based therapies for diseases such as Duchenne muscular dystrophy and Spinal Muscular Atrophy Type I. Yet others are working with research hospitals to develop successful gene therapies for diseases such as hemophilia, thalassemia, Wiskott - Aldrich Syndrome, Childhood Cerebral Adrenoleukodystrophy, Sickle Cell Disease, Batten Disease, and hereditary blindness. I will review significant fundamentals for starting and developing successful biotech companies, including the importance of geographical proximity of research universities and hospitals with a cluster of biotech companies and venture capital firms. I will stress the importance of an entrepreneurial faculty and a top scientific advisory board and board of directors. Having experienced biopharmaceutical leaders is essential, as is proprietary and protected intellectual property and a solid business plan. Additionally, one needs solid financial backing, usually by venture capital but often by patient support groups, as well a supportive infrastructure including a helpful government and regulatory environment.

lodish@wi.mit.edu

#### LARGE-SCALE SEQUENCING OF INBREED POPULATIONS AND THE COMPENDIUM OF MUTATIONS CAUSING RARE DISORDERS

NGS AND UNDIAGNOSED RARE DISEASES

Xavier Estivill and Qatar Genome Program Consortium Sidra Medicine Research Center, Doha, Qatar

Nearly two-thirds of the genetically transmitted diseases in Middle East countries follow an autosomal recessive mode of inheritance, and consanguineous marriages are considered a significant factor contributing these condition. Recessive mutations causing inherited metabolic diseases are considered to be very significant and some of them are implemented in the newborn screening programs. The Qatar Genome Project (QGP) aims to sequence the whole set of the Qatari nationals with the goal of developing personalized medicine for medical prevention, diagnosis and treatment of diseases. Qatar BioBank (QBB) is a biomedical platform for health research through the collection of samples and information on health and lifestyle from large numbers of members of the Oatari population. The pilot phase of the QGP has produced the deep coverage whole genome sequence (WGS) data of 6000 Qataris, along with dense microarray genotyping and detailed information of their anthropometric, clinical and biological features, as well as their health related phenotype. This defines an excellent reference dataset that will be utilized as controls for genomic investigations on specific health-related phenotypes that are prevalent in the Qatari population. The description of the genomic landscape of the Qatari population should help to define carrier genetic programs and will facilitate research on common traits and complex genetic disorders in Oatar. The knowledge that will be generated from the complete characterization of the genome of the 6000 participants in the QBB could also be extended to the global community of Arab countries. We anticipate that the project legacy will lead future research efforts on birth defects, developmental and disability disorders, rare diseases and complex disorders in Qatar. The future of the research activities in this field will involve a systematic molecular characterization of every person affected by these disorders, and their family members. This research effort will provide the scenario for a new dimension for the diagnosis, prevention and treatment of birth defects, developmental and disability disorders, rare diseases and complex diseases in Qatar.

xestivill@sidra.org

# IMPACT ON NGS IN DAILY PRACTICE IN AUTOINFLAMMATORY DISEASES

NGS AND UNDIAGNOSED RARE DISEASES

Marco Gattorno. UO Pediatria 2, G. Gaslini, Genova, Italy

Systemic AutoInf ammatory Diseases (SAID) are a growing number of monogenic and multifactorial conditions secondary to deregulation of mechanisms controlling innate immune responses and are characterized by sterile inf ammation. Originally these disorders were limited to a handful of rare monogenic diseases (recurrent fevers). Thanks to the great improvement in genetic diagnostic techniques, the number of known associated genes and associated autoinf ammatory phenotypes has have dramatically expanded Depending on the pattern of inheritance, the identification of one or two mutations with a known pathogenic impact and high penetrance represents an essential final step for the diagnosis of SAID. However, in a considerable proportion of cases (70-80%) molecular analysis is unable to provide diagnostic confirmation (i.e. presence of a single mutation in autosomal recessive disorders, low-penetrance mutations, functional polymorphisms or novel variants of unknown functional impact). This is important because a delay in a proper diagnosis, further delay timely treatments leading to irreversible organ damage. The Next Generation Sequencing (NGS) approach has proven to be a successful strategy for inducing a marked acceleration in rare disease gene discovery, improving clinical diagnosis, providing insight into biological mechanisms, and increasing therapeutic opportunities. Indeed, NGS represents a potential revolutionary diagnostic tool for genetic conditions, allowing the simultaneous analysis of different genes associated to a given group of inherited disorders. Moreover, NGS allows the detection of somatic mosaicism, as demonstrated in patients presenting a typical clinical phenotype, but are negative for germ-line mutations. Such NGS could present an approach to enables a definitive diagnosis in some patients with monogenic SAID, but in other cases the results can be inconclusive or even misleading. Therefore, the definitive diagnosis and classification of inherited SAID should rely on the careful interpretation of results derived from several complementary molecular analyses, in the light of the clinical phenotype. So far, formal diagnostic criteria have been developed for a few SAID, but their accuracy has not been confirmed in different ages and populations. In spite of our increasing understanding of the molecular mechanisms of SAID, there is still a large number of individuals with a clinical diagnosis of SAID and but without mutations in known disease causing genes. In this lecture we will analyze the main technical issues associated to the possible application of NGS technique in daily practice and the possible difficulties in the interpretation of the results coming from the simultaneous analysis of different genes.

marcogattorno@gaslini.org

### NEXT NGS APPROACHES TO THE UNSOLVED: TELETHON UNDIAGNOSED PROGRAM.

NGS AND UNDIAGNOSED RARE DISEASES

Next NGS approaches to the unsolved: Telethon Undiagnosed Program.

Vincenzo Nigro, Telethon Institute of Genetics and Medicine (TIGEM) - via Campi Flegrei, 34 80078 Pozzuoli, Dipartimento di Medicina di Precisione, Università della Campania "Luigi Vanvitelli"

NGS has revolutionized our approach to genetic diseases, from a single gene testing, to the genome studies. In 2016, Telethon has launched the first Undiagnosed Diseases Program (UDP) in Italy, a pilot program aimed at clinical and genetic standardized analysis of pediatric patients with unsolved severe conditions.

The pilot program has built the most accurate and sustainable strategy to solve undiagnosed diseases with childhood-onset and the discovery of new disease genes. The program is centered at the Telethon Institute of Genetics and Medicine -TIGEM- (Pozzuoli) where NGS activities converge. It relies on a growing network of a dozen of clinical centers. From April 2016, all Italian physicians can candidate their patients through a specifically developed web tool or through the network of clinical centers. Patients with unrecognizable genetic syndromes undergo a detailed annotation using Phenotips and selected cases are then discussed in clinical plenary sessions. Cases are recruited for trio/guartet whole exome analysis. We compared different WES strategies and adopted a complete whole exome enrichment with a target of ~70Mb and a coverage of ~200x. Results are shared mainly using Phenome Central to recognize more patients with the same genetic disease. We also optimized the bioinformatic pipeline obtaining a success rate of 50% in over 120 families, by identifying 60% of de novo causative variants. However, we developed a next approach for the still negative cases. We designed a "ultra exome" probe collection to be used in connection with the 10x Genomics. This produces a partitioning of high molecular weight DNA fragments (HMW-gDNA) into micelles, along with an adapter molecule and a barcode sequence. With this strategy, WES are fully covered and phased and even small structural variations may be detected. The Italian Telethon UDP team is part of UDNI.

vinnigro@gmail.com

# THE CIRCLE OF NGS INNOVATION: FROM RESEARCH TO DIAGNOSTICS AND BACK

NGS AND UNDIAGNOSED RARE DISEASES

Lisenka ELM Vissers, PhD Dept of Human Genetics, Radboud UMC, Nijmegen, The Netherlands

The last decades, technological innovations with increasing overall diagnostic yield, such as microarray-based copy number screening and whole exome sequencing (WES), have been the main driver to implement these tests into daily clinical practice. During this presentation I will discuss a 5-year clinical utility study on the diagnostic implementation of WES in routine diagnostic care, and will show examples of how clinical WES has increased diagnostic vield for rare genetic disease, and of how it has led to new insights in disease mechanisms. First, I will address a clinical utility of WES in complex pediatric neurology where we analyzed 150 patients presenting with complex neurological disorders of suspected genetic origin. In a parallel design, all patients received both the standard diagnostic workup and WES simultaneously. This unique design allowed direct comparison of diagnostic yield of both trajectories and provided insight into the economic implications of implementing WES in routine clinical practice. I will highlight how WES identifies up to five-fold more significantly more conclusive diagnoses than the standard care pathways, without incurring higher costs. Second, large-scale collection of WES in routine clinical care also fosters new scientific research projects. Here, I will show examples of novel statistical frameworks allowing disease-gene identification using meta-analysis of large scale WES data obtained in routine clinical care. I will show how two approaches using gene specific mutation rates, and mutation cluster analysis identified >15 novel genes underlying neurodevelopmental disorders, and how these analyses provided insight into the patho-physiological mechanisms underlying genetic disease. Finally, I will show our first lessons learnt from interpretation of de novo non-coding mutations in intellectual disability obtained using whole genome sequencing. Taken together, I will describe our experience with the circle of NGS innovation, pushing both clinical diagnostics and research forward.

Lisenka.Vissers@radboudumc.nl

## CAID SYNDROME: IN SEARCH OF A DRUGGABLE MOLECULAR SIGNATURE FOR A NOVEL RARE DISEASE

PATHOPHYSIOLOGY

Gregor Andelfinger, Service of Cardiology, Department of Pediatrics, Sainte Justine University Hospital Center, Université de Montréal Laboratory of Cardiovascular Genetics, Sainte Justine UHC Research Center, Canada

Cohesinopathies include an increasing number of syndromes with various phenotypic manifestations resulting from mutations in components of the cohesin complex or its requlators. The prototypical condition among these syndromes is Cornelia de Lange syndrome (CdLS), which is caused by mutations in genes encoding cohesin complex components.

We have recently described an autosomal condition consisting of progressive loss of all pacemakers in the heart and gut, termed chronic atrial and intestinal dysrhythmia, CAID syndrome (OMIM 616201). Affected patients exhibit sick sinus syndrome (SSS), atrial dysrhythmias and chronic intestinal pseudoobstruction (CIPO). Clinically, this disorder can be viewed as a progressive failure of all pacemaking tissues, the sinoatrial (SA) node in the heart and the interstitial network of Cajal (ICC) in the gut.

By whole-exome sequencing, we determined that a single shared homozygous founder mutation in SGOL1, namely K23E, causes CAID syndrome in all patients. Consistent with the known roles of SGOL1, we found that cultured dermal fibroblasts from affected individuals showed accelerated cell cycle progression, a higher rate of senescence and the typical railroad appearance of a centromeric cohesion defect. In addition, we found evidence of enhanced activation of TGF-signaling.

Interestingly, the phenotypic manifestations observed in CAID differ from the ones observed in most other cohesinopathies. CAID patients do not exhibit growth deficiency or retardation. Furthermore, whereas the majority of cohesinopathies are manifest at birth with major developmental defects, this is not the case in CAID syndrome.

We have therefore proceeded to further dissect the molecular signature of CAID syndrome by proteomics, RNAsequencing, epigenomics and functional studies in SGOL 1 K23E fibroblasts. Remarkably, we can now identify several main areas that exhibit significant dysregulation: cell cycling, including several genes involved in other cohesinopathies (e.g., RAD21, ESCO2), smooth muscle contraction / ion channels, and TGFb signalling. We suggest that CAID syndrome results from perturbation of typical functional cascades found in CIPO and arrhythmias through an epigenetic mechanism. Future studies will target the same underlying pathways to obtain a reversal of the in vitro phenotypes.

gregor.andelfinger@recherche-ste-justine.gc.ca

#### PATHOPHYSIOLOGY AND THERAPEUTIC DEVELOPMENTS IN PROGEROID SYNDROMES PATHOPHISIOLOGY

Nicolas Lévy, Département de Génétique Médicale et Biologie Cellulaire, Hôpital d'Enfants La Timone, Marseille, France. 2Inserm UMR\_S 1251, « Marseille Medical Genetics Center » Faculty of Medicine, Marseille, France.

In the last 15 years, we have identified genes and mutations involved in premature aging syndromes. While the use of NGS technologies recently implemented these discoveries. parallel explorations were conducted to identify both pathophysiologic mechanisms and therapeutic targets. In this context, Hutchinson-Gilford Progeria Syndrome (HGPS) and related Prelamin A defective maturation disorders, very rare and severe segmental premature aging and accelerated syndromes were explored and several therapeutic targets were identified. In 2003, our group identified in the LMNA gene, encoding the ubiguitous nuclear proteins Lamins A/C, a recurrent, dominant mutation causing most HGPS cases. This de novo mutation activates a cryptic pre-mRNA splicing site leading to the production of a truncated Lamin A precursor called "progerin". Progerin cannot be fully posttranslationally processed, remains aberrantly prenylated and accumulates in cells' nuclei, where it exerts several toxic effects. In the last years, we were able to demonstrate a link between other nosologic entities classified as progeroid syndromes and defective prelamin A processing, either caused by mutations LMNA or its main post-translational processing enzyme. Preclinical studies in vitro on patients' cells and in vivo from animal models generated in the lab, provided proofs-of-principle that toxicity, production or degradation of Prelamin A/Progerin isoforms could be targeted by different approaches and molecules. The combined use of prenylation inhibitors, statins and amino-bisphosphonates (N-BPs), could improve the natural course of the disease, ameliorating several disease parameters, including growth, bone density and survival. The beneficial effects of these drugs could be ascribed to the reduction of Progerin prenylation levels, as well as, probably, to their specific pharmacological activities. These data allowed to launch a phase II European trial on 12 European children affected with Progeria. This combination ameliorated several primary and secondary endpoints including weight, bone density and turnover and cardiovascular risk parameters and seems to favorably impact the natural course of this devastating disease, with potential wider impacts in the field of aging. In collaboration with Pr. Carlos Lopez-Otin, our Progeria mouse KI model was validated for Splicing directed intervention using Antisense oligonucleotides, reducing progerin/Prelamin production, and will be translated in a new trial in children affected with Progeria and associated disorders. Finally, we have recently identified proteasome inhibitors from the MG family with a strong potential to reduce Progerin transcription and drive the specific elimination of the remaining produced protein through autophagy. Toxicity and efficacy were assessed in vitro and in vivo, showing a strong efficacy of these molecules, and these results will be translated in clinics after the pre-clinical validation steps and regulatory affairs are achieved.

nicolas.levy@univ-amu.fr

### MULTI-OMICS ANALYSIS POWERED BY MASSIVE DATA INTEGRATION

PATHOPHYSIOLOGY

Kristina Hettne1, Roula Tsonaka1, Mohammed Charrout1, Olga Veth1, Alexandre Seyer2, Eleni Mina1, Peter A. C. 't Hoen1, Annemieke Aartsma-Rus1, and Pietro Spitali1 1Leiden University Medical Center, The Netherlands 2Profilomic, France

There is great hope in the rare disease scientific community that multi-level omics approaches, including transcriptomics, proteomics and metabolomics, will increase our understanding of physiological and pathological processes behind rare diseases and provide new avenues into patient management and treatment. For example, transcript, protein and metabolite bio-signatures or biomarkers in blood, urine or disease-related tissues can be correlated with disease severity or progression. Here, peripheral tissue deserves special attention since for some diseases like Huntington's disease that affects the brain, the disease tissue is unavailable for study, and for Duchenne Muscular Dystrophy, affecting the muscle, biopsies are invasive for the patient but needed for pathophysiologic, dose finding and proof of concept studies. Development of integrated approaches for data analysis and interpretation linking transcript, protein and metabolite bio-signatures to clinical phenotypes is desperately needed. We developed a method to construct multi-omics bio-signatures for disease severity and progression, and tested our method in a study on Dystrophin-deficient mdx mice, mdx mice have been used to study the downstream effect of lack of dystrophin and to develop therapeutic strategies. The main goal of this study was to find biomarkers for disease severity by comparing the blood metabolome, lipidome and transcriptome of the mdx, mdx/utrn+/+, mdx/utrn+/- and wild type (wt) mice. Additional goals were to identify biomarkers for disease progression and biomarkers in blood that ref ect specific aspects of the disease in muscle. This longitudinal study included 5 time points. Mice were fasted before samples collection of blood and muscle, which was performed at sacrifice. Blood samples were collected at all time points, and muscle samples at the last time point. Plasma was collected at all time points to measure metabolites and lipids, and full blood was collected in RNA-preserving tubes for RNA-seq. The metabolome and lipidome were measured using Liquid chromatography-mass spectrometry. The blood and muscle transcriptome was measured using paired-end 125bp Illumina sequencing. We performed Weighted Gene Co-expression Network Analysis (WGCNA) per time point on each -omic dataset to establish groups of molecules (modules) that share a similar co-expression pattern (genes) and a similar concentration pattern (metabolites and lipids). Euretos (http://euretos. com/) was used for module annotation, enabling the coupling of Gene Ontology terms to metabolites and lipids through indirect relations. Euretos includes information from more than 200 public databases and information text-mined from the scientific literature. The metabolomics data revealed statistically significant modules in week 6 between the mdx/utrn+/+ vs mdx/utrn+/- groups, possiblyref ecting disease severity. Pooling of dystrophic groups (mdx, mdx/utrn+/+, mdx/utrn+/-) resulted in statistically significant metabolite modules between the wt vs dystrophic groups in week 6, 12, 18 and 24. statistically significant lipid modules in week 12 and 18 and statistically significant gene modules in week 6. Multi-omics integration was enabled through cross-correlation of modules between the lipid and metabolite datasets, revealing statistically significant module combinations between the wt vs dystrophic groups in week 12. To investigate changes in the transcriptome between dystrophic blood and muscle tissue WGCNA modules were correlated at the last time point, revealing statistically significant module combinations.

K.M.Hettne@lumc.nl

#### THE ROLE OF ENDOPLASMIC RETICULUM -MITOCHONDRIA CROSSTALK IN AXONAL MAINTENANCE

PATHOPHYSIOLOGY

Roman Chrast, Karolinska Institute, Stockholm, Sweden

Inherited peripheral neuropathies (Charcot-Marie-Tooth diseases, CMTs) invariably lead to disrupted axonal function in the peripheral neural system of affected individuals. Multiple rodent models of both axonal and demyelinating forms of CMT are available and provide excellent paradigms to study mechanisms implicated in axonal maintenance. I will discuss the recently generated data indicating that interactions between mitochondria and endoplasmic reticulum at the level of mitochondria-associated membranes (MAMs) play a particular role in the pathophysiology of neuropathies. In particular, changes in MAMs contribute to calcium homeostasis impairment, ER stress activation and defects in mitochondrial transport in affected neurons/axons. These results highlight the importance of MAMs for maintenance of PNS integrity and may provide new ideas for therapeutic strategies for neurodegenerative diseases.

roman.chrast@ki.se

# HAPLOID STEM CELLS

GENE AND CELL THERAPY

Josef Penninger, Institute of Molecular Biotechnology, Vienna Austria

With the advent of large scale genomics or gene expression efforts, hundreds of genes have been identified with potential roles in normal development and disease pathogenesis such as inf ammation. One key question is to validate essential genes involved in fundamental physiology and disease from genes and pathways that serve bystander functions. We have developed the first haploid embryonic stem cells and technologies for genome-wide mutagenesis that can be used for rapid forward genetics experiments. In essence we can now saturate mutagenesis of the entire genome in a single day. We can also use the power of stem cell biology for reverse genetics experiments and have already developed more than 70000 haploid ES cell clones that carry defined integrations of bar-coded and repairable vectors. I will present examples for both forward and reverse genetics screens. Thus, we can combine the power of a haploid mammalian genome with the differentiation potential of embryonic stem cells. We also developed a novel approach to advance the identification of glycosylated proteins at a global scale.

Josef.Penninger@imba.oeaw.ac.at

# SMALL ANTIBODY FRAGMENTS AS ALTERNATIVE TOOLS IN HAEMOPHILIA CARE

GENE AND CELL THERAPY

Peter Lenting, Institut National de la Santé et de la Recherche Médicale, University Paris-Sud, University Paris-Saclay, Le Kremlin-Bicêtre, France.

The functional absence of coagulation factor VIII (FVIII) is associated with a severe bleeding disorder, known as haemophilia A, affecting 1-2 per 10,000 males. Clinical management mainly involves replacement therapy using purified FVIII concentrates. Due to a number of disadvantages of this approach (frequent intravenous infusions, development of inhibitory antibodies, high costs), there is a strong medical need for the development of novel therapeutic strategies. The aim of the present project is to develop in parallel a low-cost protein therapy and an innovative AAV-based gene therapy approach for haemophilia A using single domain antibody fragments (nanobodies). Nanobodies have several advantages, including a low (if any) immunogenicity when applied to humans. Further, their small size (±17 kDa) facilitates their molecular engineering and the incorporation of their cDNA in viral particles. Nanobodies will be generated that target natural anticoagulants. Inhibition of these anticoagulants restores the defective thrombin generation capacity in haemophilic mice. Analysis of a first series of anti-anticoagulant nanobodies revealed full restoration of thrombin generation in haemophilic plasma and reduce blood loss in haemophilic mice. In this research program, the SMART-HaemoCare consortium will explore two different modes of nanobody delivery: protein administration and gene transfer. The first approach will focus on the development of subcutaneous delivery, leading to an improved low-cost treatment regimen. The second approach provides the potential of a long-term therapeutic solution to minimize bleeding in haemophilia.

peter.lenting@inserm.fr

# DISSECTING THE BIOLOGY OF LYMPHEDEMA-DISTICHIASIS

GENE AND CELL THERAPY

Tatiana Petrova, Department of Fundamental Oncology, Ludwig Institute for Cancer Research, University of Lausanne, Epalinges, Switzerland.

Vertebrates have two vascular systems, both of which are indispensable for life: blood vessels, which bring oxygen and nutrients to the tissues, and lymphatic vessels, which remove proteins and excess of f uid from the interstitial space and return them back to the blood circulation. Lymphatic vessels are also important regulators of the immune response, as they transport antigens and immune cells to lymph nodes. Damage of lymphatic vasculature results in the development of lymphedema, a chronic debilitating disease characterized by the excessive tissue swelling, fibrosis and decreased immune response. We focus our research on a rare hereditary form of lymphedema, lymphedema-distichiasis, caused by the mutated forms of forkhead transcription factor FOXC2. We use a combination of the in vivo genetic approaches and in vitro studies of mechanotransduction to establish the hierarchy of molecular events regulated by FOXC2 in lymphatic vessels, in order to understand the pathophysiology of lymphedema-distichiasis and to develop better diagnostic and treatment approaches.

tatiana.petrova@unil.ch

## GENE SILENCING THERAPY FOR HUMAN NEURODEGENERATIVE DISEASE

NEUROLOGICAL DISEASES

Don W. Cleveland Ludwig Institute and Department of Cellular and Molecular Medicine, Univ. of California at San Diego, La Jolla, CA

The genes whose mutation causes human neurodegenerative disease are widely expressed within neurons and non-neurons of the nervous system, producing damage not only within the most vulnerable neurons but also within their partner neurons and. Sustained gene silencing or altered pre-mRNA splicing broadly within neurons and non-neurons throughout the nervous system has been achieved using a clinically feasible "designer DNA drug" injection of antisense oligonucleotides into the nervous system. Single dose injection of an ASO has been shown to produce sustained, catalytic (RNase H-dependent) RNA degradation of a target mRNA, thereby producing slowing of disease progression for inherited ALS in rodents or sustained partial disease reversal for Huntington's-like disease. An ASO that corrects the splicing of the SMN2 gene has been approved as an effective therapy for spinal muscular atrophy (SMA), one of the most abundant childhood inherited diseases. Hexanucleotide expansion in the C9orf72 gene is the most frequent cause of both ALS and the second most frequent human dementia, frontal temporal dementia. Single dose ASO infusion has been demonstrated to catalyze selective destruction of repeat-containing C9ORF72 RNAs, without targeting mRNAs encoding the C9ORF72 protein. Efficacy of ASOs in lowering expression or altering splicing of tau mRNA has been demonstrated, and clinical trials are now likely with ASOs in Alzheimer's disease and chronic brain injury. Finally, an extension of this approach is development of synthetic CRISPR RNAs to induce transient activation of Cas9 nuclease to cleave and permanently inactivate a selected target gene.

dcleveland@ucsd.edu

#### THE LESSON OF RARE NEUROLOGIC DISEASES TO CLINICAL NEUROLOGISTS AND NEUROSCIENTISTS FOR UNDERSTANDING NORMAL AND PATHOLOGICAL NERVOUS SYSTEM FUNCTIONS

NEUROLOGICAL DISEASES

Antonio Federico, Dept Medicine, Surgery and Neurosciences, Medical School, University of Siena, Siena, Italy

The majority of rare diseases have symptoms involving central, peripheral nervous system and muscle and neurologists have an important role in the recognition of these disorders and in their treatment. We here will report some speculations about what Rare Neurologic Diseases may teach to Clinical Neurology and to Neurosciences, for better understanding normal nervous system functions and dysfunctions.

a) Minor clinical findings in heterozygous carriers in recessive diseases

The finding that heterozygous carriers of Gaucher's mutations may have an higher incidence of Parkinson's diseases and that glucocerebrosidase activity interacts with synuclein in the brain has been reported from several years. Similarly, Nieman Pick type C patients have protein tau and amyloid deposits in the brain similar to Alzheimer disease and increase of susceptibility for dementia is present in heterozygous subjects. Several other neurometabolic genetic diseases have shown evidences that low enzyme activity in carrier range may be a susceptible factor for minor pathological conditions. b) Clinical heterogeneity

This is well known in many genetic conditions related to the presence of multigene regulation, to different molecular changes in the principal gene (point mutation, deletion, intron, etc) or to epigenetic factors. The gender inf uence in the clinical severity may suggest that some endocrine factor could also be involved.

c) Discover of new proteins and new genes

This is true for many conditions, ataxin for ataxia, huntingtin for Huntington's chorea, dystrophin for Duchen Muscular dystrophy, prion proteins, and more recently survivin, etc. The list of new proteins discovered in many rare genetic neurologic disorders is very long and stimulates the research on their role in normal physiology; it is also an useful mean to correlate the findings with the clinical data when these proteins are impaired.

d) Selective vulnerability to several cell system (basal ganglia, dentate nucleus, oligodendrocytes, astrocytes, neurons, small vessels, spinal tracts, etc) to a primary metabolic genetic defect.

We have conditions presenting mainly with leukoencephalopathy related to primary oligodendrocyte or astrocyte defect, with cortical atrophy or epilepsy related to neuronal loss, with ataxia due to primary cerebellar cell atrophy, with pyramidal tract degeneration, with extrapyramidal symptoms, etc., in relationship to a primary dysfunction of a selective cell system, suggesting that a different metabolic rate is present in the different brain areas with a different vulnerability.

e) The opening of the possibility of pathogenetic treatments

Therapeutic approach to rare neurologic diseases started by A) decreasing levels of toxic metabolites by diet B) removal toxic substrates by transfusions, plasmapheresis, peritoneal dyalisis and drugs C) substitution of deficient metabolites (Leucocyte and plasma infusions; organs transplantations; fibroblasts transplantations; bone marrow transplantation); D) direct supply of deficient metabolite E) enzymatic induction by coenzymes F) enzyme therapy. More recently gene therapy is a reality for many conditions.

f) The application of the new molecular genetic analysis (NGS,GWG, etc)

This will open a new era for neurologists, giving a pathogenetic answer to many undiagnosed cases enlarging the clinical spectrum of the diseases.

federico@unisi.it

#### IN SEARCH OF A THERAPY FOR CREUTZFELDT-JAKOB DISEASE: IDENTIFICATION OF CHEMICAL CHAPERONES THAT STABILIZE THE PRION PROTEIN PRP

NEUROLOGICAL DISEASES

Jesus Requena, CIMUS Biomedical Research Institute, University of Santiago de Compostela-IDIS, Santiago de Compostela, Spain.

Genetic Creutzfeldt-Jakob disease (CJD) is a rare fatal neurodegenerative disease caused by mutations in the human prion protein gene (PRNP). Its key pathogenic event is conversion of the cellular prion protein (PrPC) into an aggregated form (PrPSc) that self-propagates by imposing its abnormal conformation onto PrPC molecules. In the absence of a mutation, a subset of PrPC molecules can also spontaneously convert to PrPSc, a very rare molecular event, causing sporadic CJD. Finally, under rare circumstances. PrPSc can transfer between brains, for example iatrogenically, such as with the use of neurosurgical material contaminated with PrPSc. The subsequent capacity of PrPSc to drive conversion of PrPC into PrPSc in the recipient brain confers an infectious nature to it, i.e, PrPSc is a prion. Previous attempts to identify anti-prion compounds aimed to reduce the load of PrP aggregates by decreasing their stability or increasing their clearance. Some of these compounds showed activity in vitro, but little or no efficacy in vivo. Substantial evidence supports the notion that PrPC loses its native fold in the initial steps of the aggregation process. This concept provides a rationale for tackling PrPC aggregation by stabilizing the monomeric protein precursors, instead of disrupting PrPSc species. The underlying idea is to block aggregation by increasing the Gibbs free energy barrier (G) required for the initial misfolding events. This goal could be achieved with small, high affinity ligands of PrPC, i.e., pharmacological chaperones. To identify such compounds, we developed a screening method based on Dynamic Mass Redistribution (DMR), a label-free, fully automated biophysical technique performed on 384-well microplates, and capable of detecting molecular interactions at the equilibrium. We then applied the method to screen the Prestwick library of chemical compounds, all FDA-approved drugs. We identified two compounds Chp1 and Chp2, showing high binding affinity towards recombinant PrP folded into the PrPC native conformation. We then tested the ability of these compounds to inhibit PrPSc propagation in vitro, using protein misfolding cyclic amplification (PMCA), a technique that mimics PrPC conversion to PrPSc in vitro. Positive inhibitory power in both cases encouraged us to test their anti-prion properties in cell models. Again, both compounds exhibited strong anti-prion properties. Our next step will be to test these compounds in animal models of CJD.

jesus.requena@usc.es

## PROGRESS IN HUNTINGTON'S DISEASE: DRUGS, BIOMARKERS AND COMMUNITY

NEUROLOGICAL DISEASES

Edward Wild, MRC Clinician Scientist, UCL Institute of Neurology; Honorary Consultant Neurologist, National Hospital for Neurology & Neurosurgery, Queen Square, London WC1N 3BG, UK

Recent months have seen highly encouraging reports of progress towards therapeutics to slow or prevent Huntington's disease. These have been empowered by over a decade of preclinical drug development in parallel to natural history cohort studies of patient volunteers. Together these enable effective testing of safety and target engagement in early clinical trials. Here I review the progress that brought us to this pivotal point, consider future prospects, and contemplate how other rare diseases may benefit from the Huntington's experience.

e.wild@ucl.ac.uk

# ABSTRACTS

#### ORPHANET TOWARDS FAIR DATA FOR BETTER INTEROPERABILITY

ABSTRACT N° A002\_2018 / OPPORTUNITIES IN RARE DISEASES AROUND THE WORLD

Marc Hanauer1, Fanny Rigour2, Charlotte Rodwell1, Ana Rath1 1 INSERM, US14 – Orphanet, Paris, France 2 CNRS, IFB core, Orsay, France

In the field of rare diseases (RD), data is still scattered across several silos: data from the domains of care and research, genotypic and phenotypic data, different formats and languages, and finally across countries. The scarcity of patients and necessity of pooling resources has led the rare disease community to agree on data sharing principles. To optimise data sharing and the benefits to be gained from it, the RD community needs to push the sharing process further and adopt the FAIR Principles. The data must be: a) Findable: Easy to find for humans and computers, with metadata to facilitate searches; b)Accessible: Easily to access and/or download with well-defined licence and access conditions; c) Interoperable: Ready to be combined with other datasets by humans or computers; d) Reusable: Ready to be further processed using computational methods or used for future research. The FAIR Principles put specific emphasis on enhancing the ability of machines to automatically find and use the data, in addition to supporting its reuse: this promotes data integration from disparate resources. Since 2012, Orphanet shares data on its platform Orphadata providing data sets extracted from the database in reusable formats (XML, JSON, OWL). Orphanet will improve on these efforts by providing a FAIR access point to the data. To implement these principles, Orphanet provides semantic models and metadata to describe all datasets that are available, as well as the conditions of access and data licence agreement if needed. This metadata will optimise the discovery and reusability of data. A full description of the context in which the data were generated is necessary for potential end-users to evaluate their utility and relevance. Orphanet intends to setup a FAIR Data Point (FDP) for Orphadata, thus publishing its FAIR metadata and enabling discovery of this data. A FDP is software with a graphical user interface (GUI) and an Application Programming Interface (API). This allows data owners to provide datasets in a FAIR manner and allows data users to discover metadata and, if licence conditions allow, the actual data can be accessed. In order to provide our FAIR Data Point compatible with the FAIR DATA Ecosystem, we will use the DTLS (Dutch Techcentre for Life Sciences) "Data FAIR Port" interoperability platform, which provides several relevant tools including the creation and curation of metadata, as well as the publication of the FAIR Data Point.

marc.hanauer@inserm.fr

# A FACE IN THE CROWD: DOES DIAGNOSTIC CROWD SOURCING REALLY USE AN ANONYMOUS WISDOM?

ABSTRACT N° A003\_2018 / OPPORTUNITIES IN RARE DISEASES AROUND THE WORLD

Shmuel Prunts, MD & MPH, Clalit Haltn Service, Israel

BACKGROUND: Diagnostic challenge of orphan diseases has extra ordinally long time. A theoretical base point to physicians' crowd sourcing online as aim to fast achievement of a right diagnostic assumption for rare ones. METHODS: I checked presentations of undiagnosed pediatric cases made by doctors on SERMO – one of the biggest physician network worldwide. The survey included all undiagnosed children's cases presented in the site between 01.04.14 - 31.03.15. Every discussion was investigated for amount of its participants, number of independent diagnostic assumptions, the time from presentation to last assumption and result of crowd solving. RESULTS: 172 children with underdiagnosed diseases were presented for crowd sourcing by SERMO members during the survey's period. 55 (32%) of them got right diagnosis and an additional 25 (14.6%) were almost recognized. Average amount of participants per discussion was 14 (range 2-32), average independent assumptions number were 5 (range 1-11). Even though longest time for last diagnostic assumption was 26 days, an average time for this was so short as 3 days. CON-CLUSION: There is small number of physicians amongst the online community members that are actively participating in the online diagnostic challenge. However, their participation yields excellent results for fast case solving of underdiagnosed young patients.

andyc4pr@gmail.com

#### INTEGRATIVE ANALYSIS OF GENOMIC DATA REPOSI-TIONS THE USE OF 5'-AZACYTIDINE AND DECITABINE IN BLASTIC PLASMACYTOID DENDRITIC CELL NEO-PLASM TREATMENT

ABSTRACT N° A004\_2018 / OPPORTUNITIES IN RARE DISEASES AROUND THE WORLD

Maria Rosaria Sapienza1\*, Francesco Abate2.3\*, Federica Melle4, Stefania Orecchioni5, Fabio Fulioni6, Marvam Etebari1. Valentina Tabanelli4. Maria Antonella Laginestra1. Alessandro Pileri7.8. Giovanna Motta4. Maura Rossi1. Claudio Agostinelli1, Elena Sabattini1, Nicola Pimpinelli8, Mauro Truni9, Brunangelo Falini10, Lorenzo Cerroni11, Giovanna Talarico5, Rossana Piccioni12, Stefano Amente13, Valentina Indio14, Giuseppe Tarantino14, Francesco Brundu2, Marco Paulli15, Emilio Berti16, Fabio Facchetti17, Gaetano Ivan Dellino12,18, Francesco Bertolini5, Claudio Tripodo19\*, Raul Rabadan2,3\*, Stefano A. Pileri4,20\* Authors' affiliation: 1 Hematopathology Unit, Department of Experimental, Diagnostic, and Specialty Medicine, S. Orsola-Malpighi Hospital, University of Bologna, Bologna, 40138 Italy 2 Department of Systems Biology, Columbia University College of Physicians and Surgeons, New York, New York, 10032 United States of America, 3 Department of Biomedical Informatics, Columbia University College of Physicians and Surgeons, New York, New York, 10032 United States of America 4 Unit of Haematopathology, European Institute of Oncology, Milan, 20141 Italy 5 Laboratory of Hematology-Oncology, European Institute of Oncology, Milan, 20141 Italy 6 Department of Genetics and Genome Biology, The Hospital for Sick Children, Toronto, M5G 0A4 Canada 7 Dermatology Unit, Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Bologna, 40138 Italy 8 Division Dermatology, Department of Surgery and Translational Medicine, University of Florence, Florence, 50212 Italy 9 Pathological Anatomy Histology & Cytogenetics, Niguarda Cancer Center, Niguarda-Ca' Granda Hospital, Milan, 20162 Italy 10 Institute of Hematology and Center for Hemato-Oncology Research (CREO), University and Hospital of Perugia, Perugia, 06123 Italy 11 Universitätsklinik für Dermatologie und Venerologie, LKH-Univ, Klinikum Graz, Graz, 8036 Austria 12 Department of Experimental Oncology, European Institute of Oncology, Milan, 20141 Italy 13 Department of Molecular Medicine and Medical Biotechnologies, University of Naples 'Federico II', Naples, 80138 Italy 14 "Giorgio Prodi" Cancer Research Center, University of Bologna, Bologna, 40138 Italy. 15 Unit of Anatomic Pathology, Department of Molecular Medicine, University of Pavia and Fondazione IRCCS San Matteo Policlinic, Pavia, 27100 Italy 16 Department of Dermatology, Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinic and Milan University, Milan, 20122 Italy 17 Pathology Section, Department of Molecular and Translational Medicine, University of Brescia, Brescia, 2123 Italy 18 Department of Oncology and Hemato-oncology, University of Milan, Milan, 20126 Italy 19 Tumor Immunology Unit, Department of Health Science, Human Pathology Section, University of Palermo School of Medicine, Palermo, 90127 Italy 20 Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Bologna, 40138 Italy, \* Equally contributed.

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare hematological disease erroneously identified in the past as blastic NK/T-cell lymphoma or agranular CD4+/CD56+ hematodermic neoplasm. In the 2008, it has been correctly recognized as a neoplasm deriving from plasmacytoid dendritic cell precursors and classified among myeloid acute leukaemias. BPDCN patients show a very aggressive clinical course (median overall survival ranging from 12 to 14 months), and, despite an initial response to chemotherapy, regularly relapse. To date, no standardized therapeutic approach has been established and the optimal treatment remains to be defined. In this work we investigated the entire BPDCN coding exome to discover specific genetic vulnerabilities supporting the design of a new therapeutic strategy. We performed the whole exome sequencing (WES) of 14 BPDCN patients and the BPDCN patient-derived CAL-1 cell line and found that mutations accumulate in the epigenetic program, involving 25 epigenetic modifier genes, and, among them, ASXL1 is the most recurrently affected (28.6% of cases). Accordingly, the functional enrichment analysis of WES data, recognized the epigenetic process as the most undermined by genes recurrently mutated or affected by damaging mutations (P<.0001). To further substantiate the mutational impact at transcriptome level we conducted additional RNA sequencing experiments. Gene set enrichment analysis reported the significant deregulation of gene-signatures involved in the methylation pathway and responsive to hypomethylating agents, namely Decitabine. Then, to investigate if the transcriptional deregulation of BPDCNs could be linked to specific epigenetic signals, we analyzed by chromatin immunoprecipitation sequencing, the genome-wide distribution of H3K27-trimethylation/acetylation signals, related to active/inactive gene promoters. The BPDCN patients converged on the same H3K27-acetylated regions and the integration with transcriptomic data highlighted a set of genes marked by promoter-acetylation, aberrantly up-regulated and involved in the cell-cycle regulation. Globally, the integrative analysis of genomic data suggested a therapeutic approach based on epigenetic drugs. We developed a BPDCN pre-clinical mouse model to test the efficacy 5'-Azacytine, Decitabine, Romidepsine and Bortezomib. The combined use of 5'-Azacytine and Decitabine reached the best results demonstrating to significantly arrest in vivo BPDCN tumor growth.

maria.sapienza2@unibo.it

# **GENETICALLY ISOLATED POPULATIONS IN BRAZIL**

ABSTRACT N° A005\_2018 / OPPORTUNITIES IN RARE DISEASES AROUND THE WORLD

Gabriela Costa Cardoso 1; Marcelo Zagonel de Oliveira 2; Vanessa Rodrigues Paixão-Côrtes 3; Eduardo Enrique Castilla 4,5; Lavínia Schüler-Faccini 1,5 1 Post-Graduate Course in Genetics and Molecular Biology, Institute of Biosciences, Universidade Federal do Rio Grande do Sul. Bento Gonçalves Avenue, 9500, Porto Alegre, RS, Brazil. Zip Code 91501-970. 2 Advanced Visualization Laboratory (VIZLab), Universidade do Vale dos Sinos (UNISINOS). Unisinos Avenue 950, São Leopoldo, RS, Brazil. Zip Code 93020-190. 3 Biology Department, Biology Institute, Federal University of Bahia. Barão de Jeremoabo Street 147 – Campus Ondina, Salvador, BA, Brazil. Zip Code 40170-115. 4 Latin American Collaborative Study of Congenital Malformations (ECLAMC). FIOCRUZ – Genética. Brasil Avenue 4365 – Pav. L. Deane, room 617, Rio de Janeiro, RJ, Brazil. Zip Code 21040-900. 5 National Institute of Population Medical Genetics (INAGEMP). Ramiro Barcelos Street, 2350, room 21506, Porto Alegre, RS, Brazil, Zip Code 90035-90.

The objective of this study is to present a census of isolated population (CENISO) in Brazil, which aims to identify isolated communities which present a high prevalence of genetic diseases. With this intention was implemented, besides systematic literature review, a "rumor" strategy. The rumor means that any person, researchers or general public, can report a population they know or have heard about. All reports and findings in the literature review were registered in the CENISO database with the information about the population, the genetic disease and locality. After registration, the rumors pass for a stepwise investigation to validate if they are true or not. Therefore, if they are true they are classified as clusters, if they are false they are removed, and the rumors that were not validated as true or false continue to be registration phase. To date, CENISO has been able to gather 261 submissions, with 26 clusters identified through bibliographic review and 245 reported rumors. The majority of the rumors (73 cases) are still in the registration phase and 62 rumors were removed after investigation. We were able to confirm 126 rumors, of these, 55 clusters involve several rare diseases and are already being studied by research groups. The mainly rare diseases found in CENISO were: mucopolysaccharidosis type 6, Huntington disease, chondrodysplasia Blomstrand Type, aniridia, gaucher disease, spinocerebellar ataxias, trichoepithelioma multiple familial 1, chondrodysplasia Grebe Type, Usher syndrome type I, Laron syndrome, xeroderma pigmentosum, osteogenesis imperfect type 6, acheiropody, Fraser syndrome and GAPO syndrome. The majority of the genetic isolates were found in poor rural areas and the highest prevalence was found in the northeastern region of Brazil, probably due to several factors including founder effects, geographic isolation and inbreeding. Indeed, the inbreeding rate in this region can reach 40%, leading to an increase in the appearance of rare diseases. We believe that a census like the one presented here represents an important tool for the planning of health priorities for rare diseases in low and middle-income countries with large population numbers. By identifying populations with rare diseases and centralizing the available information on these patients, our national census channels scientific interest towards these diseases, as well as providing a diagnosis and promoting medical care for the patients and their families.

gabrielaccardoso@hotmail.com

# REPURPOSING SIROLIMUS AS A DRUG FOR BETA-THALASSEMIA

ABSTRACT N° A006\_2018 / OPPORTUNITIES IN RARE DISEASES AROUND THE WORLD

Marco Prosdocimi, Rare Partners srl Impresa Sociale, Milano, Italy Roberto Gambari, Department of Life Sciences and Biotechnology, Ferrara University, Italy

Sirolimus (Rapamycin, Rapamune) is a drug approved since 1999 as an immunosuppressive agent for kidney transplant patients to prevent rejection. Sirolimus acts an inhibitor of mTOR and, besides its action on immune response, exerts several other activities, leading to many clinical trials in different indications and to approval in 2015 by FDA for lymphangioleiomyomatosis (LAM), a rare, progressive lung disease that primarily affects women of childbearing age. Gambari and coworkers described in many papers, since 2004, that sirolimus increases fetal hemoglobin (HbF) in erythroid cells isolated from beta-thalassemia patients, pointing out that these observations may have clinical relevance. This view is supported by clinical data indicating that patients with high levels of HbF even in adult age have a benign prognosis and may survive with no or limited blood transfusions. As a consequence, many compounds able to increase HbF are now studied as a potential therapy for beta-thalassemia. Rare Partners is a non profit company founded in 2010 by pharma/biotech managers to develop drug and diagnostics for rare diseases, with strong emphasis on repositioning projects. To this end, collaboration with the Department was activated (in 2011) and focused on all the steps potentially able to lead to clinical applications of the experimental results. During the last 6 years professor Gambari's team academic research has been funded by several sources, including EU grants, while collaboration with Rare Partners has been instrumental for the company's development activities, leading to Orphan Drug designations by EMA and FDA in thalassemia and Sickle Cell Disease. Funding has been provided by regional grants and by a Pathfinder Award (Wellcome Trust, UK). In 2016 we considered that non-clinical data fully supported advancement of the project to clinical stage, thus EMA advice for clinical development was obtained and funding of clinical development was actively pursued. Presently we have been able to secure financial support for clinical trials in two different countries. In conclusion, our work provides evidence that non profit companies can bring repositioned drugs to clinical stage of development with limited internal financial resources, providing development expertise to academic scientists involved in translational projects with a clear cut clinical end point.

m.prosdocimi@rarepartners.org

#### APPLICATION OF A SENSITIVE READOUT SYSTEM FOR THE SCREENING OF NOVEL THERAPEUTIC MOLECULES FOR PRIMARY HYPEROXALURIA TYPE 1

ABSTRACT N° A007\_2018 / OPPORTUNITIES IN RARE DISEASES AROUND THE WORLD

Fanny Shkedy1, Ruth Belostotsky1, Keren Oved2, Orly Dorot2, Michael Chalik2, Edward Pichinuk2, Yaacov Frishberg1 1 Pediatric Nephrology, Shaare Zedek Medical Center, Jerusalem, Israel 2 Blavatnik Center for Drug Discovery, Tel Aviv University, Israel

Background: Primary hyperoxaluria type 1 (PH1) is a kidney stone disease, often leading to ESRD. Stone formation results in increased production of oxalate caused by the absence, deficiency or mistargeting of the liver peroxisomal alanine-glyoxylate aminotransferase (AGT). About 30% of Caucasians with PH1 carry the G170R mutation which leads to aberrant mitochondrial localization of the enzyme that maintains catalytic activity. Modulation of AGT maturation and folding may rescue AGT mutants and re-route them to the peroxisome. Methods: To evaluate population of peroxisome-localized AGT, we developed a novel quantitative Glow-AGT assay based on the self-assembly split GFP approach, and used it to identify drugs that can correct mislocalization of the mutant protein and reduce oxalate production. Our model is based on CHO transfected cells with vectors expressing the PH1 G170R mutant or WT AGT. Only WT or mutant AGT localized in the peroxisomes f uoresce. Results were evaluated by FACS analysis and confocal microscopy. The system was firstly set for emetine administration, a known translation elongation inhibitor. Subsequently, we confirmed the system's performance using other translation inhibitors and protein modulators. Finally, we adapted the system for automated instrumentation and High Throughput Screening (HTS). Results: Treatment of G170R-AGT with emetine showed a significant increase in the f uorescent AGT-subpopulation. GFP f uorescence colocalized with peroxisomal staining. Prolonged treatment with emetine, GC7 or the mitochondrial transport inhibitors DECA and monensin corrected G170R-AGT mislocalization. In search for additional drug candidates for re-routing mutant AGT to the peroxisomes a high-throughput screening of small-molecules-library was performed. A number of new compounds were identified. These potential therapeutic agents currently undergo a validation process. Conclusions: Mild translation inhibition by emetine and the effect of other chemochaperones confirmed the assay accuracy and supported the use of this system in search of novel therapeutic modalities for PH1. New molecules discovered by random libraries' screening, representing similar or different mechanisms of action, should be tested for improved efficacy and lower toxicity. Further investigation is necessary before being introduced for the treatment of PH1. Funding: ERA-NET Cofund-Action No. 643578

fannys@szmc.org.il

#### CALL FOR APPLICATION FOR THE SELECTION OF BELGIAN REFERENCE LABORATORIES OF CLINICAL BIOLOGY PERFORMING ANALYSES USED IN THE CONTEXT OF RARE DISEASES' DIAGNOSIS AND FOLLOW-UP.

ABSTRACT N° A008\_2018 / OPPORTUNITIES IN RARE DISEASES AROUND THE WORLD

Nathalie M. Vandevelde, Scientific Institute of Public Health (WIV-ISP), Brussels, Belgium

Purpose: One objective of the Belgian Plan for Rare diseases (RD) is to recognize & fund Belgian reference laboratories (RL's) for some specific analyses of clinical biology (CB) used in the context of RD. The goals are to improve access to care, centralize analyses performed at a very low annual volume & ensure their guality. Method: The call for application was prepared as described below: 1) Identification of non-reimbursed CB analyses used for RD; 2) Data collection from Belgian laboratories of CB about inventoried analyses; 3) Evaluation of collect data by Belgian experts & definition of the analyses for which RL's should be recognized, as well as of RL's guality & selection criteria; 4) Submission of proposals for the selection process, scope & funding of RL's to the Belgian healthcare authorities. After their approval, the call for application was opened in June 2017. Candidates had 5 months to apply. Results: Based on the evaluation of the needs of the field & relevance of inventoried analyses, 19 analyses (biochemistry[13]; hematology[2]; immunology[4]) were included in the scope of future RL's. Selected quality criteria of RL's cover different aspects: Quality Management System (participation to external guality controls [EQC]/ring tests, analytic validation, accreditation, data management), scientific expertise (annual volume of analyses, research activities & scientific publications, networking, multidisciplinary meetings, development of guidelines/algorithms/training sessions, reporting skills) & sustainability of the activities. Applications were collected for 17 analyses, from 6 Belgian academic CB laboratories (applying for 1 or more analyses). All candidates developed a very strong scientific expertise and possess the necessary infrastructure & gualified staff to ensure the sustainability of their activities. Data management was also well-performed. Methods were well-validated for 94% of applicants. However, quality evaluation remains a challenge. Indeed, for most of analyses, no EQC exists. It affects the laboratories' accreditation process, which therefore had to develop ring tests (exchange of samples) with other laboratories performing the same analyses. CCL: The recognition & funding of RL's improve the access to specialized & high-quality care. However, the development of EOC for CB analyses used for RD, and financial helps for RL's accreditation are 2 issues that should be addressed by healthcare authorities.

nathalie.vandevelde@wiv-isp.be

#### CONNECTING THE DOTS: GLOBAL NETWORKING AMONG PATIENTS WITH GIANT CONGENITAL MELANOCYTIC NEVUS AND WITH MEDICAL AND SCIENTIFIC STAKEHOLDERS

ABSTRACT N° A017\_2018 / OPPORTUNITIES IN RARE DISEASES AROUND THE WORLD

Marjolein van Kessel (1) and Heather C. Etchevers (2) 1 President of Naevus Global, Utrecht, The Netherlands. mvankessel@naevusglobal.org 2 Aix-Marseille Univ, INSERM, MMG, Marseille, France. heather.etchevers@inserm.fr

Since the patient federation Naevus Global was formalized in 2013 and joined EURORDIS. great strides have been made in continuing to connect individuals and families affected with rare forms of Congenital Melanocytic Nevi (CMN). Medical descriptions, relevant articles from the literature and uncontroversial recommendations were verified by an initial scientific advisory council of committed physicians and scientists worldwide, and made available in ten languages through the website http://www.naevusglobal.org. In 2017, we restructured in the form of a network called 'Naevus International', to provide mutual consultation between patients, scientists, clinicians, psychologists and other stakeholders. Naevus Global remains the patient advocacy branch of this network. Benefits of the new configuration include enlarging the previous advisory council and separation into more research-oriented and more clinically oriented branches for better distribution of tasks; worldwide exchange practitioners about treatment options in the case of melanoma or neurologically symptomatic complications; cross-border collaboration for research proposals; continued discussion of consensus guidelines for management or implementation of an international registry to integrate current national or regional efforts; mapping expertise (e.g. in Europe with the ERN-SKIN) for clinical checkups and experienced plastic surgical treatment; and including a working group to address the psychosocial impact of living with a visible physical difference either oneself or in one's close family, to offer concrete advice to the other branches of the network. The leader of that working group presides a nonprofit called Association Anna, whose partnership with the distributors of the film Wonder and development of a "therapeutic" comic book are being tested with focus groups in the French CMN patient community. Naevus International will hold its first board meeting in June, in conjunction with the European Society for Pediatric Dermatology meeting, and organize the 3rd international expert meeting on large CMN and neurocutaneous melanocytosis in September, 2018.

heather.etchevers@inserm.fr

#### RD-CONNECT: DATA SHARING AND ANALYSIS FOR RARE DISEASE RESEARCH WITHIN THE INTEGRATED PLATFORM AND THROUGH GA4GH BEACON AND MATCHMAKER EXCHANGE

ABSTRACT N° B003\_2018 / NGS AND UNDIAGNOSED RARE DISEASES

RD-Connect: data sharing and analysis for rare disease research within the integrated platform and through GA4GH Beacon and Matchmaker Exchange

J. Dawson10, S. Beltran1,2, D. Piscia1,2, S. Laurie1,2, J. Protasio1,2, A. Papakonstantinou1,2, I. Martinez1.2, A. Valencia3.14, S. Capella3.14, J.M. Fernández3.14, M. Thompson6, R. Kalivaperumal6. S. Lair7. P. Sernadela8. M. Girdea9. M. Brudno9. A. Blavier7. R. Thompson10. H. Lochmüller10. M. Bellgard11, D. Spalding12, M. Roos6, P.A.C. 't Hoen6, D. Salgado4,5, C. Béroud4,5,13, I. Gut1,2 and the RD-Connect Consortium 1Centro Nacional de Análisis Genómico (CNAG-CRG), Center for Genomic Regulation, Barcelona Institute of Science and Technology (BIST), Barcelona, Spain 2Universitat Pompeu Fabra (UPF), Barcelona, Spain 3Barcelona Supercomputing Center - Centro Nacional de Supercomputación (BSC-CNS), Barcelona, Spain 4Aix-Marseille Université, Marseille, France 5Inserm, UMR S 910, Marseille, France 6Department of Human Genetics, Leiden University Medical Center, Leiden, The Netherlands 7Interactive Biosoftware, Rouen, France 8DETI/IEETA, University of Aveiro, Portugal 9Centre for Computational Medicine, Hospital for Sick Children and University of Toronto, Toronto, ON, Canada 10Institute of Genetic Medicine, MRC Centre for Neuromuscular Diseases, Newcastle University, UK 11Centre for Comparative Genomics, Murdoch University, Perth, Western Australia 12European Molecular Biology Laboratory, European Bioinformatics Institute (EMBL-EBI), Wellcome Trust Genome Campus, Cambridge, United Kingdom 13APHM, Hôpital TIMONE Enfants, Laboratoire de Génétique Moléculaire, Marseille, France 14Instituto Nacional de Bioinformática (INB), Spain

The RD-Connect Genome-Phenome Analysis Platform for rare disease research brings together multiple omics data types (genomics, proteomics, transcriptomics) with biosample and clinical information at individual patient, family or whole-cohort level. It provides both a centralized data repository and a user-friendly online analysis system. Whole-genome, exome and gene panel datasets are submitted by the end-user and processed by RD-Connect's standardised analysis and annotation pipeline to make data from different sequencing providers comparable. Clinical information is recorded in PhenoTips. simplifying clinical data entry using the Human Phenotype Ontology. Results are made available to the submitter and other authorised users through the highly configurable analysis interface (platform. rd-connect.eu) which enables filtering and prioritization of variants using common genomic location, effect, pathogenicity and population frequency annotations, enabling users to do their primary genomic analysis of their own patients online and compare with other submitted cohorts. Raw data is deposited at the European Genome-phenome Archive (EGA) for long-term storage. The platform enables data sharing at various levels. At the most basic ("does this variant exist in this cohort?") is the Global Alliance Beacon (www.beacon-network.org). At a more advanced level – finding patients in different databases with matching phenotype and candidate variant in the same gene – it is further developing Matchmaker Exchange (www.matchmakerexchange.org), allowing users of different systems to exchange information to find confirmatory cases. Finally, since patients have been consented for data sharing, authorized users can access datasets from other centres for further study. The platform is open to any rare disease and already includes thousands of datasets from partner projects such as NeurOmics (www.rd-neuromics.eu) and BBMRI-LPC (www.bbmri-lpc.org). In 2018 it became the primary data sharing and analysis platform for the new Solve-RD project, which will bring in 19,000 unsolved cases from European Reference Networks over 5 years. RD-Connect is free and open for contributions from individual research groups and other projects: contact platform@rd-connect.eu.

john.dawson@ncl.ac.uk
# ON THE ROLE OF CALCIFICATION-RELATED GENES IN PXE-LIKE MANIFESTATIONS OF BETA-THALASSEMIC PATIENTS.

ABSTRACT N° B004\_2018 / NGS AND UNDIAGNOSED RARE DISEASES GENES IN PXE-LIKE MANIFESTATIONS OF BETA-THALASSEMIC PATIENTS

1Boraldi F., 1Rabacchi C., 1Costa S., 1Lofaro F.D., 2Stanghellini I., 2Calabrese O., 1Quaglino D. 1Department of Life Sciences, University of Modena and Reggio Emilia, Modena (Italy); 2Medical Genetic Service, Azienda Ospedaliero-Universitaria Policlinico, Modena (Italy)

Beta-thalassemia is characterized by severe anaemia and hepatosplenomegaly due to mutations in the HBB gene. Despite the prevalence of haematological manifestations, about 20% of these patients exhibit also dermal and ocular complications similar to those observed in Pseudoxanthoma elasticum (PXE), a rare genetic disease in which ABCC6 gene mutations are responsible for the progressive mineralization of elastic fibres. If common pathogenic mechanisms are shared in these two pathologic conditions is still question of debate. Early studies in thalassemic patients suggested that PXE-like manifestations were independent from ABCC6 disease causing mutations and, more recently, it was hypothesized that these alterations could result from reduced levels of ABCC6 protein, possibly as a consequence of epigenetic regulatory mechanisms, never the less, the pathogenesis of matrix calcification still remain unclear. Aim of the present study was to investigate by NGS three beta-thalassemic patients exhibiting PXE-like manifestations looking for the presence of mutations and/or functional polymorphysms in genes known from the literature to be associated with mineralization. A panel of 120 genes was analysed. The study, in accordance with the basic principles of the Declaration of Helsinki, was approved by the local Ethical Committee (n. 358/17). Data revealed that only 30 out of 120 genes matched with reference sequences. Interestingly, all three patients were carriers of ABCC6 gene mutations either in the homozygous or heterozygous state, two exhibited mutations in the PTH gene and one was also carrier of one ENPP1 mutation, all these genes being involved in well-known ectopic calcification processes (i.e. PXE, disorders of calcium metabolism and generalized arterial calcification of infancy, respectively). Furthermore, several sequence variations were detected in the PRSS1 gene, that has been associated with peculiar forms of calcific diseases. Although the number of patients analysed was limited, results shed light on the complexity of apparently monogenic genetic diseases and underline that, due to the continuous development of more sensitive and high-throughput technologies, a panel of several genes could be screened for prognostic purposes and for a better monitoring of patients' clinical complications Work supported by grant from FCRMO 2015.0306 and from PXE Italia Onlus.

daniela.quaglino@unimore.it

## A NEW IMMUNOMODULATORY FUNCTION FOR SLC7A7/Y+LAT1, THE GENE MUTATED IN LYSINURIC PROTEIN INTOLERANCE (LPI)

ABSTRACT N° C001\_2018 / PATHOPHYSIOLOGY

Amelia Barilli1\*, Filippo Ingoglia1, Rossana Visigalli1, Bianca Maria Rotoli1, Marco Milioli2, Benedetta Riccardi2, Paola Puccini2, and Valeria Dall'Asta1 1Dept. of Medicine and Surgery (DiMeC), Università degli Studi di Parma, Italy, 2Dept. of Biochemistry & Metabolism, Chiesi Farmaceutici, Italy

Background Lysinuric protein intolerance (LPI: MIM 222700) is a recessively inherited aminoaciduria caused by mutations of SLC7A7 gene that encodes y+LAT1 light chain of system y+L for cationic amino acid (arginine, lysine, ornithine) transport. Clinically, LPI manifests with highly heterogeneous symptoms, whose pathogenesis remains mostly unknown: hyperammonemia and nausea/vomiting after protein ingestion are explained by urea cycle slowdown due to the impairment of CAA absorption/reabsorption in intestinal and renal epithelial cells: conversely, the complex multi organ life-threatening manifestations of the disease still remain to be understood. Aim Aim of this study is to investigate whether LPI complications affecting lung and immune system are due to an abnormal accumulation of arginine in affected cells or are, rather, ascribable to a thus far unknown role of the mutated SLC7A7/y+LAT1 protein. Methods SLC7A7/y+LAT1 was silenced by means of short interference RNA (siRNA) in human THP1 macrophages maintained in the presence of increasing concentrations of extracellular arginine (0.1-10 mM), as well as in A549 airway epithelial cells, either untreated or treated with inf ammatory stimuli. Cytokine production and release were, then, evaluated with gRT-PCR and ELISA, respectively. Results A significant induction of the expression and release of inf ammatory cytokines (IL1 and TNF) was observed in macrophages upon SLC7A7 silencing, no matter arginine availability; this effect was mainly regulated at transcriptional level through the activation of NF B signalling pathway. As for respiratory epithelial cells, the down-regulation of SLC7A7/y+LAT1 both stimulated cytokine release and strengthened the stimulatory effect of IL1 on CCL5/ RANTES chemokine expression. Consistently, the conditioned medium of silenced THP-1 cells stimulated CCL5/RANTES expression in airway epithelial cells, due to the presence of IL1. Conclusion Our results point to a novel, thus far unknown function of SLC7A7/ y+LAT1 that, besides transporting arginine, may act as a physiological brake to restrain inf ammation. Defects of this protein in LPI macrophages could, thus, cause a dysregulated secretion of cytokines able to stimulate chemokine release by airway epithelial cells, hence engaging them in a positive-feedback loop. The resulting excessive inf ammatory response could explain LPI-associated immune disorders, as well as inf ammation and fibrosis in the lungs of patients.

amelia.barilli@unipr.it

### NOVEL ZEBRAFISH MODELS OF SARCOGLYCANOPATHY

ABSTRACT N° C002\_2018 / PATHOPHYSIOLOGY

Michela Soardi (1), Marcello Carotti (1), Chiara Fecchio (1), Francesco Argenton (2), Roberta Sacchetto (3), Dorianna Sandonà (1). (1) Department of Biomedical Sciences, (2) Department of Biology, (3) Department of Comparative Biomedicine and Food Science, University of Padova, Padova, Italy.

Sarcoglycanopathy, is the collective name of four rare, autosomal recessive, muscle-wasting diseases (LGMD2C, D, E and F) caused by defects in genes coding for, -, -, - and -sarcoglycan (SG), respectively. These transmembrane glycoproteins form a subcomplex that is closely linked to the major dystrophin associated protein complex (DAPC), fundamental to protect the sarcolemma from muscle contraction stress. Proper assembly and trafficking of the SG complex is essential for its structural function. The majority of SG defects are missense mutations that result in folding-defective proteins that are degraded by the guality control system of the cell thus leading to the secondary deficiency of the wild type SG partners. Interestingly most of such mutants retain their function as the entire complex can be properly rescued by skipping the degradation of the defective protein. Presently, a promising therapeutic strategy, based on the use of small-molecules able to recover the SG-complex by inhibiting their degradation or by helping their folding, was described in cell models and, notably, in primary myotubes from a patient affected by LGMD2D. To evaluate in vivo efficacy and tolerability of these molecules, we are now generating novel D.Rerio (zebrafish) models of sarcoglycanopathy. In the absence of suitable rodent models of the disease, we chose zebrafish because it is an excellent vertebrate for studying muscular disorders, for drug screening, and for the relatively easy applicability of genomeediting technologies. Moreover, the molecular pathways responsible for the premature degradation of SG missense-mutants seem conserved between human and zebrafish. Here we show first, the rationale of modeling sarcoglycanopathy in zebrafish thanks to data collected by the morpholino knockdown of -SG. Then, we describe the methodological approach that, by CRISPR/Cas9 genome editing, is allowing the stable knock out of - and -SG (the heterozygote F1 lines are ready) and the generation of -SG(T145R/T145R) and -SG(E264K/E264K) knock in. The characterization of these animals comprises histological and biochemical analyses and reproducible bioassays to evaluate muscle functionality. Once characterized, the novel zebrafish models will represent a fundamental tool to test our pharmacological approach and will be a valuable adjunction to the already available vertebrate models of sarcoglycanopathy for both basic and translational research.

michelasoardi@gmail.it

#### EXPLORATORY ANALYSIS OF INFLAMMATORY AND OXIDATIVE STRESS BIOMARKERS IN ALKAPTONURIA WITHIN THE DEVELOPAKURE PROJECT

ABSTRACT N° C004\_2018 / PATHOPHYSIOLOGY

Daniela Braconi1, Daniela Giustarini2, Barbara Marzocchi1,3, Luana Peruzzi1,4, Maria Margollicci4, Ranieri Rossi5, Giulia Bernardini1, Lia Millucci1, Lakshminarayan R Ranganath6,7, Annalisa Santucci1 1 Dipartimento di Biotecnologie, Chimica e Farmacia, Università degli Studi di Siena, Siena, IT 2 Dipartimento Scienze Mediche, Chirurgiche e Neuroscienze, Università degli Studi di Siena, Siena, IT 3 UOC Patologia Clinica, Azienda Ospedaliera Senese, Siena, IT 4 UOC Medicina Molecolare e Genetica, Azienda Ospedaliera Senese, Siena, IT 5 Dipartimento Scienze della Vita, Università degli Studi di Siena, Siena, IT 6 Department of Musculoskeletal Biology, University of Liverpool, Liverpool, UK 7 Department of Clinical Biochemistry and Metabolism, Royal Liverpool University Hospital, Liverpool, UK BACKGROUND and AIM Alkaptonuria (AKU) is a rare autosomal recessive metabolic disorder (MIM 203500) causing an early onset, chronically debilitating spondylo-arthropathy due to high circulating homogentisic acid (HGA, 2.5-dihydroxyphenylacetic acid). Reports suggest that HGA can induce oxidative stress in AKU. Recent evidence also pointed out that AKU is a multisystem disease involving secondary (AA) amyloidosis due to high circulating Serum Amyloid A (SAA) promoting inf ammation, oxidative stress and amyloidosis. However, AKU still lacks appropriate biomarkers to monitor progression and severity. The use of the drug nitisinone (NTBC) was suggested in AKU to lower circulating HGA levels, and clinical trials were undertaken under an FP7 funded grant (DevelopAKUre - Clinical Development of Nitisinone for Alkaptonuria, grant 304985). METHODS As exploratory objective of DevelopAKUre, we undertook the analysis of established serum biomarkers related to inf ammation and oxidative stress in serum of a high number of AKU subjects who were/ are enrolled in SONIA1 (Suitability Of Nitisinone In Alkaptonuria 1), SONIA2 (Suitability Of Nitisinone In Alkaptonuria 2) and SOFIA (Subclinical Ochronosis Features In Alkaptonuria) clinical trials. RESULTS and CONCLUSION Serum is an excellent and easily accessible source of protein biomarkers that can ref ect pathological conditions. Thanks to our involvement in DevelopAKUre, we had the possibility to analyse levels of established serum biomarkers related to oxidative stress and inf ammation in a large cohort of alkaptonuric patients. Due to the ultra-rarity of the disease (affecting 1:250,000-1,000,000) we were given an invaluable opportunity, as we were able to test for the very first time a high number of alkaptonuric serum specimens that were collected and stored under standardised procedures (agreed among the involved clinical centres). All the data obtained within this work could hence be used to populate a dedicated database integrating biomarker levels, demographics, patient's quality of life, environmental and life-style data, and clinical outcomes. Such a database could represent an optimal tool with potential relapses for the study of AKU and the development of a precision medicine approach for AKU and other more common rheumatic disorders.

braconi2@unisi.it

#### AN INTEGRATED INTERACTIVE ECOSYSTEM FOR ALKAPTONURIA: A TOOL FOR PHYSICIANS AND RESEARCHERS

ABSTRACT N° C005\_2018 / PATHOPHYSIOLOGY

Annalisa Santucci1, Vittoria Cicaloni1,2,#, Andrea Zatkova3, Lia Millucci1, Giulia Bernardini1, Andrea Bernini1, Neri Niccolai1, Monica Bianchini4, Andrea Zugarini4, Alberto Rossi4, Matteo Zazzeri4, Alfonso Trezza1, Daniela Braconi1, Ottavia Spiga1 1Department of Biotechnology, Chemistry and Pharmacy, University of Siena, ITALY 2Toscana Life Sciences Foundation, Siena, ITALY 3 Institute for Clinical and Translational Research, Biomedical Research Center, Slovak Academy of Sciences Bratislava, SLOVAKIA 4 Department of Information Engineering and Mathematics, University of Siena, ITALY

Background and Aim Alkaptonuria (AKU) is a rare and genetic disease that causes discoloration of bone and cartilage ('ochronosis') and induces early-onset osteoarthritis. AKU data have not been organized yet and the disease has no approved biomarkers. The ability to collect, integrate and analyse relevant data streams is the core for developing an AKU-dedicated "Precision Medicine Ecosystem" where biological resources are shared between researchers, clinicians and patients. Computational modelling can be a useful quide to generate an exhaustive and dynamic picture of the individual and to identify the molecular interactions between biomarkers on which progressive diseases are based. Methods We built a new integrated interactive database thanks to MySQL, the most frequently chosen for use in web applications. In addition, data were statistically analysed by R software (www.r-project. org) based on Pearson's correlation coefficient and P value. For a biological interpretation of statistic results, Stitch and KEGG databases were used. Results and Conclusion For Precision Medicine (PM) application to AKU, the collection of as much data as possible has been needed in order to organize them in an interactive and integrated database and to find a data-processing system for AKU biomarkers discovery. The database is an effective tool for registered researchers, clinicians and patients who could both easily access all the current information, as well as being able to insert new data, refreshing or replacing previous entries. Data are divided into different sections: genetic, protein, biochemical, histopathologic and clinical. An algorithm was developed to analyse data and build up a refreshable correlation matrix based on Pearson's correlation coefficient and P value. Together with the mathematical and statistical interpretation, a biological explanation of the results is needed in order to investigate on AKU biomarkers. This dynamic tool could be useful for biomarkers investigation also in other osteoarticular diseases and it is a good starting point for the creation of data management and analysis model appropriate for PM. With our AKU-dedicated database and this innovative analytic approach, it has been possible to become aware of the failure of biomarkers clinically used and to improve the detection of more exploitable prognostic biomarkers for a more reliable AKU patients clinical monitoring.

annalisa.santucci@unisi.it

# ANGIOGENESIS AND AUTOPHAGY IN ALKAPTONURIA

ABSTRACT N° C006\_2018 / PATHOPHYSIOLOGY

Millucci L2, Bernardini G2, Braconi D2, Bardelli M1, Marzocchi B1, Spiga O1, Orlandini M1, Sestini S3, Frediani B1and Santucci A2 1Dipartimento di Scienze Mediche, Chirurgiche e Neuroscienze; 2Dipartimento di Biotecnologie, Chimica e Farmacia, Università degli Studi di Siena, Via Aldo Moro 2, Siena, Italy; 3AIMAKU, Associazione Italiana Malati Alcaptonuria

Background Alkaptonuria (AKU) is an ultra rare disease due to a deficient activity of the enzyme homogentisate 1,2 dioxygenase (HGD), leading to accumulation of homogentisic acid (HGA). Patients experienced a severe form of arthropathy. Here, we wanted to assess if angiogenesis might occur in AKU, providing evidence on the formation of new vessels in AKU synovia. In parallel, the preminent role of HGA in autophagy, having direct impacts on the inf ammation-related AKU cartilage degeneration was also assessed to find a link between cartilage degradation and chondrocyte death. The possible contribution of autophagy to joint damage and its impact on cell death was inferred Methods We used confocal IF to characterize VW factor, VE caderin, CD93 and BDG immunolocalization in 5 AKU synovium. The expression of LC3-II protein was investigated by IF and WB in AKU chondrocytes. Finally, TEM was used to detect morphological changes attesting chondroptosis and autophagy in AKU chondrocytes Results AKU Synovia showed evidence of severe synovial inf ammation and exhibited strong WF protein staining pattern, in accordance with positive staining of VE caderin, CD93 and BDG. The immunolocalisation of BDG within endothelium of AKU blood vessels suggests that BDG plays a role in AKU angiogenesis. TEM analysis and the increased expression of LC3 in AKU chondrocytes, entails that chondroptosis involves autophagy, as suggested by the presence of autophagic vacuoles in AKU chondrocytes. Morphological observation of AKU chondrocytes might refect different physic pathological stages of cartilage degeneration, shifting from a reparative to a degradation pattern, related to peculiar cell death Conclusions We showed that AKU is accompanied by synovial angiogenesis, suggesting that inf ammation is directly implicated in the progression of AKU. Synovitis may impair chondrocyte function and homeostasis of cartilage through the generation of cytokines and low molecular weight factors. Increased autophagy may be a compensatory response to cellular stress, with damage occurring when prolonged stress exceeds the capacity of this mechanism This can be the clue that autophagic death is an alternative to apoptosis when environmental factors change, as in AKU, where HGA and inf ammatiob represent an abnormal milieu for the cells. These finding opened new perspectives for AKU therapy since the study of autophagy and angiogenesis represents a promising avenue to control inf ammation and pain.

millucci2@unisi.it

## A DETAILED OVERVIEW OF SECONDARY AMYLOIDOSIS IN ALKAPTONURIA

ABSTRACT N° C007\_2018 / PATHOPHISIOLOGY

Sestini S1, Millucci L2, Bernardini G2, Braconi D2, Bardelli M3, Marzocchi B1, Spiga O1, Orlandini M1, Frediani B3and Santucci A2 1AIMAKU, Associazione Italiana Malati Alcaptonuria, 2Dipartimento di Biotecnologie, Chimica e Farmacia, Università degli Studi di Siena, Via Aldo Moro 2, Siena, Italy, 3Dipartimento di Scienze Mediche, Chirurgiche e Neuroscienze;

Background Alkaptonuria (AKU) is an ultra-rare inborn error of metabolism due to a deficient activity of homogentisate 1.2- dioxygenase. Patients suffer from a severe arthropathy. Evidence was provided on the presence of a secondary serum amyloid A (SAA)-based amyloidosis. Here a complete microscopic and ultrastructural analysis of different AKU tissues, taken from six differently aged patients, is presented. Objectives: SAA amyloidosis is a complication in AKU, making the detection of amyloid deposits at an early phase, important for treatment. We present a study of tissues from patients of different age and relevance of symptoms, providing a detailed overview of AKU amyloidosis. Methods Tissues were obtained from a cohort of 6 AKU patients: 4M (63,68,42,44y) and 2F (66,71y) with different severity of symptoms. A complete microscopic and ultrastructural analysis is presented and patient features as radiological examination, mild-to-severe degenerative changes as joint space narrowing, cartilage irregularities, sub-chondral sclerosis or peripheral osteophytes and linear intervertebral disk calcifications were reported. SAAserum levels and other serological markers were measured too.Specimens were analysed by Congo Red, Immunof uorescence, Transmission Electron Microscopy, Results The analysis of all AKU specimens confirmed the massive presence of amyloid fibrils even in young patients. Alterations in collagen composition, associated to amyloid bundles deposition, were observed especially in labial salivary gland, cartilage, tendons and infragatellar fat pad. Histological analysis showed depletion of glycosaminoglycans in young patients, whereas, at light microscopy, calcification and fibrillation were observed only in elderly patients. Immunof uorescence assessed undoubtedly the presence of SAA in amyloid deposits in AKU, and we reported for the first timethe finding of amyloid deposition in young AKU patients and in less common regions. Conclusions We provide the first detailed overview of amyloidosis in AKU. Our findings depicted a novel biological framework underlining the pathological role of amyloidosis in several AKU tissues. Furthermore, we found that degradation of extracellular matrixin AKU is not limited to elderly. The clinical burden of AKU may notably increase, since amyloidosis was found even in young AKU patients, whereas degeneration of cartilage and tendons was limited to older subjects.

info@aimaku.it

## SPHINGOLIPID METABOLISM AS A THERAPEUTIC TARGET IN HEREDITARY SPASTIC PARAPLEGIA 11

ABSTRACT N° E004\_2018 / NEUROLOGICAL DISEASES

Giovanni Stevanin, Maxime Boutry, Julien Branchu, Alexandre Seyer+, Benoit Colsch+, Alexis Brice, Fanny Mochel, Khalid Hamid El Hachimi, Frédéric Darios Institut du Cerveau et de la Moelle épinière, Inserm 1127, Sorbonne Université, CNRS 7225, EPHE, Paris, France. + Profilomic/CEA, France

Mutations in the SPG11 gene are a good illustration of the clinical overlap of a variety of motor neuron diseases since they account for the main causes of autosomal recessive hereditary spastic paraplegia, but also for progressive juvenile-onset amyotrophic lateral sclerosis and some forms of Charcot-Marie-Tooth disease. To elucidate the physiopathological mechanism underlying these human pathologies, we have invalidated the Spg11 gene in mouse. The Spg11 knockout mouse developed early-onset motor impairments and cognitive deficit mimicking the human pathology. These behavioral deficits were associated with progressive brain atrophy with loss of neurons in the primary motor cortex, cerebellum and hippocampus, as well as with accumulation of dystrophic axons in the corticospinal tract. At the cellular level, Spg11 invalidation led to progressive accumulation of lipids in lysosomes. We demonstrated that lysosomal accumulations of sphingolipids are responsible for an increased sensitivity of neurons to cell death. Interestingly, prevention of the accumulation of specific sphingolipids in lysosomes prevented neurodegeneration and improved the motor phenotype in a zebrafish model of SPG11. Our results pinpoint sphingolipid metabolism as a rationale therapeutic target for preclinical studies in the Spg11 mouse model. Disclosure: Funded by the Erare programme and the ERC.

giovanni.stevanin@icm-institute.org

# NOTES


# LIST OF PARTICIPANTS

Adams	Chris	Cydan II, Inc	USA
Aleksandrova	Oksana	Association of patients with pulmonaty hypertension	Ukraine
Alinejad	Tahereh	University Malaya	Malaysia
Andelfinger	Gregor	Sainte Justine University Hospital Center,	Canada
5	5	Université de Montréal	
Anikster	Yair	Safra Childrens Hospital	Israel
Baldessari	Danila	FONDAZIONE TELETHON	Italy
Barilli	Amelia	University of Parma	Italy
Beckmann	Jacqui	University of Lausanne	Switzerland
Bietrix	Florence	EATRIS ERIC	Netherlands
Bonifazi	Donato	CVBF	Italy
Boraldi	Federica	University of Modena and Reggio Emilia	Italy
Braconi	Daniela	Università degli Studi di Siena	Italy
Callens	Steven	Ghent University Hospital	Belguim
CAMPANA	STEPHANE	CarthaGenetics Suisse Sarl	Switzerland
Cardoso	Gabriela	Universidade Federal do Rio Grande do Sul	Brazil
Carganico	Germano	Rare Partners srl Impresa Sociale	Italy
Carletti	Samantha	PKS Kids Italia Onlus	Italy
Cederroth	Helene	Wilhelm Foundation	Sweden
Chelly	Jamel	IGBMC	France
Chrast	Roman	Karolinska Institutet	Sweden
Ciriminna	Chiara	BLACKSWAN Foundation	Switzerland
Cleveland	Donald	Ludwig Institute for Cancer Research, UCSD	USA
D'Amato Sizonenko	Loredana	Orphanet Switzerland Geneva University Hospitals	Switzerland
Dall'Asta	Valeria	University of Parma	Italy
Daniels	Veronique	KU Leuven	Belauim
Davoudian	Ali	Rare Diseases Foundation of Iran	Iran
Dawkins	Hugh	Public and Aboriginal Health.	Australia
	Dept of Health	Western Australia	
Dawson	John	Newcastle University	United Kingdom
Dermaut	Bart	University Hospital Ghent	Belguim
Elpeleg	Orly	Hebrew University Medical Center	Israel
Estivill	Xavier	Sidra Medical and Research Center	Qatar
Etchevers	Heather	INSERM / Aix-Marseille Univ.	France
Federico	Antonio	University of Siena	Italy
Ferlini	Alessandra	UNIVERSITY HOSPITAL ST. ANNA, FERRARA, ITALY	Italy
Gahl	William	National Institutes of Health	USÁ
Garattini	Silvio	Mario Negri Institute for Pharmacological Research	Italy
Garcia	Fran	Mendelian	United Kingdom
Gattorno	Marco	IRCCS Istituto Giannina Gaslini	Italy
Graessner	Holm	Centre for Rare Diseases Tübingen	Germany
Groft	Steve	National Institutes of Health	USA
Hanauer	Marc	INSERM	France
Hanvi	Kangni	Association NEUROFIBROMA-TOGO	Togo
Hedley	Victoria	Institute of Genetic Medicine, Newcastle University	United Kingdom
Hemelsoet	Dimitri	Ghent University Hospital	Belgium
Ivanov	Dmitriy	Saint- Petersburg State Children Hospital 1	Russian Federation
Julkowska	Daria	French National Research Agency (ANR)	France
Katsanis	Nicholas	Duke University	USA
Kothary	Rashmi	Ottawa Hospital Research Institute	Canada
Kristina	Hettne	Leiden University Medical Center	Netherlands
Kulesha	Tatiana	NON-GOVERNMENTAL ORGANIZATION	Ukraine
Lang	Riccardo	CarthaGenetics Suisse Sarl	Switzerland

Lenting	Peter	CHU Bicetre, Hôpitaux Universitaires Paris-Sud	France
Lévy	Nicolas	Hôpital d'enfants de la Timone	France
Lodish	Harvey	Massachusetts Institute of Technology (MIT)	USA
Lupo	Mariangela	CVBF	Italy
MacInnes	Alyson	Academic Medical Center	Netherlands
Maiuri	Luigi	IERFC\San Raffaele Hospital	Italy
McArthur	James	Cydan II, Inc	USÁ
Menzel	Olivier	BLACKSWAN Foundation	Switzerland
Millucci	Lia	Università di Siena	Italv
Murphy	Anne	HUG	Switzerland
Naldini	Luigi	SR-TIGET, San Raffaele Telethon	Italy
	5	Institute for Gene Therapy	
Niezen-Koning	Klary	UMCG	Netherlands
Ozkan	Didem	Okan University	Turkey
Pasciullo	Gabriella	bluebird bio Inc.	Italy
Penninger	Josef	Institute of Molecular Biotechnology	Austria
Pereira	Carlos	FCT	Portugal
Petrova	Tatiana	CHUV and University of Lausanne	Switzerland
Pignatari	Antonella	ANGSA Bologna	Italy
Poppe	Bruce	Ghent University Hospital	Belguim
Prints	Shmuel	Neglected Diseases Collaboration (NDC)	Israel
Prosdocimi	Marco	Rare Partners srl Impresa Sociale	Italy
Quaglino	Daniela	University of Modena and Reggio Emilia	Italy
Reiss	Jochen	University Medicine Göttingen	Germany
Reguena	Jesús	University of Santiago de Compostela-IDIS	Spain
Riess	Olaf	Institut für Medizinische Genetik	Germany
		und Angewandte Genomik	
Rotoli	Bianca	University of Parma	Italy
Ruano Díaz	M Belén	Asociación Española del Síndrome de Joubert	Spain
Sandona'	Dorianna	University of Padova	Italy
Sangiorgi	Luca	Rizzoli Orthopedic Institute	Italy
Santucci	Annalisa	Università di Siena	Italy
Sapienza	Maria	University of Bologna, Department of Experimental,	Italy
		Diagnostic, and Specialty Medicine Bologna	
Scarpa	Maurizio	Center for Rare Diseases	Germany
Schuster	Ralph	DLR	Germany
Selmi	Carlo	University of Milan	Italy
Sestini	Silvia	aimAKU Associazione Italiana Malati di Alcaptonuria	Italy
Shkedy	Fanny	Shaare Zedek Medical Center	Israel
Soardi	Michela	university of Padova	Italy
Stevanin	Giovanni	INSERM U1127 INSTITUT DU CERVEAU	France
Stürtz	Anita	FWF	Austria
Taruscio	Domenica	Istituto Superiore di Sanità	Italy
Terol	Enrique	European Commission	Belgium
Turcatti	Gerardo	EPFL	Switzerland
Ussi	Anton	EATRIS ERIC	Netherlands
van de Veerdonk	Frank	Radboudumc	Netherlands
Vandevelde	Nathalie	Scientific institute of Public Heath	Belguim
Nigro	Vincenzo	Telethon Institute of Genetics and Medicine	Italy
Vissers	Lisenka	Genomic Disorders Nijmegen	Netherlands
Waters	Christina	WuXi NextCODE	USA
Wild	Edward	University College London	United Kingdom
Zhang	Dongdong	xiamen university	China

# **BLACKSWAN FOUNDATION**

The BLACKSWAN Foundation (BSF) is a not-for-profit organization based in Switzerland and created in 2010 to contribute to the development of research on rare and orphan diseases worldwide. Its principal mission is to encourage therapeutic research and to promote information campaigns for a better public understanding of rare conditions.

The Foundation supports rare diseases as a whole to leverage impact, takes into account the complexity and hurdles of rare disease research and helps in finding new solutions that can assist a large variety of projects. Innovation and the use of digital communication are fundamental for BSF and represent a way to improve the effectiveness of its work and empower community participation in existing best practices.

BSF has directly supported research projects on rare diseases through donations to public research institutes such as the Geneva Children Hospital, the Harvard Medical School and the University of Lausanne. In 2012, the Board of the Foundation had the idea to also promote a more sustainable use of financial resources and started focusing its action in the development of tools that support the work of the scientific community.

In this optic, BSF launched the RE(ACT) Initiative, a project aimed at increasing international scientific cooperation and knowledge sharing. The Initiative is structured on two axes: the RE(ACT) Congress (started in 2012), an international scientific conference that gives researchers the opportunity to learn about recent advances in the area, foster new collaborations and inspire new ideas; and the RE(ACT) Community (launched in 2014), an online platform with a huge potential to connect researchers working in the field of rare diseases, share knowledge and promote their projects through crowdfunding campaigns so to accelerate treatments' discovery.

Cooperation with partner organizations and stakeholders is of utmost importance for the Foundation, which collaborates with national and international patient organizations, academic institutions, research consortia and centers of expertise.

The BLACKSWAN Foundation is represented by its multi talented Board of Trustee and advised by its Scientific Advisory Board (SAB). The Board includes experts from a range of disciplines including finance, law and the health sciences. The SAB is composed by fourteen world leading researchers coming from Australia, Belgium, France, Italy and the US.

The Foundation is officially inscribed in the Swiss commercial register; it is supervised by the competent authority at the Swiss Federal Department of Home Affairs (FDHA) and recognized as a public utility foundation.

blackswanfoundation.ch facebook.com/Blackswan.Foundation twitter.com/BLACKSWAnFound #RAREvolution

## E-RARE: THE EUROPEAN RESEARCH AREA NETWORK FOR RESEARCH PROGRAMMES ON RARE DISEASES

As only a few European countries fund research on RD through specifically dedicated national programmes, the funding of collaborative research through joint transnational calls was seen as the most effective method to enhance cooperation among scientists, thus reducing fragmentation of RD research in Europe and beyond. This resulted in the implementation of the ERA-Net E-Rare in 2006, co-financed by the EU. The goal was to foster collaborative funding of relatively small and focused research consortia and enhance complementarity to the larger multinational groups usually funded by the EU. At the start of E-Rare-1 in 2006 the partnership consisted of eight countries but the focus and reach of E-Rare have evolved. Currently E-Rare-3 is composed of twenty-eight public bodies, ministries and research funding organizations from eighteen countries: Member States (Austria, Belgium, Czech Republic, France, Germany, Greece, Hungary, Italy, Latvia, Lithuania, Poland, Portugal, Romania, Spain, The Netherlands), three Associated Countries (Switzerland, Israel and Turkey) and two Third Countries (Canada and Japan). Through its easy to access transnational calls, E-Rare has provided a successful platform for entities interested in collaborative transnational research funding. The high number of proposals received in response to the JTCs of E-Rare highlights the great potential and diversity of the European RD research community and the need for funding of collaborative projects. Since 2006, E-Rare has launched nine JTCs for projects, investing over €104 million in research on RD. Exceptionally, in 2015 the European Commission contributed to funding of research projects. The competitive nature of the JTCs has resulted in the funding of high guality projects. A large proportion of submitting researchers have outstanding track records with publications in high impact journals. 556 scientific teams compose 117 funded consortia. In order to increase the level of collaboration and enhance the transfer of knowledge in specific regions, in 2015 E-Rare decided to encourage the inclusion of research teams from Eastern European countries (EEC) (Hungary, Latvia, Poland, Romania and Turkey). This resulted in eight projects with EEC components, significantly increasing their success rate.

In addition to the annual transnational calls, the collaborative approaches now extend to the relevant European Research Infrastructures with the aim to customize their services to the demand of RD researchers. The long-established collaboration with EURORDIS – Rare Diseases Patients Europe - has been further strengthened by the development of new funding models and the involvement of patients' organizations (PO) in research. In 2012 E-Rare also became a member of the International Rare Diseases Research Consortium (IRDIRC) and strongly contributes to its ambitious objectives.

# NOTES

## **SUPPORTERS**









Concept and editorial: BLACKSWAN Foundation

Graphic design: Automatico Studio, Lausanne

© 2018, RE(ACT) Congress, BLACKSWAN Foundation