CONGRESS
BROCHURE
INTERNATIONAL CONGRESS ON RESEARCH OF
RARE AND ORPHAN DISEASES
9TH–12TH MARCH, BARCELONA
RE(ACT)® CONGRESS 2016

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INTERNATIONAL CONGRESS ON RESEARCH OF
RARE AND ORPHAN DISEASES
MARCH 2016

BLACKSWAN FOUNDATION

SWISS FOUNDATION FOR RESEARCH ON ORPHAN DISEASES
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We are the RAREvolutionary people

STAND UP FOR
SCIENTIFIC RESEARCH
#RAREvolution

RE(ACT)CONGRESS

International Congress on Research of Rare Diseases - Barcelona 9-12 March
www.react-congress.org

RE(ACT)COMMUNITY

A digital platform to scale up scientific cooperation in rare disease research
www.react-community.org

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STAND UP FOR SCIENTIFIC RESEARCH

#RAREvolution

WELCOME

Dear Colleagues,

Welcome to the third «International Congress on Research of Rare and Orphan diseases», RE(ACT) Congress 2016. It is a pleasure to host you here in Barcelona, Europe's largest metropolis on the Mediterranean coast. 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 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.

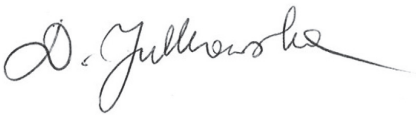
During the congress, we are going to launch an online petition to advocate for research on rare diseases. We believe that public policy plays a crucial role in advancing rare disease research. The Orphan Drug Act in the US and the European Regulation n. 141/2000 demonstrate the impact that policy decisions can have in driving forward innovative research and show the successful outcomes that public policy intervention can achieve. However, much more international attention is needed to push forward research and increase prevention, diagnosis and treatments for rare disease patients.

The petition includes the most strategic points that deserve the attention of institutions and international organizations. The contents of the petition are going to be further developed throughout the year in a position paper that will be officially handed to Rare Diseases International (RDI) during the 2017 Rare Disease Day. This document will assist RDI in its advocacy work for rare diseases at the United Nations, the World Health Organization and with other international organizations.
Sign and share the petition: blackswanfoundation.ch/en/petition/

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 Barcelona.

Dr. Olivier Menzel
BLACKSWAN Foundation

Dr. Daria Julkowska
E-RARE



KEY FACTS

Scientific program committee and advisory board
Kim Boycott, CAN - Nathalie Cartier, FR - Orly Elpeleg, IL - Olaf Horst Riess, DE - Nicholas Katsanis, USA - Yann Le Cam, FR - Hanns Lochmüller, UK - Gert Matthijs, BE - Michael Morris, CH - Francesc Palau, ES - Nick Sireau, UK - Jordi Surrallés, ES

Venue
The RE(ACT) Congress 2016 is held in the Crowne Plaza Barcelona – Fira Center. Located in the city center between the famous Plaza de Espana and Gran Via Avenue, the Fira Center is only a 25 minutes' drive from Barcelona's International Airport and close to the metro station Plaza Espana.
If you decide to enjoy the attractions of the Barcelona City Centre, you are only a few metro stops away. See Gaudi's impressive Sagrada Familia or spend some time among the pavement cafes and entertainers of Las Ramblas, or take a quick drive to Barcelona's beach.

Congress Initiator
BLACKSWAN Foundation
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CH-1418 Vuarrens
blackswanfoundation.ch

Congress Organizers
BLACKSWAN Foundation
E-Rare

Professional Congress Organizer
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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) 2016_Speaker's name_Session).

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

Important information for abstract presenters
We kindly ask all poster presenters to meet the following guidelines:
The size of your poster should not exceed DIN Format A0 Portrait - 841 mm wide and 1189 mm height. Bonding material is provided in the poster area.

- Posters may be set up on 8th March 2016 from 5pm.
- Posters should be removed on 12th March from 12pm.
- 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:
The speaker biographies and the abstracts are printed as received by the authors.

SCHEDULE AT A GLANCE

Tuesday 8th March

9.00 - 17.00 2016 E-RARE, membership meeting (closed)

Wednesday 9th March

9.00 - 16.00 Special Session European Medicine Agency (EMA)
14.00 - 17.00 A. Session : Drug repositioning and personalized medicine
17.00 - 18.00 Poster A. Session
18.00 - 20.00 Public Opening Ceremony

Thursday 10th March

9.00 - 12.00 B. Session : NGS and undiagnosed rare diseases (Session supported by Synlab)
12.00 - 13.00 Lunch
13.00 - 14.00 Poster B & C Session
14.00 - 17.00 C. Session : Pathophysiology
17.00 - 19.00 Poster B & C Session

Friday 11th March

8.30 - 13.00 D. Session : Bringing Treatments to the Clinic
12.00 - 13.00 Lunch
13.00 - 12.00 Poster D & E Session
13.00 - 17.00 E. Session : Neurological diseases
17.00 - 19.00 Poster D & E Session

Saturday 12th March

9.00 - 14.00 F. Session : Patients and research (Session supported by Actelion)

PROGRAM

Tuesday 8th March

9.00 - 19.00 2016 E-RARE, Membership meeting (closed)

Wednesday 9th March

9.00 - 13.00 Workshop

Interactions between EMA and RD researchers on pre-licensing activities

- Pre-licensing activities of EMA with the presentation of relevant EMA services (COMP, SAWP, PDCO, CAT)
- Orphan designation and incentives for researchers including information on how to submit OD and Protocol assistance – how it works
- Lessons learnt from Horizon 2020 success stories on obtaining an OD

14.00 -17.00 Face-to-face meetings with EMA officers

14.00 - 17.00 A. Session : Drug repositioning and personalized medicine

- Bruce Bloom, USA "Back to the Future-How Drug Repositioning Has and Will Create Treatments for Unsolved Diseases"
- Luigi Maiuri, IT "Drug repositioning for the personalized therapy of cystic fibrosis"
- Leena Bruckner-Tuderman, DE "Repurposing losartan to ameliorate dystrophic epidermolysis bulls"
- Alex MacKenzie, CA "Pinging the Transcriptome; Mining the Pharmacopeia for Rare Inherited Disorder Therapies"
- Martina Cornel (Abstract n° A008) "Teaching an old dog new tricks? Lessons on using n-of-one trials to repurpose treatments for rare diseases: the example of ephedrine for myasthenia gravis"
- Dorianna Sandonà (Abstract n° A010) "Novel therapeutic perspectives for sarcoglycanopathy by assisting protein folding"

17.00 - 18.00 Poster A. Session

18.00 - 20.00 Public Opening Ceremony

- Christopher P. Austin, USA "Catalyzing Translational Innovation"
- Yann Le Cam, FR

Thursday 10th March

9.00 - 12.00 B. Session : NGS and undiagnosed rare diseases (Session supported by Synlab)

- Kerstin Nagel-Wolfrum, DE "Usher syndrome – challenges fordiagnosis and treatment"
- Holger Prokisch, DE "Tracking Mitochondrial Diseases through Next Generation Sequencing"
- Corina Shtir, USA "An Effective Approach for Diagnosing Rare Genetic Diseases within the Saudi Population"
- Joris Veltman, NL "De novo mutations in intellectual disability: From gene to genome and from research to diagnostics"
- Ana Rath (Abstract n° B008) "HIPBI-RD: Harmonising phenomics information for a better interoperability in the rare disease field"

12.00 - 13.00 Lunch

13.00 - 14.00 Poster B&C Session

14.00 - 17.00 C. Session : Pathophysiology

- Inderjeet Dokal, UK "Dyskeratosis congenita and related diseases of telomeres"
- Hélène Dollfus, FR "Bardet-Biedl, Alström and related ciliopathies pathogenesis : from ultra rare diseases to more common diseases"
- Jan Hoeijmakers, NL "DNA Repair syndromes: key for understanding aging"
- Marguerite Neerman-Arbez, CH "Of Fish and Men – using zebrafish to study rare genetic disorders of hemostasis"
- Marco Tartaglia, IT "RASopathies – The other face of RAS signalling dysregulation"
- Cristina Borralleras Fumaña (Abstract n° C004) "Epigallocatechin gallate effect on a Williams-Beuren syndrome mouse model"
- Stephan Pabinger (Abstract n° B005) "Interactive software for the integrated analysis and identification of rare and undiagnosed diseases using NGS data"

17.00 - 19.00 Poster B&C Session

Friday 11th March

8.30 - 12.00 D. Session : Bringing Treatments to the Clinic

- Juan Bueren, ES "Non targeted and Targeted Gene Therapy Approaches in Fanconi Anemia"
- Coen Ottenheijm, NL "Fast Skeletal Troponin Activation for Restoring Muscle Strength in Mouse Models of Nemaline Myopathy"
- Gert Matthijs, BE "Therapies and treatment for (very) rare and genetically heterogeneous disorders: why (not) CDG ?"
- Danilo A. Tagle, USA "Innovative Tools for Drug Development and Disease Modeling"
- Renée Zwanenburg (Abstract n° D003) "Challenges and experiences of conducting a randomized, double-blind, placebo-controlled trial for a rare genetic disorder: Intranasal insulin in Phelan-McDermid syndrome"
- Juan R. Rodriguez-Madoz (Abstract n° D006) "Generation of tools for disease modelling of Primary Hyperoxaluria by cell reprogramming"
- Hiroshi Mizushima (Abstract n° F009) "Development of Remote Data Entry System for National Nambyo (Intractable Rare Disease) registry in Japan"

12.00 - 13.00 Lunch

13.00 - 14.00 Poster D&E Session

13.00 - 17.00 E. Session Neurological diseases

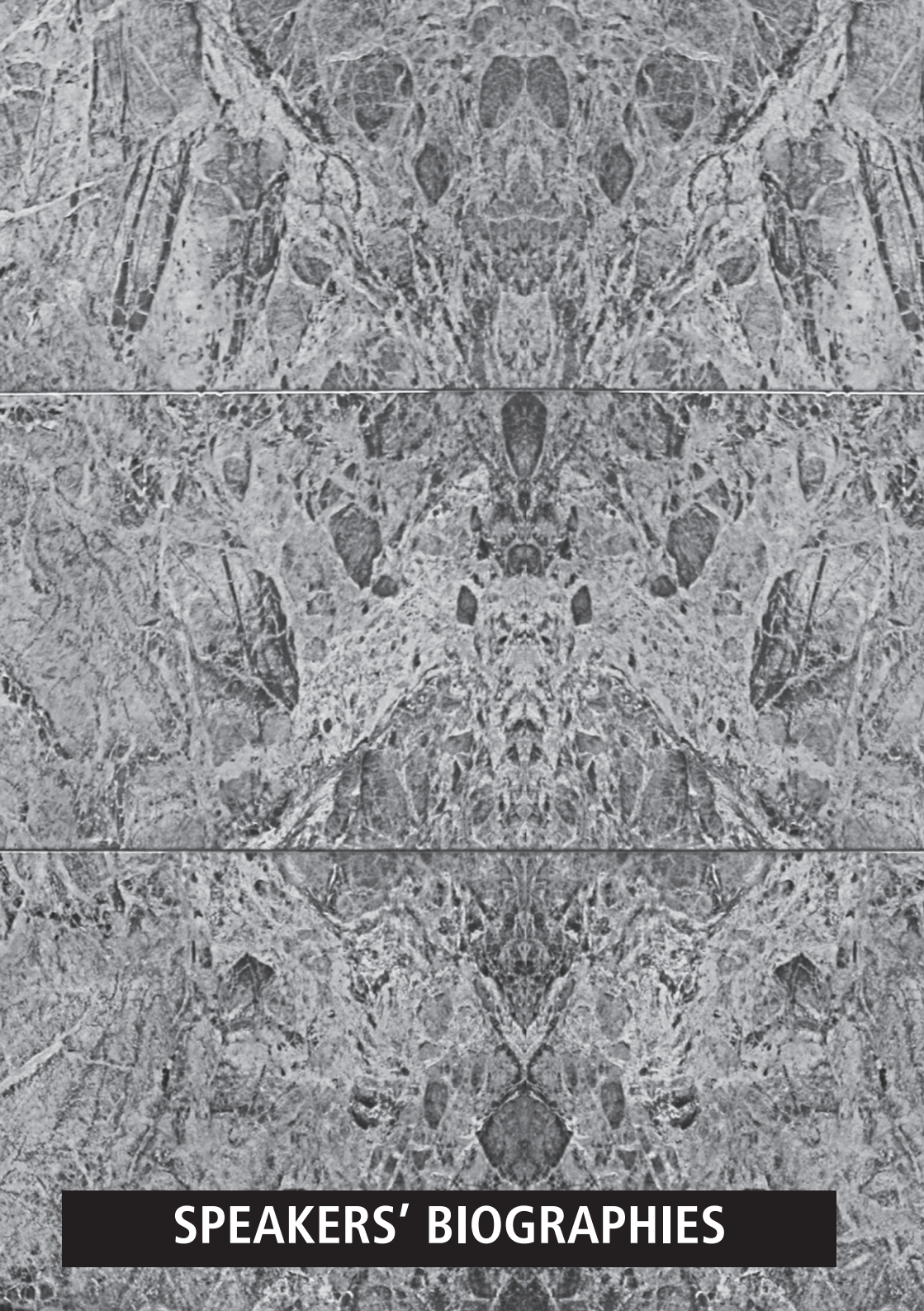
- Giovanni Stevanin, FR "Delving into the complexity of spinocerebellar degenerations, how next generation sequencing improved our knowledge"
- Shimon Edvardson, IL "Rare neurogenetic disorders: the clinicians perspective"
- Julio Montoya, ES "Mitochondrial diseases: state of the art"
- Olaf Horst Riess, DE " The new role of Medical Genetics in Clinical Guiding"
- Marjo Van der Knaap, NL "Update on leukodystrophies"
- Heike Heuer (Abstract n° E009) "Therapeutic potential of thyroid hormone analogs Triac and Ditpa in Allan-Herndon-Dudley Syndrome"

17.00 - 19.00 Poster D&E Session

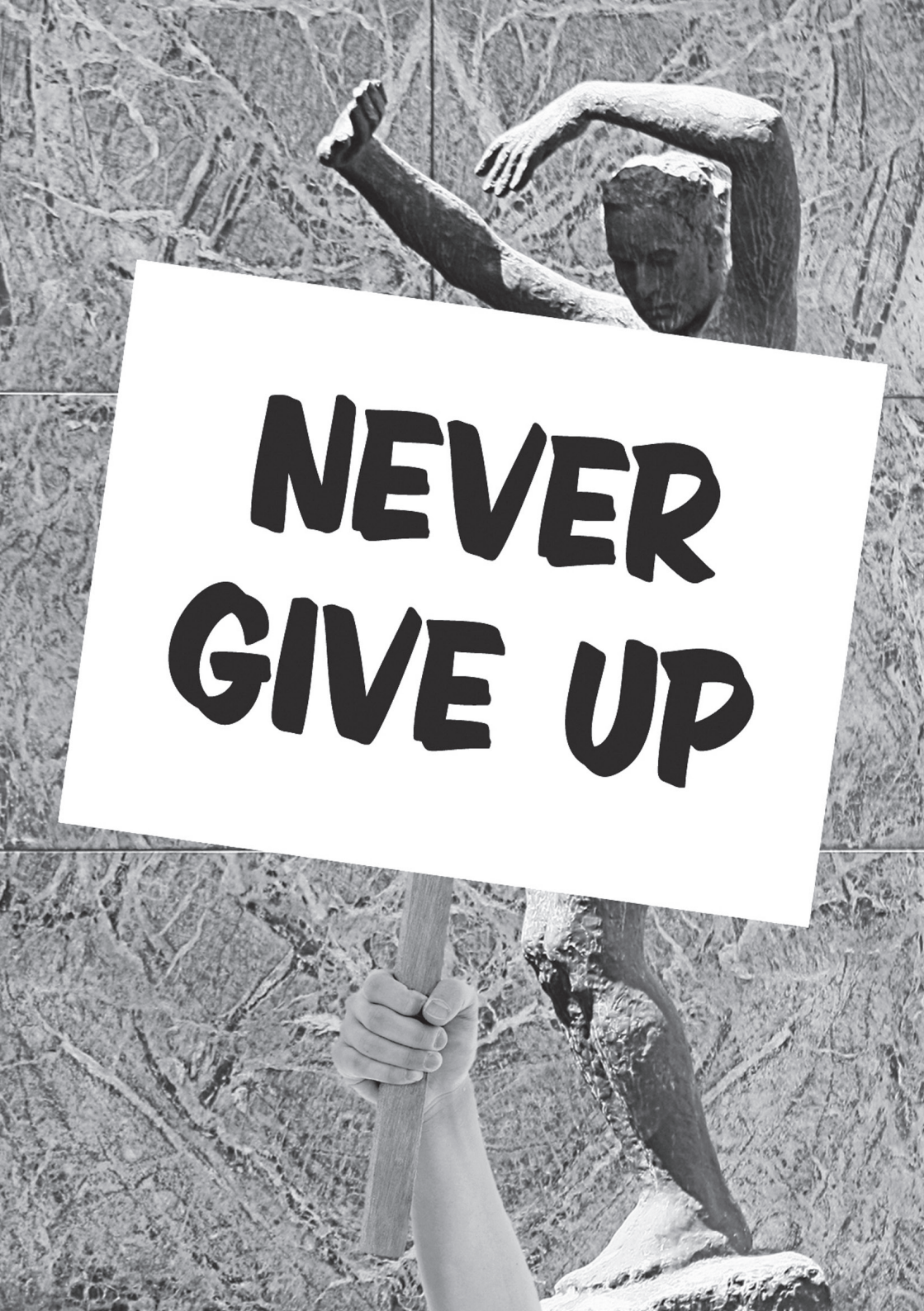
Saturday 12th March

9.00 - 12.00 F. Session : Patients and research (Session supported by Actelion)

- Erica Daina, IT "Rare diseases registries as tools for clinical research"
- Heather Etchevers, FR "Crowdfunding primary rare disease research : bootstraps and biobanks"
- Jan Geissler, DE "The benefits of patient involvement in research and development"
- Virginia Llera, AR "LA&C: Opportunities and Challenges to Rare Diseases Research"
- Conny van Ravenswaaij-Arts (Abstract n° F003) "The power of social media for karyotype-phenotype analysis of rare chromosome disorders"



SPEAKERS' BIOGRAPHIES


NEVER
GIVE UP

AUSTIN CHRISTOPHER P.

Christopher Austin is Director of the National Center for Advancing Translational Sciences (NCATS) at the U.S. National Institutes of Health. NCATS' mission is to catalyze the generation of innovative methods and technologies that will enhance the development, testing and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions. Before becoming NCATS Director in September 2012, he was Director of the NCATS Division of Preclinical Innovation, which focuses on translating basic science discoveries into new treatments, particularly for rare and neglected diseases, and developing new technologies and paradigms to improve the efficiency of therapeutic and diagnostic development. In this role, he founded and directed numerous initiatives including the NIH Chemical Genomics Center (NCGC), the Therapeutics for Rare and Neglected Diseases (TRND) program, and the Toxicology in the 21st Century (Tox21) program. Before joining NIH in 2002, Dr. Austin directed research programs genomics-based target discovery, pharmacogenomics, and neuropsychiatric drug development at Merck, with a particular focus on schizophrenia. Austin earned an A.B. in biology from Princeton University and an M.D. from Harvard Medical School. He completed clinical training in internal medicine and neurology at Massachusetts General Hospital, and a research fellowship in genetics at Harvard.

BLOOM BRUCE

Dr. Bruce Bloom is President and Chief Science Officer of Cures Within Reach, a US based global charity that improves patient quality and length of life by facilitating proof of concept clinical trials testing the repurposing of human approved drugs, devices and nutriceuticals for new indications, especially in rare and neglected diseases.
Cures Within Reach's newest venture is CureAccelerator™, the only global online repurposing research collaboration platform designed to bring together funders, clinicians, researchers, industry and lay stakeholders to create and conduct pilot clinical trials that drive more repurposed treatments to more patients more quickly.
Dr. Bloom was selected as an International Ashoka Social Entrepreneur Fellow in 2010 for his system-changing solutions to one the world's most urgent social problems, cure development. His business experience spans not-for-profit and for-profit work in research, law, healthcare, medical malpractice, risk management, regulatory affairs, product development, food service, art, and education.
Dr. Bloom is on the Science Advisory Board (SAB) of Rediscovery Life Sciences, SAB member for the GARROD AKU Consortium, Trustee of the Kendall College Charitable Trust, member of the Board of Councilors of Midwestern University, and Client Advisor to Northwestern Mutual Financial Network. Dr. Bloom hosts the Clinician's Roundtable on ReachMD.com, and is a facilitator for Pathways to Successful Living.

BRUCKNER-TUDERMAN LEENA

Leena Bruckner-Tuderman is professor and chair of the Department of Dermatology at the Medical Center – University of Freiburg, in Freiburg, Germany, and coordinator of the Freiburg Center for Rare Diseases. As a physician-scientist she combines basic and translational research with patient care.
She studied medicine in Oulu, Finland, and after an experimental dissertation in molecular

medicine, continued her postdoctoral work in biochemistry in Piscataway, N.J., USA, and in structural biology in Basel, Switzerland. She specialized in dermatology at University of Zurich, Switzerland and was a Score-Fellow of the Swiss National Science Foundation. Thereafter she became a Heisenberg fellow of the German Research Foundation (DFG) and moved to the Münster University, Germany, where she became professor of dermatology. During this period in Münster she was also a visiting professor at the University of Hong Kong and at the Harvard Medical School, Boston. In 2003 she relocated to University of Freiburg, where she also was fellow and director of the School of Life Sciences – LIFENET of the Freiburg Institute for Advanced Studies in 2007 – 2013.
She has been and continues to be a board member of numerous national and international committees, organizations and foundations, organizer of programmes and conferences, e.g. Gordon Research Conferences. She has received numerous prizes, is a member of the German Academy of Sciences Leopoldina and the Vice President for Medicine of the German Research Foundation, DFG.The research focus of the Bruckner-Tuderman lab encompasses molecular genetics and disease mechanisms of rare skin diseases, and development of molecular therapies, as well as biology of basement membranes and the extracellular matrix, epithelial-mesenchymal communication, cell-matrix interactions.

BUEREN A. JUAN

Juan Bueren is the Head of the Hematopoietic Innovative Therapies Division at the CIEMAT and the Centre for Biomedical Research on Rare Diseases (CIBERER). Since 2004 is also the Coordinator of the Advanced Therapies Unit of the Fundación Jiménez Díaz and CIEMAT. Awards of Appreciation and Distinguished Service Award from the Fanconi Anemia Research Foundation (FARF). Former President of the Spanish Society for Gene and Cell Therapy (2011-2013). Board member of the European Society for Gene and Cell Therapy. Member of the Hematologic and Immunologic Gene and Cell Therapy Committee from the American Society for Gene and Cell Therapy. Author of 125 papers in international journals on topics related with hematopoietic stem cells, gene therapy and cell reprogramming.

DAINA ERICA

Dr. Erica Daina is a senior representative member of the Clinical Research Centre for Rare Diseases (CRCRD) established in 1992 in Italy, as part of the Mario Negri Institute for Pharmacological Research.
The Centre mission is to promote independent clinical research, particularly focussed on rare, genetic diseases. It has also developed as a clearinghouse of information to patients, families, physicians and health authorities, and has established one of the first helpline for patients in Italy. Since 2001 the CRCRD is the Coordinating Centre of the Regional Network for Rare Diseases in the Lombardy Region and it collaborates with the National Center for Rare Diseases, which is part of the Italian Istituto Superiore di Sanità.
Erica Daina got her degree in Medicine at the University of Milan in 1987 and the specialisation in Medical Nephrology in 1990. She performed her training at the II° Medical Division – San Raffaele Hospital – Milan, and at the Division of Nephrology and Dialysis – Riuniti Hospital – Bergamo. In 1991 she started her collaboration with the Mario Negri Institute and she got the specialization in Pharmacological Research.

Professional positions: 1996 – 2009:Head, Information Center for Rare Diseases. June 2009 – present: Head, Laboratory of Rare Diseases Documentation and Research. January 2002 – present: Representative of Coordinating Centre – Regional Network for Rare Diseases.
She is involved in several national and international projects and collaborations in the field of public health issues and research in rare diseases.

DOKAL INDERJEET

Professor Inderjeet Dokal graduated in Medicine from the University of Leicester in 1983. He moved to Hammersmith Hospital (London) in 1984 where he received his post graduate clinical and research training. He was appointed Consultant in Paediatric Haematology in 1995 and was conferred the title of Professor of Haematology at Imperial College London in 2003. In 2006 he was recruited to the Chair of Child Health at Barts and The London/Queen Mary University of London where he currently leads the Centre for Genomics and Child Health. His principal research interest is the pathophysiology of aplastic anaemia (AA)/bone marrow failure. Over the past 20 years his group has determined the genetic basis and pathophysiology of several sub types of bone marrow failure. This has shown the importance of telomerase and telomeres in humans and the consequences of their dysfunction. Current research is focussed on elucidating the genetic basis and pathophysiology of the many uncharacterized cases of dyskeratosis congenita, aplastic anaemia, myelodysplasia and related disorders. He was elected Fellow of The Academy of Medical Sciences (FMedSci) in 2010.

DOLLFUS HÉLÈNE

Hélène Dollfus trained in Strasbourg, Paris and London and is a MD specialized in ophthalmology as well as medical genetics. She is appointed as a professor in medical genetics and as a consultant in medical genetics at the Strasbourg University Hospital (HUS) where she is the head of the medical genetics department. She is the coordinator of the Centre for Rare Genetic Ophthalmic Diseases located in Strasbourg and is the national coordinator for the rare disease network on sensorial genetics: the SENSGENE filière. After obtaining her PhD she set a research group focused on the field of syndromic retinal degenerations and more widely on the ciliopathies group of diseases. She has set the Medical Genetics Research Laboratory at the Strasbourg University (UNISTRA) also recognised as an INSERM unit (U1112). Since 2011 she is the vice president for research of the steering committee of the second French National Rare Disease Plan (PNMR2). HD is a senior member of the Institut Universitaire de France (IUF). In the last two years she has been awarded : the Grand Prix Robert Debré (2014) ; the Prix recherche INSERM (2014) ; the Prix FondactionAlsace Talent d'avenir (2015).

EDVARDSON SIMON

Dr. Edvardson is a consultant and researcher at the Hadassah University Hospital of the Hebrew University of Jerusalem. His special interests are the genetic underpinnings of rare inherited neurological disorders. The main focus of his work has been to integrate the novel genetic tools such as Next Generation Sequencing into the routine care of patients and bring those techniques to the bedside. Dr. Edvardson completed his fellowship in Hadassah in 2006 and has since then worked there as a consultant at the Neuropediatric unit. He

has been part of the neurogenetic team, headed by Prof. Orly Elpeleg, which has discovered several novel genes responsible for rare neurogenetic disorders. Further collaborations with German, Japanese, American and Swedish scientists have been established in the process to elucidate the pathophysiology of the mutations identified.

ETCHEVERS HEATHER

Heather Etchevers is a tenured scientist with the Institut National de la Santé et la Recherche Médicale in Marseille, France. She earned a joint Ph.D. with the University of California at Berkeley and Université Pierre et Marie Curie in Paris. Her research group is located at the Université Aix-Marseille, within a department devoted to the diagnosis, study and treatment of rare genetic disorders. Using experimental approaches from basic developmental biology, animal and cellular models, and human tissues, Dr. Etchevers and her collaborators have published over 45 peer-reviewed articles on the etiology of multiple congenital malformations. Since 1999, Dr. Etchevers regularly addresses rare disease patient advocacy groups and offers courses in embryology for continuing medical education around the world. She is currently on the editorial boards of Birth Defects Research Part A: Clinical and Molecular Teratology and PeerJ, and chairs the Scientific Advisory Board for the international Naevus Global federation.

GEISSLER JAN

Jan Geissler is working for the European Patients' Forum in his role as director of the 'European Patients Academy on Therapeutic Innovation', a project funded by Innovative Medicines Initiative (IMI). EUPATI develops educational material and training courses to educate patient representatives and the lay public about all processes involved in medicines development. He is also founder and managing director of Patvocates and acts as independent advisor in the triangle of cancer policy, patient advocacy and social media.
After his University diploma in Business Management in the UK and Germany, Jan held various managerial positions in telecommunications R&D and media industry think tanks before he focused his professional life on patient advocacy in 2008. Being a leukemia survivor who participated in various clinical trials himself, Jan founded the online patient community Leukämie-Online/LeukaNET in 2002, which is one of the most frequented online platforms for leukemia patients on the German speaking Internet today. In 2003, he co-founded the European Cancer Patient Coalition and became its first full time director 2008. In 2007, Jan also co-founded the CML Advocates Network which is connecting 102 leukemia patient groups from 78 countries on all continents today. He is a patients' representative in various advisory boards, e.g. the European Commission Group of Experts on Rare Diseases, the European Commission Expert Group on Cancer Control, the editorial journals of "Journal of European CME", "Journal of Cancer Policy" and "Journal of Research Involvement and Engagement", the ESMO Patient Advocacy Working Group, the ECCO Patient Advisory Committee, the Institutional Review Board of EORTC, the scientific advisory board of the International CML Foundation, and the External Advisory Board of the University Clinic of Jena. He also acts as an independent expert for the European Commission. He is also founder and managing director of Patvocates, acting as independent consultant in cancer policy, patient advocacy and social media.

HOEJIMAKERS JAN

Jan Hoeijmakers joined the Dept. of Genetics of the Erasmus University in Rotterdam in 1981 to work on DNA repair. His team succeeded in cloning the first of many subsequent human DNA-repair genes allowing elucidation of the reaction mechanism of nucleotide excision repair, discovered the strong evolutionary conservation of DNA repair, resolved the basis of a variety of enigmatic human repair syndromes and identified a new class of 'basal transcription disorders'. His laboratory generated a comprehensive series of mouse DNA repair mutants, strikingly mimicking the corresponding human syndromes, which provided detailed insight into the complex etiology of human repair diseases. He discovered a very strong, initially highly controversial connection between DNA damage and (bona fide) aging, and on this basis proposed a trade-off between cancer and aging. By modulating DNA repair, damage induction and nutrition my team succeeded in largely controlling the process of aging in mice. The type of DNA repair defect is found to determine the type of segmental accelerated aging and/or cancer. The severity of DNA repair deficiency correlates with the rate of accelerated aging: shortening lifespan and time of onset of many aging-related diseases from years to weeks. Conditional repair mutants allow targeting accelerated aging to any organ, tissue or stage of development. Expression profiling revealed an unexpected similarity between short- and long-lived mice: both suppress the somatotrophic axis, which extends lifespan. This work led to the identification of a highly intriguing 'survival response' that promotes healthy aging and counteracts cancer by redirecting energy from growth to maintenance. Importantly, by nutritional interventions in collaboration with the RIVM (Bilthoven), his team very recently succeeded in extending lifespan of some repair mutants over 2-fold, which for mammals is unprecedented. Moreover, the mouse mutants turned out to be far superior models for neurodegenerative disorders, like Alzheimer and Parkinson diseases, than any currently available model. Nutritional interventions strongly delayed the development of this dementia. Additionally his laboratory developed a new line of in vivo research revealing the highly dynamic organization of DNA repair in living cells and intact organisms. His group also generated the first mouse mutants with intrinsic defects in the biological clock. In summary, his work places DNA damage at the basis of cancer and aging, highlights the flexible nature of aging and establishes the repair mutants as suitable tools for identification of life span extending pharmaceutical and nutraceutical interventions in mammals. This opens new perspectives for prevention or treatment of aging-related diseases, which are associated with enormous loss of QoL and constitute the main medical and health care challenges in all developed countries.

LLERA VIRGINIA

Coordinator of the first multi-centric rare diseases survey granted by the Health-Research Division of the Argentina National Ministry of Health (MSN). Author of several research and awareness articles on rare diseases and orphan drugs, published at Science, ActaPaediatrica, Rare Journal, among others, and including journalist articles. Awarded by different patient institutions including EURORDIS (France, 2007), Crystal Children Organization (Panama, 2011), FEMEXER (Mexico, 2014), ICORD (Sweden 2015) and others. Advisor/consultant for the development of Rare Diseases legislations in different countries (Argentina, Brazil, Columbia, Peru). External Advisor of the Health Ministry at the Province of Buenos Airesfor the regulation of the Rare Diseases Law. HTAi member (Health Technology Assessments International).

MACKENZIE ALEX

Alex MacKenzie, an attending pediatrician at the Children's Hospital of Eastern Ontario (CHEO) in Ottawa Canada has served as the CEO and Science Director of the CHEO Research Institute as well as Vice President of Research for both CHEO and Genome Canada in addition to being founding scientist of the AeGera biotech company. Dr. MacKenzie's laboratory has conducted translational research on the rare pediatric disorder spinal muscular atrophy over the past 25 years; in recent years has broadened its focus with its involvement in the enhance Care for Rare project to search for therapies for a larger number of rare diseases.

MAIURI LUIGI

Prof. Luigi Maiuri, is Research Director of the European Institute for Research in Cystic Fibrosis at the San Raffaele Scientific Institute in Milan since 2007 and Associate Professor of Pediatrics at the University of Eastern Pedmont. Since 2002 to 2007 he was appointed as Honorary Senior Lecturer at the Institute of Child Health and Great Ormond Street Hospital, University College of London and from 2008 to 2011 as Visiting Professor at the Cancer Sciences Division of the University of Southampton.

His scientific interest focusses on disease mechanisms and their modulation. Firstly, his studies focused on the modulation of the innate immune response in celiac disease. He discovered the rules of cooperation between innate and adaptive mucosal immune response to gliadin and unveiled the role of IL15 in driving immune/autoimmune disease phenotype in celiac disease (Lancet, 2003). Moreover, he studied how degenerate self-reactive human T cell receptor may cause spontaneous autoimmune disease in mice (Nature Med 2004). Since 2007, his scientific interest has focussed on cystic fibrosis. His pioneering studies on autophagy have deciphered the relationship between the genetic CFTR defect and proteostasis and demonstrated how manipulating autophagy can circumvent CFTR defect (Nature Cell Biol 2010).

While as a clinician he is interested in drug repositioning for the personalized therapy of cystic fibrosis. He implemented at the laboratories of the European Institute for Research in Cystic Fibrosis a multifaceted cascade of pre-clinical models for translational and reverse translational approaches to therapy. Recently, in collaboration with Prof. Guido Kroemer, Prof. Valeria Raia and Dr. Anil Mehta he translated pre-clinical data to patient's therapy showing that a combination of two repurposed proteostasis regulators can reverse the CFTR defect of the most common CFTR mutant and ameliorate disease phenotype in CF patients (Autophagy 2014). In February 2014 the Orphan Drug Designation for the use of cysteamine in Cystic Fibrosis was granted to Prof. Maiuri's lab by the European Medicines Agency.

He has published more than 90 peer-reviewed scientific papers on international journals of high impact factor, and contributed to review articles and book chapters. He has a relevant teaching experience in national and international Universities and was invited speaker in more than 50 international research meetings. His research activity is supported by several national and European grants.

MATTHIJS GERT

Gert MATTHIJS is head of the Laboratory for Molecular Diagnostics at the Center for Human Genetics in Leuven, and Professor at the University of Leuven, Belgium. He has been involved in the diagnostics of inherited diseases since 1994. The Center for Human Genetics is the largest genetic department in Belgium. The laboratory is offering molecular tests for the more common genetic diseases like cystic fibrosis, fragile X syndrome, Huntington's disease, myotonic dystrophy, spinal muscular atrophy, hemophilia and Duchenne/Becker Muscular Dystrophy, and for a series of less frequent disorders. The laboratory also offers testing for familial breast- and ovarium cancer (BRCA1 and BRCA2) and familial colon cancer and other familial cancer syndromes.

His major research interest is in Congenital Disorders of Glycosylation (CDG), a group of rare inborn errors of metabolism. He was the coordinator of EUROGLYCANET, a European project focusing on the identification of novel defects and the generation of models for CDG. For this work on CDG, he received the "Körber European Science Award" in 2004, together with Prof. von Figura, Prof. Aebi, Prof. Hennet, Prof. Jaeken and Prof. Lehle.

He was coordinator of EUROGENTEST2, a network for the further development, harmonization, validation and standardization of genetic testing in Europe, funded by the European Commission, and a member of TECHGENE, a European project for the introduction of next generation sequencing tools in diagnostics.

He is the coordinator of EURO-CDG-2, a European research network directed towards improving diagnosis and treatment of inborn errors of glycosylation. This project has received funding from the European Union's Horizon 2020 research and innovation program under the ERA-Net Cofund action N°643578. It was supported by FWO, under the frame of E-Rare, the ERA-Net for research on Rare Diseases.

He was a Board member and chaired the Patenting and Licensing Committee of the European Society of Human Genetics (ESHG), and played an important role in the European opposition against the BRCA patents.

He is a member of the Scientific Diagnostic Committee of IRDiRC (International Rare Disease Research Consortium) and an Alternate member of the Commission Expert Group on Rare Diseases (formally EUCERD).

At the national level, he has been a thriving force for a revision of the reimbursement system for genetic tests.

Together with J. Vermeesch, he has coordinated a workgroup on legal, ethical and societal aspects of total genome analysis (in the context of the Metaforum initiative of the university).

Together with P. Borry (Center for Biomedical Ethics and Law), he organized an exposition on cartoons and genetics in the summer of 2014, and published a book about genetics for the public ('Iedereen GENiaal'), that will soon be translated in English.

MONTOYA JULIO

Professor, Department of Biochemistry and Molecular Biology. University of Zaragoza. Member of CIBERER (CIBER for Rare Diseases). Spain. Education and training: Graduation (1973) and Master (1974) in Pharmacy; PhD in Biochemistry (1977). University Complutense of Madrid. Positions and Employment: Teaching Assistant at Dpt Biochemistry. University Complutense. Madrid. Spain (1979); Department of Microbiology. Bristol University, England . 1976; Division of Biology. California Institute of Technology. USA. 1979-83; 1984; 1989; 1998; Associate

Professor. Dpt. Biochemistry. University of Zaragoza. Spain (1983-2003); Profesore a Contratto. Università di Bari. Italy (1987). Honors: Prize to Research Excellency to the best Scientific carrer. 2004; Royal Academy of Science Prize. Zaragoza. 2005. Research interest: My research interest has always been related to the mitochondrial genetic system. During my stay at the California Institute of Technology (USA), laboratory of Giuseppe Attardi, I was involved in the Human Mitochondrial Genome. This project gave rise to important contributions on the mitochondrial transcriptome: isolation, identification and sequencing chararacterization of the human mitochondrial RNAs. Thus it was described, for the first time, the existance of mRNAs starting directly by the initiation codon, constructed a transcription map, proposed a model of transcription of the human mtDNA and described the mode of RNA processing (tRNA punctuation model). Later on, in the University of Zaragoza I continued with the analysis of the mtDNA expression in differentiated mammalian organs, obtaining the first experimental evidences for the existence of autonomous regulation mechanisms in the mtDNA expression and the regulation of the mtDNA transcription by phosphorylation of the transcription termination factor.
After the first mtDNA mutation was associated with human disease, I decided to focus my reseach interest to the study mitochondrial diseases from different points of view: clinical, morphological, biochemical and genetic diagnosis (more than 3,100 patient's samples from different Spanish, European and Latin-american countries hospitals have been analyzed), and using cellular models for determining the pathogeneicity of the mutations. New mutations causing mitochondrial diseases have been discovered and population variants in the mtDNA have been associated with different phenotypes. We also use cellular models for the stydy of OXPHOS in neurodegenerative diseases such as Alzheimer, Prkinson, etc.
I have 242 publications.

NAGEL-WOLFRUM KERSTIN

Nagel-Wolfrum Kerstin, Dr. phil. nat. is group leader at the Johannes Gutenberg University of Mainz (JGU), Germany. She studied biology at the University of Karlsruhe (TH), Germany, and completed her Diploma thesis in developmental biology and genetics at the Karlsruhe Institute for Technology (KIT). During her PhD conducted at the Georg Speyer Haus, associated with the Johann Wolfgang Goethe University of Frankfurt, Germany, she developed a strong interest in translational medicine. She identified peptide aptamers, which interfere with the oncogenic transcription factor Stat3. Afterwards she focused on translational research related to hereditary retinal disorders, mainly on the human Usher syndrome, the most common form of combined deaf-blindness. As a postdoctoral research fellow at the Powell Gene Therapy Centre, University of Florida, Gainesville, USA in W.W. Hauswirth´s lab, she focused on the generation of adeno-associated virus (AAV). At the JGU Mainz she leads the ocular gene therapy team and is currently evaluating gene-based therapy strategies for hereditary retinal disorders, including i) gene augmentation via AAVs, ii) gene repair mediated by homologues recombination using zinc finger nucleases and TALENS as well as iii) translational read-through therapy. For her achievements she received the research award from "ProRetina Germany" and "Retina Suisse" in 2012. Since 2013 she is the coordinator of the E-RARE funded project "EUR-USH".

NEERMAN-ARBEZ MARGUERITE

Marguerite Neerman-Arbez received her Ph.D. in Molecular Biology at the University of Geneva in 1994. It is during her three year post-doctoral training with Professor Stylianos Antonarakis that she became interested in the molecular basis of human bleeding disorders. In 2002 Dr. Neerman-Arbez was awarded a Swiss National Science Foundation Professorship (Career Development Award, 2002-2008). In 2013 she became a Full Professor of Genetics in the Department of Genetic Medicine and Development, University of Geneva Faculty of Medicine.
Marguerite Neerman-Arbez has received several international scientific prizes for her work on the molecular basis of fibrinogen disorders (European Society of Human Genetics Young Investigator Award; International Prize for Research on Coagulation Disorders from the Angelo Bianchi Bonomi Foundation, Roche Prize for Advancement in Hemostasis Research.) Dr. Neerman-Arbez is a former member of the Swiss National Academy of Sciences Forum for Genetic Research and current member of the Board of Counselors of the International Fibrinogen Research Society.

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OTTENHEIJM COEN

The unifying theme of Dr. Ottenheijm's research concerns the regulatory and pathogenic role of myofilament proteins in striated muscle contraction.
Dr. Ottenheijm received his doctorate at the dept of Pulmonology at the Radboud University Nijmegen Medical Center in 2006, where he investigated the contribution of myofilament dysfunction to diaphragm weakness in patients with Chronic Obstructive Pulmonary Disease. His PhD research prompted Dr. Ottenheijm to pursue a postdoctoral position in the lab of Dr. Henk Granzier at the University of Arizona (funded by a NWO Rubicon grant), where he focussed on the role of the giant myofilament proteins titin (the largest protein known to date) and nebulin in muscle function in health and disease. Subsequently, he moved to the dept of Physiology at VUmc to further increase his understanding of the role of nebulin and other myofilament proteins in muscle disease; this work was funded by a NWO VENI grant. Currently, Dr Ottenheijm is working at the dept of Physiology at VUmc – supported by a NWO VIDI grant – and is prinicipal investigator in three collaborative EU-funded studies investigating novel transgenic mouse models of nebulin-based nemaline myopathy, and the therapeutic potential of tropnin activators. Furthermore, in collaboration with the depts of Intensive Care Medicine, Surgery and Anesthesiology at VUmc, Dr Ottenheijm's research group focusses on the pathogenesis of diaphragm weakness in conditions associated with altered diaphragm activity, such as pulmonary hypertension and mechanical ventilation. In 2014, he received a R01 grant (National Institutes of Health) to support his diaphragm research.

PROKISCH HOLGER

Holger Prokisch is head of the research group "Genetics of Mitochondrial Disorders" at the Institute of Human Genetic of the Technical University Munich and of the Helmholtz Zentrum München, Germany. He undertook his graduate studies in Germany at the Technical University Hannover. After his postdoctoral training at the Institute for Physiological Chemistry, University of Munich, Dr. Prokisch became head of the Biogenesis of Mitochondria research group at the same institute with Prof. W Neupert before attaining his current position.

His research focus seeks to understand genetic variation in both rare and common disorders leading to mitochondria-related disease. He was very successful in integrating genomic approaches with detailed functional biochemical investigations. By applying next generation sequencing the group has contributed to the discovery of more than 30 novel mitochondrial disease genes and diagnosed more than 400 patients. In his work, Dr. Prokisch undertakes genomic, proteomic, metabolomic, and transcriptomic studies to produce a comprehensive picture of mitochondrial dysfunction. Dr. Prokisch is principle investigator of two subprojects in the German Network for mitochondrial disorders and he is coordinating the E-rare funded European network for mitochondrial disorders GENOMIT.

RIESS HORST OLAF

Prof Riess, MD, is full professor for Medical Genetics, director of the Institute of Medical Genetics and Applied Genomics, and founder and acting director of the Rare Disease Center Tübingen. He has more than 20 years of experience in clinical genetics and research of genetically caused disorders. Main focus on neurodegenerative and syndromal diseases; both from the clinical as well as from the basic research perspective. Special focus on genetically inherited movement disorders such as ataxias, Huntington's disease, Parkinson's disease, and dystonia, and on the application of genomic HTP technology in the clinical practise. To faster transfer genomic medicine into university settings he is co-founder of the Center for personalized medicine of the University of Tübingen. His group is also well known for genetically modified rat models of neurodegenerative diseases and for preclinical studies. Current research approaches also include rare cancer and the development of biomarkers for rare diseases. Olaf Riess is founder and owner of the SME "Genes and Therapy GmbH" with the focus to accelerate personalized targeted treatment in cancer. He currently is and has been coordinator of numerous international, European and national funded consortia such as EUROSCA, MEFOPA, TECHGENE, RATstream and Neuromics. OR serves in numerous advisory boards such as the German initiative for Rare Diseases (NAMSE), the EFSN task force on spinocerebellar ataxias, the executive member of the Ataxia study group (ASG), as a board member of the study section Neuroscience (Fachgutachter) of the German Research Foundation (DFG), as associated Member of the Commission on genetic diagnostics (Gendiagnostik-Kommission) of the Ministry of Health (BfG), or as a board member of the International Rare Disease Research Consortium IRDiRC (Diagnostics Scientific Committee). He was recently elected as President-elect of the European Society of Human Genetics (ESHG). Published >350 papers.

SHTIR CORINA

Dr. Corina Shtir is Senior Director of Translational Medicine at Thermo Fisher Scientific. She joined the company in 2013, from the Wellcome Trust Diabetes and Inflammatory Lab (DIL) in Cambridge, UK. Her expertise spans many areas, enabling her to take an integrative approach to driving population-scale programs for both rare and complex disorders. Her specialties include population genetics and biostatistics (PhD), statistical genetics, mathematics, epidemiology, and computational biology. Her research collaborators in these areas include world-renowned scientists. She directs programs such as the Saudi Human Genome Program, Stratified Medicine Scotland, the Taiwan National Genome Program, and other mid-East and European large-scale efforts. Dr. Shtir serves as a scientific advisor on many committees and

initiatives, including the US Million Veteran Program, the largest US government program aimed at correlating genome sequences with health care information for use in personalized medicine. Prior to joining Thermo Fisher, Corina worked with John Todd, director of the Wellcome Trust DIL, and with David Clayton, previously head of Statistical Genetics at Cambridge Institute of Medical Research (CIMR), UK. While at the DIL, she developed a comprehensive method for detection and correction of artifacts in estimation of rare copy number variants and analysis of rare deletions in type 1 diabetes, a collaborative work between the Wellcome Trust, CIMR, and the University of Virginia. In the UK, she also collaborated with Kings College leaders on studying autoimmune disorders. Corina also collaborated and published with scientific specialists in neurodevelopmental disorders (UCLA, USC, University of Pennsylvania, Cardiff Centre for Neuropsychiatric Genomics, UK), and in age-related macular degeneration and other complex disorders.

STEVANIN GIOVANNI

Giovanni Stevanin is a neuroscientist and molecular biologist specialized on hereditary movement disorders. After a PhD at the Pité-Salpêtrière Hospital and a postdoctoral training at the Institut de Génétique Biologie Moléculaire et Cellulaire (IGBMC, Strasbourg), he was recruited as associate professor in 2000 and is now research director at INSERM (France) and Professor of Neurogenetics at Ecole Pratique des Hautes Etudes university (France). He manages a team at the Institut du Cerveau et de la Moelle épinière (Paris, France) that focuses its studies on spinocerebellar degenerations, which include cerebellar ataxias and spastic paraplegias. The current projects cover both the genetic and physiopathological aspects of these diseases with the objectives to 1) identify new genes responsible for spinocerebellar degenerations using next generation sequencing in order to improve the nosology ot these disorders (the team has identified 15 causative genes in the field during the last 15 years) and 2) understand the mechanisms implicated in neurodegeneration to develop and design rational therapies to treat these diseases. This last aspect is investigated in 2 prototypes of these diseases; a) SPG11 and SPG56, 2 genes identified in the lab responsible for complex spastic paraplegias. To these ends, he benefits from an international network on these diseases: SPATAX and the associated collections of patients.

TAGLE DANILO A.

Dr. Danilo Tagle is Associate Director for Special Initiatives at the National Center for Advancing Translational Sciences (NCATS). He leads and provides scientific and programmatic oversight and coordination to the following trans-NIH programs: 1) NIH Microphysiological Systems (a.k.a. tissue chip) program, 2) Extracellular RNA Communication program, and 3) SPARC (Stimulating Peripheral Activity to Relieve Conditions) program. These activities involve coordination with other NIH institutes and centers, as well as partnerships with other government agencies, such FDA, DARPA, DTRA and the private sector. Prior to joining NCATS, Dr. Tagle was a Program Director for Neurogenetics at the National Institute of Neurological Disorders and Stroke (NINDS) where he was involved in developing programs in genomics–based approaches for basic and translational research in inherited brain disorders. Dr. Tagle obtained his Ph.D. in Molecular Biology and Genetics from Wayne State University School of Medicine in 1990. He was an NIH NRSA postdoctoral fellow in Human Genetics at the laboratory of Dr. Francis S. Collins at the University of Michigan. Prior to joining NINDS in 2001, Dr. Tagle was an Investigator and Section Head of Molecular Neurogenetics at the National

Human Genome Research Institute (NHGRI) beginning in 1993, and has been involved in the highly collaborative effort towards the positional cloning of genes for Huntington's disease, ataxia-telangiectasia, and Niemann-Pick type C disease. In addition to being Associate Director for Special Initiatives, Dr. Tagle recently served as Acting Director for the NCATS Office of Grants Management and Scientific Review, and currently serves as Executive Secretary to the NCATS Advisory Council, as well as the Cures Acceleration Network Review Board. He has served in numerous committees and advisory boards, and was on the Editorial Board of the journal Gene, as well as International Journal of Biotechnology. He has more than 150 scientific publications, and has garnered numerous awards and patents. Central to Dr. Tagle's accomplishments and goals is leveraging key resources and expertise through partnerships with various stakeholders in biomedical research, including various government agencies, non-profits and patient advocacy groups, industry and pharmaceutical corporations.

TARTAGLIA MARCO

Dr. Tartaglia is senior scientist, and Head of the Molecular Genetics and Functional Genomics Research Unit and Genetics and Rare Diseases Research Division at the Ospedale Pediatrico Bambino Gesù, Rome, Italy. He is also Adjunct Associate Professor, Department of Pediatrics, at the Icahn School of Medicine at Mount Sinai, New York, NY. For 10 years, he served as Section Director at the Istituto Superiore di Sanità, the Italian National Health Institute.
Dr. Tartaglia and his team conduct research that employs molecular genetics- and genomics-based strategies to understand the molecular bases of diseases affecting development and growth, and identify genes with role in oncogenesis and predisposing to cancer. Research is also directed to comprehend the mechanisms of disease by using complementary in vitro approaches and animal models. A major focus of his research are RASopathies. His work has allowed the discovery of PTPN11 as the first gene implicated in Noonan syndrome and the identification of seven additional disease genes underlying this disorder and clinically related traits. More recently, his work has been directed at defining the genetic basis of other rare developmental disorders. Major discoveries include the identification of the disease genes underlying Myhre syndrome, Kaufman syndrome, Primrose syndrome, Zimmermann-Laband syndrome, and Fine-Lubinsky syndrome.
Dr. Tartaglia is coordinator of the transnational NSEuroNet Consortium, funded by E-Rare on 2009 and 2015, focused on the molecular bases of RASopathies.

VAN DER KNAAP MARJO

Marjo van der Knaap was trained in Adult and Pediatric Neurology. She wrote a PhD thesis on MRI and MRS of myelination and white matter disorders in children and young adults (1991). She is currently professor of Child Neurology, VU University Medical Center, Amsterdam and head of the department of Child Neurology.
Since 1987, her research has been focused on magnetic resonance of childhood white matter disorders with a special focus on unclassified childhood leukoencephalopathies. She developed MRI pattern recognition to facilitate the diagnostic work-up of white matter disorders and used this tool to define numerous novel disorders. Her research group has identified the mutated genes in most of these novel disorders, including vanishing white matter. Her subsequent studies are focused on elucidation of disease mechanisms and more recently development of treatment. In 2000, she founded the Center for Childhood White Matter

Disorders in Amsterdam, in which diagnostics, patient care and research are integrated. She is co-author of the book: Van der Knaap MS, Valk J. Magnetic resonance of myelination and myelin disorders. Springer, 1989, 1995 and 2005. She co-authored >300 peer-reviewed papers in international scientific journals. She received many international awards and honors, including the gold medal of the ISMRM (1999), Winkler medal of the Dutch Society of Neurology (2000), honorary membership of the ASNR (2001), Prichard award of the ICNA (2002), Sidney Carter Award of the AAN (2008), Spinoza award in The Netherlands (2008, € 1 500 000), the Peter-Emil-Becker Award of the Gesellschaft für Neuropädiatrie (2010) and the gold medal of the ASPNR (2014). She was elected a member of the Dutch Royal Academy of Sciences (2010).

VELTMAN JORIS A.

Professor in Translational Genomics
Head of genome research division, department of Human Genetics, Radboud University Medical Center, Nijmegen, The Netherlands & department of clinical genetics, Maastricht University Medical Center, Maastricht, The Netherlands
Joris Veltman is a molecular geneticist who has been instrumental in the set-up, application and implementation of genomics approaches in medical genetics. He developed and then experimentally validated the hypothesis that a major part of intellectual disability should be due to de novo gene mutations, given the severity, early-onset and genetic heterogeneity of ID. For this prof. Veltman uses genomic microarrays, exome and genome sequencing approaches. This de novo paradigm has now been widely validated in other neurocognitive phenotypes, autism, epileptic encephalopathies, and schizophrenia, and represents one of the recent major breakthroughs in human genetics.
References: Gilissen et al. Genome sequencing identifies major causes of severe intellectual disability. Nature (2014). de Ligt et al. Diagnostic Exome Sequencing in Persons with Severe Intellectual Disability. New England Journal of Medicine (2012). Vissers et al. A de novo paradigm for mental retardation. Nature Genetics (2010). Hoischen et al. De novo mutations of SETBP1 cause Schinzel-Giedion syndrome. Nature Genetics (2010). Vissers et al. Mutations in a novel member of the chromodomain gene family cause CHARGE syndrome. Nature Genetics (2004).

SPEAKERS' ABSTRACTS

JUAN FY PEREZ
M. SOLÁ CALVO
(1888-1939)
NO MORE
ORPHAN STATUS

PINGING THE TRANSCRIPTOME; MINING THE PHARMACOPEIA FOR RARE INHERITED DISORDER THERAPIES

DRUG REPOSITIONING AND PERSONALIZED MEDICINE

Alex MacKenzie, Children's Hospital of Eastern Ontario, Faculty of Medicine, University of Ottawa, Ottawa, Canada K1H 8L1

The genetic analysis of monogenic disorders has over the past three decades resulted in the identification of 1000's of genes which either cause or impact these conditions; most of these disorders have no therapies. The modulation of the transcripts and proteins encoded by these genes might be anticipated to have therapeutic utility, either by their upregulation (e.g. of mutated recessive disease genes encoding proteins with residual enzymatic activity, of genes that are sequentially similar to, and that functionally recapitulate, mutated recessive disease genes or of genes that cause disease when haploinsufficient) or downregulation (e.g. of mutated dominant genes which confer a gain of pathologic function or of genes which, when present in increased number, cause disease). Moreover, it is known that small molecules including clinically approved drugs can affect the human transcriptome. Given the number of genes that cause or effect inherited human conditions and the substantial subset of the transcriptome that is impacted by drugs, we believe that there are likely genes which are both modifiers of rare disease and responsive to pharmacologic modulation. The enhanced Care for Rare in Canada project is therefore exploring whether previously unknown off target effects of clinically approved drugs may lead to new therapies. We have screened approximately 80 rare conditions, (haploinsufficient, rescuing paralogous genes and hypomorphic mutation with residual function) using this approach. There are currently five conditions which show some induction (GLUT1, SMAD3, DDHD2, NEU1, HPRT); the most promising results and lessons learned from this approach shall be presented.

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REPURPOSING LOSARTAN TO AMELIORATE DYSTROPHIC EPIDERMOLYSIS BULLOSA

DRUG REPOSITIONING AND PERSONALIZED MEDICINE

Leena Bruckner-Tuderman, Medical Center – University of Freiburg

This talk will focus on an emerging conceptual approach to alleviate symptoms in recessive dystrophic epidermolysis bullosa (RDEB), a rare skin fragility disorder characterized by injury-driven blister formation, progressive soft tissue fibrosis, and a highly elevated risk of early-onset aggressive skin cancer. Since RDEB is caused by genetic loss of collagen VII, gene / protein-based strategies have been in the focus of most efforts for RDEB therapy. However, major hurdles have to be overcome before such therapies can be implemented in the clinics. Since RDEB is largely driven by progressive secondary disease mechanisms, a 100% efficiency of causal therapies cannot be expected, and alternative approaches to need to be pursued. From our and other investigators' research it has become evident that although the mutations and the protein at fault differ, common disease mechanisms are at play in a range of genetic connective tissue disorders, including RDEB. Targeting these mechanisms provides means to slow down disease progression, reduce its burden, and facilitate clinical implementation. We took an evidence-based approach for a first symptom-relief therapy for RDEB. Based on findings that TGF activity is elevated in injured RDEB skin, we repurposed the angiotensin II type 1 receptor antagonist losartan to treat RDEB in a preclinical setting. The drug has been used in other connective tissue disorders to ameliorate fibrosis, but the data cannot be automatically transferred, since the effects are tissue-, context- and disease-specific. In the RDEB mouse, losartan efficiently limited TGF activity and attenuated fibrosis, as seen by lower fibrotic markers, longer and fewer fused toes and softer skin. - To gain better knowledge on mechanisms determining disease progression in RDEB and mechanisms of action of losartan we employed global unbiased mass spectrometry-based proteomics. This revealed molecular events linked to tissue inflammation as major drivers of disease progression. Our recent research revealed a new mechanism by which RDEB tissue becomes malignant and new druggable therapeutic targets. Treatment of 3D organotypic RDEB skin cultures with inhibitors of TGFβsignaling, lysyl oxidase, or integrin ß1-mediated mechanosignaling limited tumor cell invasion. In conclusion, our studies suggest that limiting unrestrained responses to tissue damage poses a relatively risk-free approach to reduce disease burden in RDEB.

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BACK TO THE FUTURE-HOW DRUG REPOSITIONING HAS AND WILL CREATE TREATMENTS FOR UNSOLVED DISEASES

DRUG REPOSITIONING AND PERSONALIZED MEDICINE

Dr. Bruce E. Bloom President and Chief Science Officer, Cures Within Reach 8025 Lamon Avenue, Suite 440, Skokie, IL 60077

There are at least 7000 unsolved diseases in the world affecting as many as 500 million people. The majority of these are rare or neglected diseases affecting people who have little or no access to effective medical solutions. The global for-profit medical research industry can create 15-40 new drug treatments per year, with only a few of them are focused on rare diseases. When industry does create a treatment for a rare disease, the yearly cost can exceed $100,000 per patient. At this rate, if all we can depend on is industry to create treatments for unsolved diseases, we are likely to leave most patients without a treatment, and our economies depleted. We need to find a way to supplement the good work of industry to create more effective treatments and bring down the cost of healthcare. The good news is that there is a simple and cost-effective solution to unsolved diseases, if we can only create the economic and other incentives to support it. This solution is drug repositioning. There are thousands of inexpensive and relatively safe drugs and nutriceuticals already human approved or human used that can be quickly repositioned to provide affordable and effective treatments and cures for these unsolved diseases. We know drug repositioning works for two reasons: 1) There are hundreds of examples of approved drugs that have already received further regulatory approval for a new disease indication, from thalidomide repositioned for the rare diseases leprosy and multiple myeloma, to colchicine repositioned from gout to the rare disease Mediterranean fever, and 2) physicians prescribe off-label treatment to between 18%-90% of their patients, depending on their treatment specialty, with rare diseases, pediatrics, oncology, pain and mental health having the highest rates of off-label prescribing. This presentation will discuss the historical successes of drug repositioning, examine the current landscape of drug repositioning in industry, bioscience, academia and clinical care, and hypothesize about how we can improve patient outcomes and reduce healthcare costs in the future, if we are able to create the right incentives for drug repositioning.

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DRUG REPOSITIONING FOR THE PERSONALIZED THERAPY OF CYSTIC FIBROSIS

DRUG REPOSITIONING AND PERSONALIZED MEDICINE

Luigi Maiuri Research Director European Institute for Research in Cystic Fibrosis Division of Genetics and Cell Biology San Raffaele Scientific Institute via Olgettina 58, 20132, Milan, Italy

Discordance in patient's responsiveness to treatment complicates the assessment of efficacy of new candidate drugs and entails the need to enrol thousands of people in large clinical trials with the result that a great proportion of individuals may take medications that could not help them. Personalized approaches that focus on individual and not average responses to therapy are encouraged. Cystic Fibrosis (CF), the most common lethal recessive disease in Caucasians, is a paradigm of heterogeneity in patient response rates to treatments. Mutation-specific highly expensive treatments, aiming at directly targeting the mutant CFTR protein, are available for a small fraction of CF patients with a rare channel-dead mutant, but are only marginally effective in rescuing CFTR function in the vast majority (70-90%) of CF patients bearing the most common class II F508del-CFTR mutation. Emerging mechanistic target-driven discovery programs aim to identify novel targets for therapeutic intervention by targeting the proteostasis network perturbed by the lack of a functional CFTR. To this purpose, drug repositioning strategies for affordable patient-centred therapies able to restore CFTR function are required to fill the gap between basic research and clinical application and favor a personalized approach to CF therapy. A target-driven drug repositioning strategy led to the discovery that a combination of two molecules which target two major nodes of the hub-dysfunction in CF, disabled autophagy and CK2 overactivation, may circumvent F508del-CFTR defect. The repurposed drug cysteamine, FDA approved for the treatment of cystinosis, which reestablishes autophagy, synergizes with the over-the-counter flavonoid epigallocatechin gallate (EGCG), which inhibits the over-active CK2, thereby rescuing and stabilizing a functional F508del-CFTR, both in mice and in primary nasal cells from F508del homozygotes and restores CFTR function in vivo in a pilot clinical trial on CF patients. Personalized medicine should benefit the patient and not the disease by targeting the right medicine to the right patient in the right time frame, provided that proper biomarkers are available to either predict individual patient's responsiveness to treatments or to monitor the early stages of disease reversion during treatment. Thus, new "mechanistic" drug discovery programs and affordable predictive tests of responsiveness to treatments are required for a patient-centred medical approach to CF.

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AN EFFECTIVE APPROACH FOR DIAGNOSING RARE GENETIC DISEASES WITHIN THE SAUDI POPULATION

NGS AND UNDIAGNOSED RARE DISEASES

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Personalized Medicine enables the convergence of information from the population to the individual level, necessary for making optimal decisions for screening of high-risk mutations, diagnosis, or optimal treatment, relative to an individual's unique genetic architecture. Time and cost effective solutions have been tested within the Saudi population, which carries one of the highest incidence rates of rare disorders worldwide. Here, we provide a summary of clinical genomics measures within the spectrum of preventive, diagnostic, and screening for rare disorders within Saudi Arabia. The Mendeliome, a set of 13 next-generation sequencing-based multiplexing assays that encompass ~3000 known Mendelian genes have been tested within the Saudi population for their to the burden of undiagnosed diseases suspected to be of genetic origin. A total of 2,357 patients suspected to have a genetic disease were examined. A likely causal mutation was identified in 1,018 patients, giving an overall clinical sensitivity of 43 % vs. ~25% reported by several large clinical whole exome sequencing (WES) studies. Only 11 % of negative cases were consequently identified by WES to harbor a likely causal mutation in a known disease gene not included in the current assays. Although the Saudi population is enriched for consanguinity, 24 % of solved cases were autosomal dominant and 4 % were X-linked, suggesting that this approach is also applicable to outbred populations.The high degree of consanguinity allowed observation of many variants in homozygosity as a result of autozygosity. Observing them in at a relatively high population frequency strongly argues against their asserted disease link. Arab specific vs. Caucasian mechanisms have been detected and will help elucidate future population genomic studies worldwide. 342 HGMD variants at high frequency (minor allele frequency [MAF] >1 %) in the Saudi in-house database, including 133 variants with MAF >5 % are rare in the Human variome database. Of these variants, 137 are listed in the 1000 Genomes Project with a MAF <1 %, highlighting the unique distribution of variants in various populations. Finally, 433 novel disease alleles from a total of 788 variants were identified, the largest to be reported in a single study. The Mendeliome assays can account for a large proportion of suspected genetic disorders and provide significant practical advantages over clinical WES.

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TRACKING MITOCHONDRIAL DISEASES THROUGH NEXT GENERATION SEQUENCING

NGS AND UNDIAGNOSED RARE DISEASES

Holger Prokisch, PhD., Institute of Human Genetics, Klinikum rechts der Isar, Technical University Munich and Hemholtz Zentrum München

Mitochondrial disorders are a genetically heterogeneous group of individually rare, highly incapacitating human diseases for which no effective treatment is available. The large number of more than 250 clinically similar mitochondrial disorders together with the multisystemic nature of mitochondrial diseases makes molecular diagnosis difficult, as many different medical specialties are involved and many physicians are discouraged by the complex phenotypes. The introduction of whole exome and whole genome sequencing in clinical practice of medicine has dramatically improved diagnostic success for mitochondrial diseases and moved investigative efforts from mitochondrial DNA to the nuclear genome. The increasingly broad application of sequencing is not only allowing us to better diagnose well-established Mendelian syndromes, but also to discover new disease genes and defining new syndromes. Moreover, it has expanded the phenotypic spectrum of established conditions.

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USHER SYNDROME – CHALLENGES FOR DIAGNOSIS AND TREATMENT

NGS AND UNDIAGNOSED RARE DISEASES

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The Usher syndrome (USH) is the most common form of inherited deaf-blindness. Hearing impairment is the first symptom to develop and is detected by the newborn screening at birth. In contrast, visual symptoms (retinitis pigmentosa, RP) manifest before or during puberty. This variable onset of the clinical symptoms makes diagnosis of USH challenging. Clinically USH is divided into three clinical types (USH1, USH2, and USH3) depending on the age of onset, severity and progression of the symptoms. However, additional atypical forms have been described due to the genetic heterogeneity of USH. To date, 10 causative genes, three additional loci and genetic modifiers have been identified. To date the diagnosis "Usher syndrome" is normally established in the second decade of life. However an earlier diagnosis would support parents in their choice for cochlear implants instead of learning sign language. Cochlear implants can successfully compensate the hearing deficiency especially when they are implanted as early as possible. In < one year of age, the auditory pathway can mature normally resulting in close to normal speech development as well as hearing abilities. In contrast, there are currently no effective cures for the retinal phenotype available. Although gene addition is in the focus for many hereditary retinal disorders, the size of genes and the expression of various splice variants with yet undefined functions hamper gene addition approaches for USH. Patient screenings conducted over the last years have provided insights into USH-causing mutations revealing that ~ 11% of all USH causing mutations are nonsense mutation. For patients carrying a nonsense mutation the so-called translational read-through therapy is a promising therapeutic option. Nonsense mutations generate a premature termination codon in the coding sequence of genes, leading to early termination of protein translation resulting in non-functional proteins that manifest in USH. Translational read-through-inducing drugs allow the translation machinery to suppress a nonsense codon and consequently result in the synthesis of full-length protein. Recent research has raised hope for the usage of translational read-through therapy as a gene-based pharmacogenetic therapy for a variety of hereditary retinal disorders caused by nonsense mutations.

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DE NOVO MUTATIONS IN INTELLECTUAL DISABILITY: FROM GENE TO GENOME AND FROM RESEARCH TO DIAGNOSTICS

NGS AND UNDIAGNOSED RARE DISEASES

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Germline coding de novo mutations have recently been indicated to play an important role in moderate to severe forms of intellectual disability (ID). The frequent occurrence of new deleterious mutations in the germline may explain why these disorders with a severe effect on fitness remain so frequent in our population. Widespread application of unbiased methodologies such as genomic microarrays, and more recently exome and genome sequencing of patient-parent trios now provides us with a detailed insight into the presence, distribution, frequency and role of de novo mutations in these disorders. In this presentation, I will describe our recent work on using both family-based exome and genome sequencing to detect and interpret de novo mutations in patients with severe ID. Our data and those of other groups indicate that de novo germline mutations (SNVs, indels as well as CNVs) may explain the majority of all sporadic forms of severe ID. This has great implications for the diagnostic process of patients with ID and for estimating the recurrence risk within families. These studies provide fundamental insight into the mutational processes ongoing during spermatogenesis and oogenesis, and reveal risk factors that increase the number of de novo mutations in the offspring (e.g. advanced paternal age). Moreover, the detection of recurrent de novo mutations in genes as well as non-coding regulatory elements gives an enormous boost to our understanding of the underlying biology of ID. Also I will discuss our progress with the implementation of exome sequencing as a routine diagnostics test for genetically heterogeneous disorders and our plans to implement genome sequencing in diagnostics.

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DYSKERATOSIS CONGENITA AND RELATED DISEASES OF TELOMERES

PATHOPHYSIOLOGY

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Dyskeratosis Congenita (DC) is a pleotropic syndrome. In its classical form it is characterised by mucocutaneous abnormalities, bone marrow failure (BMF) and a predisposition to malignancy. BMF is the principal cause of mortality and patients display features of premature aging. Studies over the last two decades have led to significant advances with 11 disease genes (DKC1, TERC, TERT, NOP10, NHP2, TINF2, USB1, TCAB1, CTC1, RTEL1, and ACD) having been characterized. Ten of these are important in telomere maintenance. DC is therefore principally a disease of defective telomere maintenance and patients usually have very short/ and or abnormal telomeres. The genetic advances have also led to the unification of DC with a number of other disorders. This includes the multi-system disorder Hoyeraal-Hreidarsson as well as a subset of patients with aplastic anaemia (AA), myelodysplasia, leukaemia, liver disease and pulmonary fibrosis. This wide spectrum of diseases ranging from classical DC to AA can be regarded as disorders of defective telomere maintenance, "telomeropathies", highlighting the importance of telomere maintenance in humans. Correct diagnosis is important as haematopoietic failure associated with this group of disorders is unlikely to respond to immunosuppressive agents and is more likely to respond to drugs such as oxymetholone and danazol. For patients who are unresponsive to these agents haematopoietic stem cell transplantation using Fludarabine based low intensity protocols is producing encouraging results. Some cases of DC remain uncharacterized. Using whole exome sequencing we recently identified novel biallelic mutations in the poly(A)-specific ribonuclease (PARN) gene, in families exhibiting severe DC. PARN is an exonuclease whose deadenylation activity in part controls mRNA stability and therefore regulation of a large number of genes. The mutations identified affect key domains within the protein and studies on patient cells show reduced deadenylation activity. This deficiency causes an early DNA damage response and reduced cell viability upon UV treatment. Individuals with biallelic PARN mutations have reduced RNA levels for several key genes associated with telomere biology. They also possess very short telomeres. Collectively, these results identify a role for PARN in telomere maintenance and demonstrate that it is a disease-causing gene in a subset of cases with severe DC.

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OF FISH AND MEN
PATHOPHYSIOLOGY

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We are studying human genetic disorders of hemostasis in particular fibrinogen deficiencies. These are rare and affect either the quantity or the quality of circulating fibrinogen, which is the precursor of the major protein component of the blood clot, fibrin. My laboratory identified the gene and the first causative mutations for complete deficiency of fibrinogen, afibrinogenemia, in 1999. Fibrinogen is a hexamer comprising two copies of three polypeptides encoded by the fibrinogen alpha, beta and gamma genes clustered on human chromosome 4. Mutations in the fibrinogen genes lead to deficiency of fibrinogen by several mechanisms: at the DNA level, at the RNA level by affecting messenger RNA splicing or stability, or at the protein level by affecting protein synthesis, hexamer assembly or hexamer secretion. Interestingly complete fibrinogen deficiency is associated with a variable bleeding phenotype, which may be influenced by environment and genotype. We sought to use the zebrafish as a model for fibrinogen disorders because of its accessible vasculature and because the coagulation system proteins are generally conserved throughout vertebrates. Targeted mutations were introduced into the zebrafish fga gene using zinc finger nuclease technology. Animals carrying three distinct frameshift mutations in fga were raised and bred to produce homozygous mutants. We observed hemorrhaging in fga mutants and reduced survival compared to control animals. This first transmissible zebrafish model of a defined human bleeding disorder validates the use of zebrafish for thrombosis and hemostasis research and will now serve in the search for afibrinogenemia modifying genes or agents.

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BARDET-BIEDL, ALSTRÖM AND RELATED CILIOPATHIES PATHOGENESIS: FROM ULTRA RARE DISEASES TO MORE COMMON DISEASES

PATHOPHYSIOLOGY

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Bardet-Biedl (BBS), Alström and related syndromes are defined as a group of rare disorders due to the dysfunction of the primary cilia, a major organelle found in almost all cell types. They share for most of them an early onset retinal degeneration, renal dysfunction and /or obesity as well as many other complications such as intellectual deficiency and polydactyly for BBS or type 2 diabetes and cardiomyopathy for Alström syndrome. The challenge for this group of disorders if to understand the general and organ specific pathogenesis to better target future therapies. The first clue is gene identification, although most genes have now been identified, pieces are still missing in the jigsaw of the various networks identified for ciliopathies. Ultra rare ciliopathies gene identification may still lead to pinpoint key players of various pathways . this will be illustrated by a few examples. More over the most severe clinical manifestations warrants mechanisms elucidation. Retinal degeneration is a common highly disabling manifestation due to photoreceptor dysfunction at the level of the ciliary connecting structure with altered transport of proteins leading to apoptosis. We will highlight the pathogenesis of the retinal degeneration taking into account ciliary networks. The potential metabolic consequences of ciliopathies, such as obesity or diabetes, are studied and show the importance of these actors in various processes and are indicating novel insights that can be useful for the understanding of common diseases.

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RASOPATHIES – THE OTHER FACE OF RAS SIGNALING DYSREGULATION

PATHOPHYSIOLOGY

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RAS proteins are small monomeric GTPases that function as molecular switches controlling a major intracellular signaling network that, depending on the cellular context, guides diverse biological functions, such as proliferation, migration, survival, cell fate determination, differentiation, and senescence. Within this network, signal flow through the RAF-MEK-ERK pathway, the first identified mitogen-associated protein kinase (MAPK) cascade, mediates early and late developmental processes, including determination of morphology, organogenesis, synaptic plasticity, and growth. Signaling through the RAS-MAPK cascade is tightly controlled, and its enhanced activation has been known for decades to represent a major event in oncogenesis. Activating somatic RAS gene mutations occur in approximately 30% of human cancers, and upregulation of this signaling pathway also results from enhanced function of upstream signal transducers and RAS effectors, as well as from defective negative control of feedback mechanisms. Unexpectedly, discoveries derived from a massive disease gene hunting effort performed in the last 15 years have established a novel scenario in which the upregulation of this signaling cascade underlies a group of clinically related developmental disorders, collectively known as "RASopathies", characterized by facial dysmorphism, a wide spectrum of cardiac defects, reduced growth, variable cognitive deficits, ectodermal and musculoskeletal anomalies, and increased risk for certain malignancies. These disorders are caused by mutations in an increasing number of genes encoding RAS proteins, regulators of RAS function, modulators of RAS interaction with effectors, or downstream signal transducers. While individually rare, RASopathies constitute the most common family of non-chromosomal disorders affecting development and growth, with an estimated aggregate prevalence of 1:1,500 live births. The largely collaborative research performed in the recent years has provided novel molecular tools for a prompt diagnosis, new data for a more effective patient management and risk assessment, and insights for efforts directed to the development of therapeutic intervention to treat postnatal complications of these disorders. These discoveries have also significantly contributed to deepen our understanding of the complex biology of RAS signaling and multifaced functional role of several signal transducers with role in this network.

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DNA REPAIR SYNDROMES: KEY FOR UNDERSTANDING AGING

PATHOPHYSIOLOGY

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The molecular basis underlying ageing and ageing-related diseases is one of the main unsolved questions in biology. Ageing in various model organisms appears remarkably plastic: e.g. suppressing insulin signalling extends lifespan in worms flies and mice. On the other hand, virtually all premature aging syndromes in man provide a link with genome instability. We have generated mouse models which strikingly mimic human DNA repair deficiency syndromes and display wide-spread accelerated aging. For instance, DNA repair-deficient Ercc1Δ/- mice defective in 3 or more repair pathways show numerous accelerated aging features limiting lifespan to 4-6 month. Simultaneously they exhibit an anti-aging 'survival response', which suppresses growth and enhances maintenance, resembling the longevity response induced by dietary restriction (DR). Interestingly, subjecting these progeroid, dwarf mutants to actual DR resulted in the largest lifespan increase recorded in mammals. Thirty percent DR tripled median and maximal remaining lifespan, and drastically retarded numerous aspects of accelerated aging, e.g. DR animals retained 50% more neurons and maintained full motoric function. Repair-deficient Xpg-/- mice also showing many premature aging symptoms responded similarly to DR, extending this observation beyond Ercc1. The DR response in Ercc1Δ/- mice resembled DR in wild type animals including reduced insulin signaling. Interestingly, ad libitum Ercc1Δ/- liver expression profiles showed gradual preferential extinction of expression of long genes, consistent with genome-wide accumulation of stochastic, transcription-blocking lesions, which affect long genes more than short ones. DR largely prevented this decline of transcriptional output, indicating that DR prolongs genome function.We will present phenotypes of conditional DNA repair models targeting aging to selected organs, striking parallels with Alzheimer's disease. Our findings strengthen the link between DNA damage and aging, establish Ercc1Δ/- mice as powerful model for identifying interventions to promote healthy aging, reveal untapped potential for reducing endogenous damage, provide new venues for understanding the molecular mechanism of DR, and suggest a counterintuitive DR-like therapy for human progeroid genome instability syndromes and DR-like interventions for preventing neurodegenerative diseases.

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INNOVATIVE TOOLS FOR DRUG DEVELOPMENT AND DISEASE MODELING

BRINGING TREATMENTS TO THE CLINIC

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There are fewer than 400 approved treatments for approximately 7000 rare diseases affecting more than 30 million Americans. The NIH have More than 30% of promising medications have failed in human clinical trials because they are determined to be toxic despite promising pre-clinical studies in animal models, and another 60% fail due to lack of efficacy. The challenge of accurately predicting drug toxicities and efficacies is in part due to inherent species differences in drug metabolizing enzyme activities and cell-type specific sensitivities to toxicants. These challenges are particularly acute for rare diseases where adequate tools and resources are severely lacking. To address this challenge in drug development and regulatory science, the Tissue Chips program aims to develop alternative approaches that would enable early indications and potentially more reliable readouts of toxicity or efficacy. The goal this program is to develop bio-engineered microdevices that mimic functional units of the 10 major human organ systems: circulatory, respiratory, integumentary, reproductive, endocrine, gastrointestinal, nervous, urinary, musculoskeletal, and immune. The opportunities for significant advancements in the prediction of human drug toxicities through the development of microphysiological systems, requires a multidisciplinary approach that relies on an understanding of human physiology, stem cell biology, material sciences and bioengineering. This unique and novel in vitro platform could help ensure that safe and effective therapeutics are identified sooner, and ineffective or toxic ones are rejected early in the drug development process. These microfabricated devices are also useful for modeling human diseases, especially for studies in rare diseases, as well as precision medicine, environment exposures, reproduction and development, infectious diseases, microbiome and countermeasures agents.

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NON TARGETED AND TARGETED GENE THERAPY APPROACHES IN FANCONI ANEMIA

BRINGING TREATMENTS TO THE CLINIC

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Fanconi anemia (FA) is an inherited disease mainly characterized by congenital abnormalities, progressive bone marrow failure, and cancer predisposition. In contrast to other hematopoietic disorders already treated by hematopoietic gene therapy, marked proliferation and differentiation defects have been observed at the stem cell level both in FA experimental models and FA patients. This characteristic FA stem cell phenotype implies significant difficulties for collecting clinically relevant numbers of hematopoietic stem cells (HSCs) from FA patients. On the other hand, the proliferation advantage of gene-corrected FA HSCs may facilitate the hematopoietic reconstitution of the patient by a low number of transduced HSCs. To facilitate the collection of HSCs from FA patients filgrastim and plerixafor have been used as mobilizing agents. Small aliquots of mPB CD34+ cells have been transduced with a lentiviral vector carrying the FANCA gene under the regulation of the PGK promoter and a mutated WPRE* sequence. This vector efficiently reverted the hematopoietic phenotype of these cells both in vitro and also after transplantation into immunodeficient mice. Using a FA mouse model we have also demonstrated the long-term phenotypic correction of their hematopoiesis after gene therapy, without noting genotoxic insertions, as deduced from the polyclonal HSC repopulation pattern, the absence of dominant integrations and active HSC turnover. In addition to conventional gene therapy, we have also investigated the possibility of generating gene corrected FA HSCs by conducting untargeted and also targeted gene addition approaches on FA fibroblasts that were subsequently reprogrammed to generate hematopoietic progenitor cells. Improvements of gene editing tools, mainly engineered nucleases and donor constructs, have allowed us to attempt the targeted insertion of FANCA in primary HSCs from FA patients. An update of data obtained in our preclinical and clinical studies will be presented.

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THERAPIES AND TREATMENT FOR (VERY) RARE AND GENETICALLY HETEROGENEOUS DISORDERS: WHY (NOT) CDG ?

BRINGING TREATMENTS TO THE CLINIC

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Congenital Disorders of Glycosylation (CDG) are rare inborn errors of glycosylation. With more than 70 different types and a number of cases constantly growing, CDG becomes an impressive group of metabolic diseases. However, because of the complex nature of glycosylation defects, the number of patients that receive effective treatment is small. Several cellular and animal models have been prepared for the study of the pathophysiology of the different types of CDG but the challenges for the development of therapies remain huge: CDG is clinically and genetically heterogeneous and the deficiencies reside in cellular compartments that cannot be reached by e.g. enzyme replacement therapies. Neither is gene therapy a good option because of the methodological challenges and small numbers of patients. Cell therapy may well come of age eventually but at this stage it is not easily conceivable for CDG (apart from bone marrow transplants that may be considered in specific patients).Thus, it would be good to explore other lines of research on therapies for CDG. First, PMI-CDG and PGM1-CDG are characterized by the deficit of sugar intermediates for glycan synthesis. The oral application of mannose and galactose, respectively, to a small group of patients was shown to result in biochemical and clinical improvements. However, better galenic formulations and/or combinations of these sugars might improve therapeutic benefit. Second, for PMM2-CDG and other types of CDG which are characterized by a low residual activity of the mutant protein, chaperones and other pharmacological agents might alleviate the enzymatic deficiencies. Third, a few types of CDG are caused by intra-compartmental pH and ion alterations. The patients may benefit from drugs that alter the intracellular environment. Evidently, even if these approaches look attractive, money is needed to test the different hypotheses.On the other hand, one may wonder whether causal treatments and cure must be the primary aim. In CDG, there is room for optimization of the classical, supportive therapies to improve the patients' life and alleviate the burden for the parents and families. Unfortunately, studies of the natural history of the disease, and funds to involve the parents and primary care takers in collecting the data, are not often included in research grants and applications. Nevertheless, in the field of CDG, clinical and basic researchers are joining forces to try and reach at least some of the se aims.

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FAST SKELETAL TROPONIN ACTIVATION FOR RESTORING MUSCLE STRENGTH IN MOUSE MODELS OF NEMALINE MYOPATHY

BRINGING TREATMENTS TO THE CLINIC

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Nemaline myopathy (NM) is a rare and fatal neuromuscular disorder with an estimated prevalence of 1 in 50.000 live births. The main clinical feature of NM is muscle weakness, which impairs swallowing and causes severe respiratory problems. In children suffering from NM, the diaphragm is often severely affected, leading to suffocation. There is currently no treatment for NM, and efforts are directed at alleviating symptoms and compensating for disabilities as far as possible. Our E-Rare 1 project NEMMYOP has yielded important results on (1) the pathophysiology of muscle weakness in NM, on (2) new NM biomarkers, and on (3) in vitro effects of troponin activators on muscle fibres of NM patients. The insights gained in NEMMYOP have provided the first indications for a possible treatment for NM. To build upon this promising finding, TREAT-NEMMYOP will determine the efficacy of tirasemtiv, a fast skeletal troponin activator, in four NM mouse models. TREAT- NEMMYOP will make the next pivotal step towards clinical trials and future treatment of NM. To reach our aim, TREAT-NEMMYOP will assess the effect of tirasemtiv on (i) muscle function, (ii) energy metabolism and (iii) NM biomarkers. To obtain an in-depth evaluation of tirasemtiv efficacy, we will combine measurements of in vivo and ex vivo muscle strength, non-invasive magnetic resonance imaging (MRI) and spectroscopy with analysis of the involved signalling pathways and proteome. This also enables us to better understand the pathology of NM and the molecular mechanisms by which compounds such as tirasemtiv increase muscle strength in NM patients. TREAT-NEMMYOP is a powerful consortium of three academic groups and complementary collaborative partners, including the developer of tirasemtiv (Cytokinetics Inc.). The consortium has access to four unique NM mouse models and a high-end infrastructure that enables thorough assessment of muscle- and whole body performance. This makes TREAT- NEMMYOP well equipped to assess the efficacy of this highly promising treatment option for NM.

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MITOCHONDRIAL DISEASES: STATE OF THE ART.

NEUROLOGICAL DISEASES

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Mitochondrial diseases, or diseases of the oxidative phosphorylation system, consist of a group of disorders originated by a deficient synthesis of ATP. This system is composed of proteins codified in the two genetic systems of the cell, the nuclear and the mitochondrial genomes and, therefore, the mode of inheritance of these disorders could be either mendelian or maternal. They are in general multisystemic and show a large phenotypic variability with symptoms that affect different organs and tissues. Sometimes, it is possible to define specific syndromes but, in general, overlaping symptoms and a large variety of phenotypes are found. All this makes diagnosis of these disorders very complicated and require the participation of specialists from different areas. These disorders collectively affect aproximately 1/6,000 births. Human mtDNA is composed of 16,569 base pairs that encode 37 genes: 2 rRNAs, 22 tRNAs and 13 polypeptide components of four of the five OXPHOS complexes. There are several mtDNA copies per mitochondrion and many mitochondria per cell. The basic features of the mitochondrial genetic system, the mode of replication and transcription, and the proteins that encode were described in the 1980's. The location of mtDNA in a cytoplasmic organelle has conferred genetic features that differentiate it from nuclear DNA. The main genetic features of this genome are: maternal inheritance, polyplasmy (homoplasmy and heteroplasmy), mitotic segregation, threshold effect, and high mutational rate. MtDNA diseases are also unique inasmuch different mutations in the same or in different genes might give rise to the same phenotype, just as the same mutation can give rise to very different phenotyes. NGS has allowed to associate different nDNA mutations to these diseases. Cellular models (transmitochondrial cybrids and transfected fibroblast) are used to determine the pathogenicity of the mutations. Recently, there are several proposals of therapy to cure or avoid the transmission of these diseases.

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DELVING INTO THE COMPLEXITY OF SPINOCEREBELLAR DEGENERATIONS, HOW NEXT GENERATION SEQUENCING IMPROVED OUR KNOWLEDGE

NEUROLOGICAL DISEASES

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Spinocerebellar degenerations are clinically and genetically heterogeneous neurodegenerative disorders. Their genetic diagnosis has been improved by next-generation sequencing techniques. Novel types of mutations or transmissions in known genes are constantly being identified. The phenotypic spectrum associated with a single gene constantly gains in complexity. Numerous novel genes have been identified; some have been implicated in these diseases in addition to being responsible for other diseases. Novel pathological mechanisms have been identified. All these factors make genotype-phenotype correlations particularly difficult. Some but not all of this variability can be explained by different pathophysiological consequences (loss of function, gain of function, variable levels of haploinsufficiency) but also raises the question of modifier genes.

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RARE NEUROGENETIC DISORDERS: THE CLINICIANS PERSPECTIVE

NEUROLOGICAL DISEASES

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The clinician investigating rare genetic disorders interfaces not only with patients and families but with numerous other professionals that form a team. Several pitfalls in communication and management of cases are discussed in this talk and illustrated by case-reports. The following potential pitfalls will be highlighted: -Delineation of Neurogenetic disorders start with a careful phenotypic description, this process may be complicated by lumping together unrelated symptoms or vice-versa. -Establishing a tentative mode of inheritance depends on understanding culture-dependent definitions of relatedness. -The process of filtering sequencing-data should be clear to the clinician as several assumptions derived from the clinical data go in to the process. -Once a list of possible causative variants has been assembled, the discussion of what pathways are relevant to the patient's symptoms should be informed by the clinician. - Reaching a molecular genetic diagnosis is not the end of the patient-clinician relationship, and expectations should be set accordingly.

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THE NEW ROLE OF MEDICAL GENETICS IN CLINICAL GUIDING

NEUROLOGICAL DISEASES

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Genomic testing rates number one even before telecommunnication and imaging technology as a disruptive technology in medicine. Nearly all concepts currently known to play a role in personalized medicine are based on genomic analysis of individual patients. This is a challange for Medical Genetics as it moves away from pedigree analysis to identify novel genes or even from testing for specific mutations in affected individuals towards genetic screening. This has been made possible through the recent developments of „Next Generation Sequencing" technologies, having placed this technology within less then 5 years into a routine diagnostics in the clinic. However, even if the technical part of genome sequencing has been solved widely the extend of interpretation of individual genome data in the clinical practise is still a matter of debate. Most of the current approaches are thus focussing on symptome based genetic diagnosis groups using targeted enrichment of genes, the so-called gene panels. However, depending on the diagnosis, these panels may cover as many as 1000 genes (for instance for intellectual disability, ID). Knowing that today only about 50% of the genetic causes of ID are being identified and at the same time that extensive data sets are being generated which are for the most parts not yet classified for their pathogeneity, geneticists are „playing back" comprehensive variant sets to the clinicians. Currently, „Mendeliome" enrichment strategies are in testing basically allowing to test all proven disease genes in one analysis. However, with these huge data information the specificity of the data is reduced with generating „unwanted" information at the same time. This raises a new ethical dimension whether geneticists should be allowed or even requested to play back genetic data with clinical implication for disease prevention (cancer, cardiomyopathy, aso).

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AN UPDATE ON LEUKODYSTROPHIES

NEUROLOGICAL DISEASES

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Leukodystrophies are rare, genetic disorders primarily affecting the white matter of the central nervous system (CNS). When the studies on leukodystrophies started in 1987, only a limited number of disorders was known and it was estimate that over 60% of the cases remained with a specific diagnosis. With MRI pattern recognition an increasing number of disorders could be defined and for the most prevalent disorders the basic genetic defect was determined by genetic linkage studies. Despite this progress, the % of unsolved cases was still found to be 50% in 2010. The problem was that the remaining cases comprised numerous exceedingly rare disorders, which escaped disease definition by clinical and MRI observations and gene identification by conventional genetic linkage. The introduction of massive parallel sequencing, allowing whole exome and whole genome sequencing (WES and WGS) changed the situation completely and allowed disease definition and gene identification in very small groups of patients and even single families and individual patients. A recent retrospective study showed that now 80% and probably soon 90% of the leukodystrophy patients can receive a specific diagnosis. Disease definition and identification of the gene defect underlying the disease is essential for all further studies on clinical insights, disease mechanisms and therapy development. One example is megalencephalic leukoencephalopathy with subcortical cysts (MLC), a disease first described in 1995. Genetic linkage helped identify the first gene, MLC1, harboring recessive mutations in ~70% of the patients. MLC1 protein interaction studies led to the identification of HEPACAM / GLIALCAM as second gene, harboring recessive mutations in ~10% of the patients and dominant mutations in ~20% of the patients. The recessive disease was classical, but the dominant disease had an improving phenotype. Since then it has become clear that the loss of MLC1 function is central in the disease. GlialCAM is a chaperone of MLC1 to ensure its normal location in astrocytic endfeet at the blood- and CSF-brain barriers. MLC1 has been shown to be involved in volume regulation by astrocytes. Mouse models for MLC have been developed allowing further studies on disease mechanisms and therapy.

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LA&C: OPPORTUNITIES AND CHALLENGES TO RARE DISEASES RESEARCH

PATIENTS AND RESEARCH

Virginia A. LLera, MD President GEISER Foundation (Rare Diseases LA&C)

The first step to understand the opportunities and limits of our region regarding rare diseases research, is to know the different sides that take place on the results: the culture of the researchers (basic research made by universities vs clinical trials made by clinicians without any academicals training on research , lack of articulation between basic and clinical trials, GCP and Ethics only as a formal procedure, so there are lots of sensitive information, the gap between needs from people and the academically vision, the market growth vs the unmet needs), the patients are not aware about the benefits of research (less proactive attitude , more lost opportunities for all) the regulatory policies playing as barriers instead of favoring opportunities caring citizens, etc. Maybe most of these aspects are similar to the rest of the world, but in a most detailed view, these are differences in our region, having its particularity. In the other hand interest from the public policies and the local industry are getting involved to this field. The researchers initiate first steps toward translational criteria. The Knowledge of all these aspects, help us to be able to find strategies and solutions to develop the maximum opportunity for research in our region in order to help more people all over the world, but also taking into account that our region has a lot of possibilities to be developed in this sense. These specific strategies and suggestions could arise from an international collaboration. International collaboration speeds up the creativity and the better solutions. As an example there are many collaborative programs between Europe and LA&C but there is no one devoted to develop educational programs on this specific item. GEISER propose to include Rare Diseases research programs into the international collaboration. As It is a sensitive issue, for that reason and in order to be more efficient, the start might be a round table including all the stakeholders, delivering an educational program proposal to maximize efforts and answers for the affected citizens. GEISER proposes a draft agenda to be considered as a first step for an international collaboration program for rare disease research, articulating all the current initiatives and the new ones coming from the developing countries.

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CROWDFUNDING PRIMARY RARE DISEASE RESEARCH: BOOTSTRAPS AND BIOBANKS

PATIENTS AND RESEARCH

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The RE(ACT) Community aims to promote both scientific knowledge sharing and to allow all interested stakeholders an innovative and targeted tool to raise funds for rare disease research projects. In 2014, I initiated the first crowdfunded project on this platform. Our lab proposed to collect biological resources nationwide concerning the large congenital giant nevus for our current and prospective research. With the support of multiple patient advocacy groups and individuals worldwide, we have reached our fourth milestone at over thirty six thousand euros to date, research is underway, and results are coming in. This talk will share some of our experiences, both disappointing and encouraging, so that others can gauge how crowdfunding approaches could kickstart their own original scientific endeavors.

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RARE DISEASES REGISTRIES AS TOOLS FOR CLINICAL RESEARCH

PATIENTS AND RESEARCH

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The double-blind randomized controlled trials (RCTs) are accepted by medicine as objective scientific methodology that, when ideally performed, produce knowledge untainted by bias. These complex, expensive studies can involve hundreds or even thousands of patients. In common conditions, such as hypertension, the population is so large that it is not difficult to select from the whole, those patients who fit the enrollment criteria. On the contrary, clinical trials in rare diseases (RDs) have to deal with the geographic spread of patients but also with the strong heterogeneity within the same condition. Different patient subsets and fluctuating disease course can be often documented. Patient registries and databases are useful tools in the field of RDs and they are sometimes the only way to pool data in order to achieve a sufficient sample size for clinical research. In order to better characterize patients and establish long-term prognosis, patient-specific data are most often collected in registries linked with biorepositories. The Clinical Research Center for Rare Diseases of the Mario Negri Institute has gained great experience in implementing rare disease registries and results of our studies emphasize the clinical importance of such effort. Examples showing the utility of registries are moreover numerous in scientific literature and must lead to overcome difficulties encountered in their implementation and maintenance. The approval process of orphan drugs by regulatory agencies may have also to deal with limitation inherent to the small populations. Patient registries are often a mandatory item (requested by regulatory authorities such as the US FDA or the European EMA) to capture long-term safety and efficacy data of new drugs in the post-marketing phase. Genotype-phenotype correlations in patients with genetic RDs enrolled in registries may allow to identify different subgroups of subjects responsive to targeted treatments. Over the last 20 years RDs have received more attention from health authorities and from the public at large. To date a lot of experience has been accumulated in Europe as far as information to the patients and coordination of patient support groups. Actions to collect relevant information about the patients, with registries linked with biorepositories, as a mean to implement clinical research and treatment possibilities should be considered a priority for the near future.

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CATALYZING TRANSLATIONAL INNOVATION
PATIENTS AND RESEARCH

Abstract keynote speaker OPENING CEREMONY Christopher P. Austin,
M.D. Director, National Center for Advancing Translational Sciences

The process by which observations in the laboratory or the clinic are transformed into demonstrably useful interventions that tangibly improve human health is frequently termed "translation." This multi-stage and multifaceted process is poorly understood scientifically, and the current research ecosystem is operationally not well suited to the distinct needs of translation. As a result, biomedical science is in an era of unprecedented accomplishment without a concomitant improvement in meaningful health outcomes, and this is creating pressures that extend from the scientific to the societal and political. To meet the opportunities and needs in translational science, NCATS was created as NIH's newest component in December 2011, via a concatenation of extant NIH programs previously resident in other components of NIH. NCATS is scientifically and organizationally different from other NIH Institutes and Centers. It focuses on what is common to diseases and the translational process, and acts a catalyst to bring together the collaborative teams necessary to develop new technologies and paradigms to improve the efficiency and effectiveness of the translational process, from target validation through intervention development to demonstration of public health impact. This talk will provide an overview of NCATS mission, programs, and deliverables, with a view toward future developments.

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ABSTRACTS

IT'S TIME TO
IMAGINE
A NEW STORY

GENETIC EDITING WITH THE CRISPR/CAS9 SYSTEM FOR HUNTINGON'S DISEASE

ABSTRACT N° A004_2016 / DRUG REPOSITIONING AND PERSONALIZED MEDICINE

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Huntington's disease (HD) is a neurodegenerative disorder caused by a pathological CAG expansion at the 3' end of the first exon of the huntingtin gene (HTT). Currently, there is no efficient treatment for HD. Editing of the mutant HTT gene with the Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) system represents a new and promising approach. Recognition of the HTT target sequence by a single-guide RNA sequences (sgRNA) and the Cas9 protein is inducing DNA double-strand breaks (DSB), which activate endogenous cellular repair pathways. Non-homologous end joining (NHEJ) will introduce small insertion/deletion (indel) that alter the reading frame of HTT gene while homologous directed repair (HDR) is activated in the presence of a DNA template. To validate the approach and optimize the delivery of the CRISPR system with viral vectors, we first targeted artificial sequences containing fluorescent reporter genes in HEK 293T cells. An efficient gene disruption was measured and associated with a loss of fluorescence in neurons, astrocytes, in vitro and in vivo. Furthermore, we developed multiple strategies to disrupt the mutant HTT gene. Quantification demonstrated a high rate of indels, leading to a strong reduction of HTT protein in HEK 293T cells, mouse cortical neurons and human iPS-derived neurons. Blocking HTT expression in vitro HD models is improving several physiopathological parameters. We are currently evaluating the impact of allele or non-allele specific mutant HTT editing in human neurons from HD patients. Altogether, these data demonstrate the potential of the CRISPR technology as therapeutic strategy for HD.

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AUTOPHAGY INDUCTION AS A POTENTIAL TREATMENT FOR LYSOSOMAL DISEASES.

ABSTRACT N° A006_2016 / DRUG REPOSITIONING AND PERSONALIZED MEDICINE

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Lysosomal storage disorders (LSDs) are genetic diseases caused by the abnormal accumulation of non-degraded macromolecules into lysosomes leading, in most cases, to a biochemical cascade that results in the impairment of the autophagy flux and the prevention of lysosomal clearance. Recent studies have demonstrated that the induction of autophagy in LSDs could decrease the abnormally stored material by enhancing lysosomal exocytosis. Bicalutamide is a synthetic non-steroidal anti-androgen molecule reported to be involved in the induction of autophagy in human prostate cancer cells. The aim of our work was to evaluate the potential benefits of Bicalutamide treatment, and its enantiomers (R and S), in skin fibroblasts derived from patients affected by seven different LSDs. Treatment response was evaluated in cultured fibroblasts by monitoring lysosomal exocytosis, substrate accumulation and cell viability. Treatment with (S)-Bicalutamide enantiomer was able to ameliorate significantly the altered biochemical parameters in all the cell lines, while the response to (R)-Bicalutamide, the racemic Bicalutamide or Ciclodextrin (a previously described autophagy inductor in LSDs) was less effective. Moreover, we have studied the molecular mechanism underlying Bicalutamide's action and we found that Bicalutamide acts through the activation of the transcription factor TFEB. This transcription factor enhances the transcription of genes involved in autophagy and lysosomal biogenesis, leading to the subsequent increase ofthe autophagy flux and the lysosomal exocytosis. These results are encouraging as this approach circumvents the primary enzyme deficiency responsible for these diseases by exploiting the ability of lysosomes to expel their content into the extracellular space, resulting in the clearance of the pathogenic stored material.

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BBRM02, A READ-THROUGH REPURPOSED DRUG FOR NONSENSE-MUTATIONS, SHOWS PROOF OF EFFICACY IN TREATMENT OF SPINAL MUSCULAR ATROPHY (SMA)

ABSTRACT N° A007_2016 / DRUG REPOSITIONING AND PERSONALIZED MEDICINE

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Background: Administration of read-through agents (e.g. aminoglycosides) acting on the stop codon located at exon 8 of the Survival of Motor Neuron (SMN-del7) protein, was found to be effective in inducing higher level of functional SMN protein. Prior attempts to translate these agents into therapeutic candidate drugs were hampered by prohibitive toxicity. Bioblast Pharma is currently developing a proprietary therapy for Spinal Muscular Atrophy (SMA), using FDA-approved macrolide antibiotic drugs as read-through agents, known as the BBrm family. Results: BBrm02, intrathecal formulation of Azithromycin, increased SMN protein expression levels and function (shown by nuclear GEMs presence) in SMA patients' cell lines. Intracerebroventricular (ICV) administration of BBrm02 to the well-known delta7 mouse model caused an increase in SMN expression levels in brain, spinal cord and muscle at 2.1, 2.4 and 5.7 fold, respectively, above vehicle-treated animals. The unique PK profile of BBrm02 enabled sustained effect in this model on body weight, motor function and increased survival, following a single administration, especially at low dose. Moreover, 30 days following a single ICV administration of BBrm02 to the Regeneron C/C mouse model (the Jackson Laboratory), demonstrated statistically significant increase in both tail length and body weight, phenomena that are indicative of effective intervention in this mouse model. Combination of BBrm02 therapy with ASO therapy resulted in synergistic effect on the delta7 mouse model. Toxicological studies with intrathecal administrations to rats and dogs have been complete, showing no observed adverse effect level (NOAEL). Conclusions: Our encouraging combined results demonstrate a proof of efficacy of the Bioblast approach for the treatment of SMA using its lead molecule, BBrm02. The completion of safety studies enables Bioblast to initiate a Phase I clinical study in the near future. Acknowledgements: E Osman, C Washington, CL Lorson, University of Missouri, Columbia, MO, USA M Osborne and C Lutz, Rare and Orphan Disease Center, The Jackson Laboratory, Bar Harbor, ME, USA

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EACHING AN OLD DOG NEW TRICKS? LESSONS ON USING N-OF-ONE TRIALS TO REPURPOSE TREATMENTS FOR RARE DISEASES: THE EXAMPLE OF EPHEDRINE FOR MYASTHENIA GRAVIS.

ABSTRACT N° A008_2016 / DRUG REPOSITIONING AND PERSONALIZED MEDICINE

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Background During the first edition of the RE(ACT) Congress, we reported on the development of an n-of-one trial service for rare diseases to examine the efficacy and safety of off-label treatments. An n-of-one trial is an efficient method because a patient can be his own control, using a cross-over design. We now describe the results of the first series of n-of-one RCTs, using ephedrine, a drug (previously) used for asthma in some countries, for autoimmune myasthenia gravis (MG) as a case study, and the regulatory implications of these results. Ephedrine may postpone or abolish the need for immunosuppressive therapy when added to acetylcholinesterase inhibitors or low-dose prednisone but its effect in MG has not been systematically evaluated. Objectives To study the effect and safety of ephedrine as add-on treatment for MG in a Cochrane systematic literature review and a series of n-of-1 trials, and to examine how this treatment can be made available to patients via the current regulatory frameworks for market approval and reimbursement. Results Our review reported on 53 non-randomised studies including 308 patients, but showed that there was no evidence from RCTs. Our series of four n-of-one RCTs found a small but statistically significant improvement in all four patients (1,0 point improvement on the Quantitative Myasthenia Gravis score), and minimal adverse effects. The Netherlands Medicines Evaluation Board (CBG) and National Health Care Institute (ZIN) were asked to advise on how these results can be used to make this treatment available to patients. CBG stated that data of n-of-one trials could be sufficient to warrant registration as a last resort option for rare diseases under certain conditions such as fast onset of the effect. However, both ZIN and CBG considered the clinical relevance of the effect inconclusive. A different study design e.g. parallel group trial with a longer treatment duration was suggested. Currently only companies have the means to apply for market approval. Investments in old drugs may cause companies to raise prices of rediscovered drugs beyond cost-effectivity. Conclusion N-of-one RCTs can provide evidence of efficacy of treatment for rare diseases, particularly when repurposing existing treatments where companies can expect little return on investment. It seems warranted to use public funding for evidence development for such drugs to ensure reasonable prices.

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MILD INHIBITION OF ALANINE-GLYOXYLATE AMINOTRANSFERASE TRANSLATION AS A POSSIBLE TREATMENT OF PRIMARY HYPEROXALURIA TYPE I

ABSTRACT N° A009_2016 / DRUG REPOSITIONING AND PERSONALIZED MEDICINE

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Background: Primary hyperoxaluria type 1 (PH1) is a kidney stone disease, often leading to ESRD, caused by absence, deficiency or mistargeting of the liver peroxisomal alanine-glyoxylate aminotransferase (AGT), encoded by AGXT. The most frequent mutation G170R, responsible for 30% of PH1 cases in Caucasians, results in aberrant mitochondrial localization rather than catalytic inactivity. Modulating AGT maturation and folding has long been perceived as a therapeutic approach. Yet, numerous attempts over the years failed to rescue AGT mutants. We propose mild translational inhibition as a novel approach to improve folding and localization of AGT mutants. Methods: Our model is CHO cells transfected with appropriate vectors as well as hepatocytes from PH1 patients with G170R mutated and WT AGT. We used the FDA-approved drug emetine, as a translation inhibitor. To ensure selective and specific discrimination between the mitochondrial (major) and the peroxisomal (minor) subpopulations of mutated AGT we developed the GlowAGT system based on the recently described self-assembly split GFP approach. Only those GlowAGT molecules (WT or mutant) that are localized in peroxisomes are fluorescent. Results: WT-AGT but not G170R-AGT was detectable by GlowAGT fluorescence due to mitochondrial mislocalization of the mutant. However, both variants were visible by indirect immunofluorescence. Treatment of G170R-AGT with emetine showed statistically significant increase of fluorescent subpopulation of G170R-AGT. GFP fluorescence was exclusively co-distributed with the peroxisomal staining in all cases. Treatment G170R-AGT human hepatocytes with emetine had rescued the elevated level of oxalate excretion by human hepatocytes. Conclusions: We show that mild translation inhibition by emetine is a novel therapeutic approach for PH I caused by AGT misfolding/mislocalization. We suggest that mild translation inhibition could be used as a therapeutic approach for many conformational diseases.
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NOVEL THERAPEUTIC PERSPECTIVES FOR SARCOGLYCANOPATHY BY ASSISTING PROTEIN FOLDING

ABSTRACT N° A010_2016 / DRUG REPOSITIONING AND PERSONALIZED MEDICINE

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Sarcoglycanopathy, the collective name of four forms of Limb Girdle Muscular Dystrophy (LGMD 2C-2F), is a rare genetic disorder affecting mainly the proximal musculature. Defects in any one of the genes coding for α-, β-, γ- or δ -sarcoglycan (SG), forming a key structural tetramer in the sarcolemma of striated muscles, strongly affect SG-complex formation/stability. Disease severity is strictly related to the residual level of sarcoglycans in the sarcolemma, with the most severe forms characterized by the almost complete loss of the proteins. Most of the sarcoglycan defects are missense mutations producing a full length but folding defective protein. We have proven that the primary pathological event in sarcoglycanopathy occurs in the Endoplasmic Reticulum, where the quality control system, by proof-reading newly synthesized sarcoglycans, recognizes and directs to the proteasomal degradation the folding-defective mutants. This event causes the secondary loss of the wild-type partners. We have also demonstrated that many missense mutants retain their function and that the entire complex can be properly rescued by blocking the degradation of these mutants. These findings opened new perspectives for the therapy of this neglected disease allowing to design small molecule-based approaches aimed not only to merely inhibit sarcoglycan mutants degradation, but particularly to help their folding so that, structurally stabilized, these mutants can skip disposal and traffic at the proper site of action. To this intent, we have tested several small molecules, known as protein folding correctors screened for the treatment of cystic fibrosis, in both cell models expressing folding defective forms of α-SG and primary myogenic cells isolated from a patient suffering of LGMD2D*. We have observed, by western blot and immunofluorescence analyses, that treatments with these compounds lead to the accumulation of different α-SG mutants that are competent to assemble with the wild type partners and traffic to the cell membrane. Although the mechanism of action of CFTR correctors on sarcoglycans is still unknown and needs to be clarify, these data represent the proof of principle of a "protein repair strategy" that can be developed to treat LGMD2D utilizing well-known and available small molecules correcting mutant folding. * Human samples have been provided by the Neuromuscular Bank of Tissues and DNA samples of the Italian Telethon Foundation.

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HUMAN BRODY DISEASE AND ITS ANIMAL MODEL CATTLE PSEUDOMYOTONIA: FROM UNDERSTANDING THE PATHOGENETIC MECHANISM TO IDENTIFICATION OF NOVEL THERAPEUTIC APPROACHES

ABSTRACT N° A011_2016 / DRUG REPOSITIONING AND PERSONALIZED MEDICINE

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Human Brody disease is a rare inherited myopathy clinically characterized by an exercise induced impairment of muscle relaxation due to a deficiency of the sarco(endo)plasmic reticulum Ca2+-ATPase (SERCA1), resulting from a defect of ATP2A1 gene coding for SERCA1. In skeletal muscle fibres, SERCA1 allows relaxation by removing Ca2+ from cytosol to restore resting Ca2+ concentration. Brody disease is transmitted as an autosomal recessive trait and is genetically heterogeneous. SERCA1 deficiency has been attributed to a reduction either in SERCA1 protein content at sarcoplasmic reticulum (SR) membranes of pathological fibres, or in Ca2+-ATPase activity. Large animals have emerged as genetically relevant models for human inherited diseases. Cattle congenital pseudomyotonia (PMT) is a muscular disorder characterized by stiffness and delayed muscle relaxation. All PMT affected animals are homozygous for the ATP2A1 gene mutations and, like Brody disease, cattle PMT turned out to be genetically heterogeneous. Bovine pathological muscles are characterized by a selective reduction of SERCA1 protein. Clinical symptoms genetic and biochemical findings, clearly demonstrated that cattle PMT is the true animal model of Brody disease. Using both HEK293 cells overexpressing SERCA1 mutants and biopsies from cattle pathological muscles (collected in conformance with the institutional guidelines for the care and use of animals), we provided evidence that SERCA1 mutants were polyubiquitinated and prematurely degraded by the ubiquitin-proteasome system. The treatment with proteasome inhibitors rescued the expression level of mutated SERCA1 at SR membranes both in HEK293 cell model and in muscle fibres from PMT affected animals. Although corrupted in proper folding , SERCA1 retained the catalytic properties, therefore by monitoring Ca2+ re-uptake we demonstrated that the recovered SERCA1 was able to re-establishing resting cytosolic Ca2+ concentration. At present, no specific therapy exists for Brody disease. We have found that small molecules known as "CFTR correctors" are able to reverse Brody pathological phenotype by promoting correct folding and proper targeting at SR membranes of the mutated misfolded SERCA1. So, a possible pharmacological therapy could be hypothesized for the specific population of Brody patients in which ATP2A1 mutations impair SERCA1 protein folding causing its rapid degradation, but leave unaffected the Ca2+-ATPase activity of the protein.

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REPOSITIONING & RARE DISEASES: A FAST DRUG DEVELOPMENT PROCESS

ABSTRACT N° A012_2016 / DRUG REPOSITIONING AND PERSONALIZED MEDICINE

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Purpose: Drug repositioning is the process by which a drug already used for a certain condition is used to treat other diseases, expanding the range of use of the medicine. An advantage over traditional drug development is that a repositioned drug has already passed toxicity and clinical trials (like Phase I), its safety is well-known and the risk of failure for reasons of adverse toxicology is reduced. Thus, they can bypass much of the early cost and time; representing a profitable way to achieve success. Computational chemistry is a promising strategy in drug repositioning. SOM Biotech's approach is drug-based and, in particular, based on chemical similarity. Orphan diseases are also attractive as there is a focus in unmet needs; facilitated development and availability of drug through priority review, accelerated approval, fast track designation, breakthrough therapy designation, market exclusivity period; small clinical trials; and a targeted commercial footprint. SOM is devoted to combine these two concepts in order to avoid the safety risks, costs and time needed to bring the drug onto the market. Methods: SOM's discovery platform is proprietary ligand-based virtual screening software which identifies new drug activities. It compares physicochemical properties of a selected reference compound, with those of a database of marketed products plus products that have reached clinical research. As a result, products with potential similar biological activity but with different structure than the reference compound are identified. Once a new activity is in silico determined, disease relevant in vitro and in vivo studies are performed to confirm it, and protected with an international patent. Experimental validations are carried out by consortia partners or outsourced when appropriate. Results: Among the different projects on orphan diseases carried out since 2009, two of them reached clinical phases. SOM0226 has been demonstrated to be effective for Transthyretin Amyloidosis in a 20-patient proof-of-concept trial. SOM3355 showed to be effective in preclinical experiments for the treatment of chorea associated to Huntington's disease and a clinical proof-of-concept is ongoing. Conclusion: SOM's technology showed to be effective in repositioning drugs for rare diseases as successful cases demonstrate. The company is devoted to obtain fast potential cures for orphan diseases, diseases with a very high medical need and with no treatment available.

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A NEW CHANCE FOR CYSTINOSIS THERAPY

ABSTRACT N° A013_2016 / DRUG REPOSITIONING AND PERSONALIZED MEDICINE

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Cystinosis is a rare autosomal inherited disease caused by functional deficit of the lysosomal cystine transporter cystinosin, coded by CTNS gene. The accumulation of cystine crystals causes impairment of several organs, in particular, end-stage kidney failure and ocular complications in the first decade of life, if not treated early with cysteamine. Oral and ophthalmic cysteamine therapy postpone the need for renal transplantation and ocular complications, respectively. However, the resulting side effects of cysteamine therapy adversely affect the lifestyle of patients and their relatives. Large scale drug screening was performed on immortalized proximal tubule epithelial cells of patient (ciPTEC CTNS -/-) to find molecules that improve the cystinotic phenotype. Prestwick Chemical Library, collecting 1,200 small molecules 100% FDA and EMA approved, was assayed at 10 μM for 24 hours on ciPTEC CTNS -/-. Two drugs were identified by crosschecking positive hits found by quantification of the intracellular cystine level measured by HPLC, and by determining the apoptosis, assessed as caspase 3/7 activation state in an automatized platform. Molecule #4176 was chosen for its bioavailability and molecular stability. Pharmacokinetics studies in ciPTEC CTNS -/- showed that molecule #4176 reduced intracellular cystine more efficiently than cysteamine, in a dose ranging 0.1-20 μM. This result was confirmed in PBMCs of patients, furthermore an addictive effect was observed when molecule #4176 and cysteamine were combined in a ratio 1:1. Molecule #4176 reduced significantly ROS by about 25% and by about 50% in combination with cysteamine. Finally, an in vitro cystine crystallization assay showed the capability of molecule #4176 to reduce, in a supersaturated cystine aqueous solution, the formation of crystals. The pre-clinical experimental evidences show that repositioning of molecule #4176, used alone or coupled with cysteamine, could represent a potential therapy for systemic and topical treatment of cystinosis.

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IN VITRO MODEL OF PROXIMAL TUBULAR DYSFUNCTION IN CYSTINOSIS

ABSTRACT N° A014_2016 / DRUG REPOSITIONING AND PERSONALIZED MEDICINE

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Background: Cystinosis is a homozygous recessive lysosomal storage disorder caused by mutations in cystinosin (CTNS). Patients with this disease develop a severe renal phenotype with polyuria and proteinurea at the age of 6 months (renal Fanconi syndrome) and kidney failure before the age of ten. The current therapies are not able to restore proximal tubular function or improve water and protein reabsorption by the kidneys. Aim: Develop a high throughput in vitro assay that can be used to evaluate the cystinostic proximal tubular cell function for drug testing Methods: We used conditionally immortalised proximal tubular cells (ciPTEC) from both cystinosis patients and healthy controls. To evaluate the protein uptake we compared the uptake of labelled bovine serum albumin (BSA-FITC) or receptor associated protein (RAP-GST), both ligands of the megalin mulitiligand receptor which is responsible for protein reabsorption in the proximal tubles. Next we evaluated the co-localisation of the internalised protein with the endosomes (EEA1 staining) or lysosomes (LAMP1 staining). Images were taken with the CV7000 high content imager to get high resolution confocal images. Results: RAP-GST showed a clear vascular pattern that overlapped with the endosomal and lysosomal compartment. BSA-FITC binding showed high background staining and was not used for further anlalysis. RAP-GST co-localised well with EEA1 and LAMP1 after 1 hr incubation, compared to no overlap on ice. Protein uptake experiments showed that protein degradation was delayed in cystinotic cells as compared to the controls. Furthermore, the lysosomes were less regularly distributed on the cell surface in cystinotic cells and prone to forming larger clumbs. This phenotype was used to grade the cystinotic phenotype and will be used as a model to select for drug candidates that may have a positive effect on the proximal tubule function in cystinotic patients. Conclusion: The in vitro model of human proximal tubular cells shows a clear defect in lysosomal patterning and protein degradation which we can use as a functional readout to identify drug compounds that can improve cystinotic proximal tubular function.

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ENDOGENOUS METABOLIC PROFILING AS A FUNDAMENT IN PERSONALIZED THERANOSTICS.

ABSTRACT N° A015_2016 / DRUG REPOSITIONING AND PERSONALIZED MEDICINE

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Metabolomics has grown into an established tool in research as; A. Diagnosis, i.e. classification B. Identification of biomarkers in relation to e.g. diseases. C. Dynamic studies i.e. to identify effects from e.g. medical treatment, changes in food intake, environmental or genetically changes to a living species such as human, animal, or plants. In this presentation the use of metabonomics as a tool in drug discovery and theranostics will be highlighted. In the first part the differences in biochemical profile between healthy volunteers and persons with the diagnosis rheumatoid arthritis (RA) are discussed and identification of novel biochemical pathways for understanding the underlying factors of the disease is discussed. In the next part a comparison to different animal models is made, in order to identify the most relevant for describing the disease in humans to be used for evaluation of novel treatments, can be drugs nutrition…. In the last part an attempt to understand the origin of the endogenous metabolites we observe in the circulating blood. i.e biochemical pathway used to identify enzymes involved in the disturbed metabolic pattern caused by a mal condition, which is the base foe develop treatments for orphane indications like Battens. Acknowledgement To EU Horizon 2020 for a grant supporting Battcure

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BATCURE: DEVELOPING NEW THERAPIES FOR BATTEN DISEASE

ABSTRACT N° A018_2016 / DRUG REPOSITIONING AND PERSONALIZED MEDICINE

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Purpose: The goal of BATCure is to develop the first effective treatments for patients living with a group of rare lysosomal diseases known as the neuronal ceroid lipofuscinoses (NCL) or Batten disease. We will provide and test novel compounds and gene therapies, and increase understanding of the biochemical pathways and tissues affected in Batten disease to aid the selection and testing of these therapeutic leads. We shall provide this real breakthrough in knowledge and innovative therapies to treat three genetically distinct NCL sub-types caused by mutations in intracellular transmembrane proteins. These affect more than 50% of all children and young adults with NCL living across Europe but are not amenable to the current therapeutic strategies that involve the direct replacement of defective soluble enzymes. They include the most prevalent type of NCL, juvenile CLN3 disease, and about half of all adult-onset cases. Methods: BATCure will provide a concerted, focused and synergistic action over 3 years from January 2016 by experts from 13 organisations in 8 different countries (UK, Sweden, Latvia, Italy, Germany, Spain, Denmark) committed to work together towards our common goal. We will: 1. Create new models, tools and technologies for developing and testing therapies 2. Further delineate disease biology and gene function to identify new therapeutic target pathways 3. Identify biochemical therapeutic target pathways, facilitate effective evaluation of preclinical therapies and improve diagnostics 4. Extend a comprehensive natural history beyond the brain to include cardiology, the spinal cord, peripheral nervous system, psychiatric and metabolic changes 5. Identify new and repurpose existing small molecule therapy 6. Triage new compound treatments in zebrafish, a high-throughput small vertebrate model 7. Deliver and monitor new treatments using mouse models 8. Provide a novel mechanism to involve patients and their families to inform and fully contribute to therapy development and prepare all stakeholders for clinical trials Summary: The proposal BATCure comprehensively tackles the challenges and scope of EU Horizon 2020 PHC-14-2015 – new therapies for rare diseases. The project combines the expertise of (i) recognised European research teams, both basic scientists (partners 1, 3, 4, 5, 6, 8, 9, 10, 12, 13) and clinicians (partner 6), (ii) high-technology SMEs and micro-SMEs (partners 2, 7, 11), and (iii) an NCL patients' organisation (partner 14).

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MAGEL2 AS A GENE RESPONSIBLE FOR THE OPITZ C SYNDROME

ABSTRACT N° B002_2016 / NGS AND UNDIAGNOSED RARE DISEASES

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Opitz C syndrome (OTCS, MIM #211750) is a rare (with less than 60 cases described in the literature) and heterogeneous genetic disorder characterized by severe malformations as trigonocephaly, variable mental and psychomotor retardation and variable cardiac defects with a high mortality rate. Opitz C shows phenotypic overlap with Bohring-Opitz syndrome (BOS, MIM #605039), a disorder with more severe features, and it has been suggested that there is a gradient of spectrum between them rather than being separate syndromes. Different patterns of inheritance and high genetic heterogeneity have been suggested for this syndrome. In this context, next generation sequencing technologies represent a valuable tool in investigating the molecular basis of this disease. The purpose of this study is to find the gene or genes responsible for the OTCS and BOS syndromes. We studied a cohort of 17 patients from 14 unrelated pedigrees with OTCS or BOS phenotype. Whole exome sequences (WES) of 4 nuclear families and 2 additional patients have been analysed. We have found a mutation in the MAGEL2 gene in an 18-year old girl (OC7) diagnosed with OTCS. MAGEL2 is an imprinted gene located at 15q11-13, within the Prader-Willy region, and it is maternally silenced. Patient OC7 was found to be a carrier of a de novo nonsense mutation (p.Q638*) in this gene. By means of a methylation-sensitive restriction followed by PCR amplification (Schaaf et al., 2013, Nat Genet) we have demonstrated that the mutation was in the paternal chromosome. Recently, mutations in MAGEL2 have been associated with a Prader-Willy like syndrome named Shaaf-Yang (Schaaf et al., 2013, Nat Genet; Soden et al., 2014, Sci Transl Med) and, independently, with severe arthrogryposis (Mejlachowicz et al., 2015, Am J Hum Genet). The OC7 patient presented with severe mental retardation and seizures as well as trigonocephalia, micrognatia, hypotelorism, scoliosis, arthrogryposis, and hypotonia, symptons that are consistent with those present in Shaaf-Yang and severe arthrogryposis patients. MAGEL2 is being analysed in the remaining patients of the cohort but no other mutation has been found so far. These results provide the first molecular genetic basis for Opitz C and indicate that there is an overlap between Opitz C and other syndromes. This result also emphasizes the high genetic heterogeneity among this syndrome. In this sense, WES has become a reliable tool in the diagnosis of these patients.

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A NOVEL SPLICING MUTATION IN THE IQSEC2 GENE THAT MODULATES THE PHENOTYPE SEVERITY IN A FAMILY WITH INTELLECTUAL DISABILITY

ABSTRACT N° B003_2016 / NGS AND UNDIAGNOSED RARE DISEASES

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The IQSEC2 gene is located on chromosome Xp11.22 and encodes a guanine nucleotide exchange factor for the ADPribosylation factor family of small GTPases. This gene is known to have a significant role in cytoskeletal organization, dendritic spine morphology and synaptic organization. Variants in IQSEC2 cause moderate to severe intellectual disability in males and a variable phenotype in females because this gene escapes from X-chromosome inactivation. Here we report on the first splicing variant in IQSEC2 (g.88032_88033del; NG_021296.1) that co-segregates in a family diagnosed with an X-linked form of ID. In a percentage of the cells, the variant activates an intraexonic splice acceptor site that abolishes 26 amino acids from the highly conserved PH domain of IQSEC2 and creates a premature stop codon 36 amino acids later in exon 13. Interestingly, the percentage of aberrant splicing seems to correlate with the severity of the disease in each patient. The impact of this variant in the target tissue is unknown, but we can hypothesize that these differences may be related to the amount of abnormal IQSEC2 transcript. To our knowledge, we are reporting a novel mechanism of IQSEC2 involvement in ID. Variants that affect splicing are related to many genetic diseases and the understanding of their role in disease expands potential opportunities for gene therapy. Modulation of aberrant splicing transcripts can become a potent therapeutic approach for many of these diseases.

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EXOME SEQUENCING REVEALED MUTATIONS IN NADK2 IN A PATIENT WITH CLINICAL IMPROVEMENT UPON LYSINE RESTRICTION AND PYRIDOXAL PHOSTATE ADMINISTRATION

ABSTRACT N° B004_2016 / NGS AND UNDIAGNOSED RARE DISEASES

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We report a 10 years old Spanish female with mutations in NADK2. Antenatal CNS abnormalities showed ventriculomegaly, colpocephaly and hypoplasia of the corpus callosum. At birth, axial hypotonia along with uncoordinated movements, microcephaly and generalized cerebellar atrophy were detected. Metabolic investigations revealed high lysine, lactate and pipecolic acid levels in blood and cerebrospinal fluid. Pyruvate carboxylase and pyruvate dehydrogensae activity in fibroblasts were normal. Since the newborn period she received biotin, thiamine and carnitine supplementation. Lysine restricted diet was started at one month old. As pipecolic acid was high, pyridoxine was added to treatment. Later on, at 3 years of age, astatic myoclonic epilepsy appeared with no response to Levetiracetam. We switched pyridoxine to pyridoxal phosphate with electroclinical improvement. Because the activity of mitochondrial respiratory chain complexes III and IV were slightly low in muscle, other cofactors such as ubidecorenone, idebenone, vitamin E and creatine were added to the treatment. At 8 years of age plasma acylcarnitines were performed and high levels of C10:2 were found. Whole exome sequencing identified a homozygous splice site mutation in NADK2 (c.468+6T>C; p.Trp156Cysfs*21). This substitution generates an exon skipping, leading to a truncated protein. In fact, NADK2 mRNA and the corresponding protein were almost absent. Now, at 10 years of age she presents ataxia and incoordination. She has oromotor dysphasia but is able to understand fluid language and is a very friendly girl. We hypothesize that patient clinical improvement could be due to lysine restricted diet together with cofactors and pyridoxal phosphate administration, a cofactor of several enzymes in the CNS. The rationale for this treatment was the fact that pipecolic acid was high in CSF and, consequently its product, piperideine-6-carboxylate, could also be high. Since it is known that piperideine-6-carboxylate inactivates pyridoxal phosphate by a Knoevenagel reaction we provide a potential explanation for the clinical improvement of our patient upon pyridoxal phosphate administration.

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INTERACTIVE SOFTWARE FOR THE INTEGRATED ANALYSIS AND IDENTIFICATION OF RARE AND UNDIAGNOSED DISEASES USING NGS DATA

ABSTRACT N° B005_2016 / NGS AND UNDIAGNOSED RARE DISEASES

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The growing number of known rare diseases is estimated to be larger than 7,000, with more being discovered each day. However, for only half of these diseases the underlying genes are not known. Often, rare disease patients go for long periods of testing without a diagnosis. Recent advances in next-generation sequencing (NGS) have revolutionized genomics allowing physicians and scientists to examine patients at a level that allows finding the proverbial "needle in a haystack". The current challenge with NGS technologies is no longer the development of equipment, but rather the interpretation and analysis of data. Here we present an integrated solution that facilitates analysis and identification of potential causing mutations in rare and undiagnosed diseases from NGS-based genome sequencing studies. The application is made of several steps covering the whole analyses workflow, from raw data to a final report. All complex analysis steps are abstracted from the end user and results are presented in an intuitive and interactive way. The application annotates identified variants with over 50 properties, including descriptive statistics, prediction scores, frequencies from public databases (e.g., 1000 genome, ExAC), and information from disease related databases (ClinVar, OMIM, BIC). In order to support researchers with finding the disease causing mutations, an interactive filtering, prioritization, and classification mechanism is included offering unprecedented ways to analyze variants. Family studies can be collectively analyzed using sophisticated querying and filtering methods including graphical representations of the relationships. The whole system is available as a web-based application integrated into the Platomics platform, which offers powerful features for heterogeneous data handling of samples, performing analysis runs using optimized parameter settings, and tracking of previously completed analyses. As a proof of principle, using the new software we have analyzed targeted sequencing data in a cohort of patients with primary immunodeficiency disorders (PIDs) of unknown molecular origin. PIDs are a diverse group of congenital disorders affecting both naïve and adaptive immune response resulting in severe, life-threatening, early-onset defects. Therefore, the new application will contribute to fast and reliable diagnosis, which could have a major impact for the PID patient treatment, as well as for personalized medicine.

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EXOME SEQUENCING REVEALS TWO AUTOSOMAL RECESSIVE VARIATIONS IN THE BTD AND NLGN1 GENES IN TWO INTELLECTUAL DISABILITY AND AUTISTIC MONOZYGOTIC TWINS BORN OF HEALTHY, FIRST COUSINS PARENTS

ABSTRACT N° B006_2016 / NGS AND UNDIAGNOSED RARE DISEASES

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Intellectual disability (ID) and autism are serious medical and social problems and establishing their cause is essential. Exome sequencing has been proven to be a powerful tool in the identification of their genetic causes and the strategy using trio analysis that compare the proband's genome against the parental ones is thought to give a diagnostic rate of 15-40%. In this line, this study was designed in order to find out the genetic causes of ID and autism in families with at least two male brothers affected. We present here two monozygotic twin brothers born with normal phenotype of healthy first cousins parents. They have always presented with significant psychomotor developmental delay and autistic features including repetitive movements. They also have an atypical behavior with symbiosis between them. On recent assessment at 15 years of age, their motor skills had improved significantly as well as their knowledge, but they still have social interaction difficulties, as well as learning disability. The Ampliseq Exome kit was used to enrich the exon regions of the genomes which were sequenced using the Ion Proton sequencing system with 200bp single end reads Hi-Q Chemistry. NGS were performed in Genetracer Biotech Company and mutations found by NGS were verified by Sanger sequencing in our laboratory. Two autosomal recessive changes have been found in homozygosis in both brothers. Sanger sequencing of their parents confirmed that both variations were inherited. 1) The first one was a c.G1330>C, (p.Asp444His) missense change in the BTD gene (Biotinidase). This variation is a very well documented mutation (D444H) found in individuals with a mild form of Biotinidase deficiency but our patients do not have any symptoms of Biotinidase deficiency, and their levels of Biotinidase are similar to those described for heterozygotes. 2) The second one has not been described to date: It's a nonsense c.74T>A variation in the NLGN1 gene (Neuroligin-1) that results in a truncated protein (p.Leu25*) predicted to be deleterious in in silico prediction programs. In fact, multiple members of the NL family (including NLGN1) have been linked to autism and ID. In addition, NLGN1 KO mice exhibit a dramatic increase in repetitive, stereotyped grooming behavior. So, we consider that this mutation is highly suggestive to be the cause of the pathology of these brothers. Work financially supported by FIS (ISCIII) grant No. PI14/00321, co-financed by FEDER.

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IMPROVING THE MANAGEMENT OF INHERITED RETINAL DYSTROPHIES BY TARGETED SEQUENCING OF A POPULATION-SPECIFIC GENE PANEL.

ABSTRACT N° B007_2016 / NGS AND UNDIAGNOSED RARE DISEASES

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Purpose: The aim of this study was the development of an efficient next generation sequencing (NGS)-based diagnostic tool for the identification of causative mutations in a Spanish cohort with diverse Inherited Retinal Dystrophies (IRD). Methods: We implemented a custom panel of 64 retinal genes and three disease-associated intronic regions for the molecular diagnosis of 32 families with a wide range of IRD. Targeted bases were captured and sequenced on the Illumina MiSeq platform. Subsequently, bioinformatics and cosegregation analyses were performed to identify causative variants. Results: The mutation detection rate of this panel was 100%, with 99% of target bases covered >70x. Pathogenic mutations were found in 73% (22/30) of IRD patients ranging from 50% (4/8) for autosomal dominant cases, 75% (6/8) for syndromic cases, 83% (10/12) for autosomal recessive cases, and 100% (2/2) for X-linked cases. Two cases unsuccessfully studied by exome sequencing were resolved by applying this panel. Moreover, the phenotype and genotype were not in full agreement in 6 probands, which led to the refinement of clinical diagnoses. Furthermore, intra- and interfamilial phenotypic variability was also observed in two cases, respectively. Conclusions: To our knowledge, this is the first study to apply a population-specific panel to seek for causative mutations in a cohort of unselected patients of IRD. Our results demonstrate that this approach is highly efficient for the diagnosis of this heterogeneous hereditary condition. The molecular information found in this study has aid clinical diagnosis in some cases, and has improved family counseling and patient management in others.

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HIPBI-RD: HARMONISING PHENOMICS INFORMATION FOR A BETTER INTEROPERABILITY IN THE RARE DISEASE FIELD

ABSTRACT N° B008_2016 / NGS AND UNDIAGNOSED RARE DISEASES

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Statement of purpose : Rare disease (RD) research is a field of medicine increasingly reliant on information technology, with the advent of low-cost whole-genome sequencing revolutionising the discovery of genetic causes of disorders. Detailed phenotype data, combined with genomic data, have an enormous potential to accelerate the identification of clinically actionable prognostic or therapeutic implications and to improve our understanding of RD. The harmonisation of phenomics information, including disorders and phenotype traits that are stored in different contexts in a non-standardised way, is a cornerstone for producing sound data to foster research. Summary : HIPBI-RD («Harmonising phenomics information for a better interoperability in the rare disease field ») is a three-year project starting in 2016 funded via the E-Rare 3 ERA-NET. This project builds on three resources largely adopted by the RD community: Orphanet, its ontology ORDO (the Orphanet Rare Disease Ontology), HPO (the Human Phenotype Ontology) and PhenoTips, with the support of outstanding bio-ontologies players, the European Bioinformatics Institute and the Garvan Institute. The project aims to provide the community with an integrated, RD-specific bioinformatics ecosystem that will harmonse the way phenomics information is stored in databases and patient files worldwide, and thereby contribute to interoperability. This ecosystem will consist of a suite of tools and ontologies, optimised to work together, made available through commonly used software repositories. Conclusion : The HIPBI-RD ecosystem will contribute to the interpretation of variants identified through exome and full genome sequencing by harmonising the way phenotypic information is collected, thus improving diagnostics. The ultimate goal of HIPBI-RD is to provide a resource that will contribute to bridging genome-scale biology and a disease-centered view on human pathobiology. Acknowledgements : This project has received funding in the scope of the E-Rare3 ERA-NET mechanism for the years 2016-2019.

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A NEXT GENERATION SEQUENCING APPROACH FOR MOLECULAR DIAGNOSIS OF PRIMARY IMMUNODEFICIENCIES

ABSTRACT N° B009_2016 / NGS AND UNDIAGNOSED RARE DISEASES

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Primary immunodeficiencies (PID) are a group of rare genetic diseases that can affect all arms of the immune system. Heterogeneity in the severity, frequency and anatomical distribution of the symptoms highly contribute to the difficulty in clinical interpretation. Indeed, clinical presentations often vary within a specific disease and different diseases have overlapping features, challenging the establishment of a clear diagnosis and potentially delaying access to appropriate treatments. To meet the need for molecular diagnosis, we have designed a blueprint to identify variants associated with undiagnosed phenotypes, by combining high throughput technology to scientific knowledge and deep clinical assessment of PID patients. We used next generation sequencing to screen DNA from peripheral blood samples harvested from individuals presenting with clinical features of PIDs. Patient's specific libraries were created from a unique panel of 361 candidate genes involved in pathways for disorders of the immune system, based both on scientific and clinical knowledge. The primer pools design allowed to target 5477 specific amplicons and was highly customized to allow the coverage of 97% of targeted exons. Bar-coded libraries were pooled, amplified using the emulsion-PCR based technology and templates were sequenced with the semi-conductor Ion PGM instrument. More than 1 million reads per patient were analysed with dedicated softwares in a two-step approach involving: 1.- annotation of genetic variants, in terms of SNPs and Indels, shared between patients family members and 2.- assessment of their biological impact by applying appropriate filters to reveal their potential functional role in the targeted protein. This strategy will help associating clinical relevant variants to precise clinical features. We expect this strategy to yield confirmation of known genetic etiologies in patients with atypical clinical phenotypes, as well as identification of new key molecules involved in mechanisms causing PIDs and, ultimately, point the way towards new therapeutic targets.

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A GENETIC APPROACH TO COMPLEMENT NEWBORN SCREENING FOR ACTIONABLE GENETIC CONDITIONS

ABSTRACT N° B012_2016 / NGS AND UNDIAGNOSED RARE DISEASES

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Newborn screening is a public health program for the detection, diagnosis, and intervention of genetic disorders that may otherwise produce serious clinical consequences. In the last years, tandem mass spectrometry allowed for expanded programs in most developed countries. While the sensitivity and specificity of the method can be up to 99% for metabolic disorders, they are lower for cystic fibrosis or hypothyroidism. Thus, new challenges are reducing false positives and avoiding false negatives by using fast and appropriate second-tier tests. In order to shorten diagnosis time and provide genetic diagnosis and counseling, we are evaluating the use of next generation sequencing as second-tier test. Methods: We use dried blood spot from newborns with positive results in the newborn screening from Spain to isolate DNA and subject it to NGS library preparation. We have developed a panel of 71 known genes commonly affected in the disorders detected by this programs. A bioinformatic pipeline has been designed to identify genetic variants that may be disease causing. We have retrospectively analyzed ~100 samples to establish the sensitivity and specificity. In a second phase, we will prospectively analyze positive hits from the screening in real time and will assess the turnaround time and the cost-effectiveness. In all cases, we generate a report with the genetic variants identified and classified according to the American College of Medical Genetics and Genomics guidelines. Results: Samples in the retrospective phase have been sequenced. Preliminary results show high specificity and sensitivity. Two candidate variants were identified in 88% of the 100 retrospective samples and in 7%, 1 candidate variant was found. In samples where previous genetic diagnosis was available (n=16), 100% concordance was found. These values will have to be confirmed by analyzing the entire retrospective series. We have currently enrolled 2 screening centers for the prospective phase. Conclusion: We have successfully developed an NGS panel that allows a sensitive and specific genetic diagnosis of diseases included in newborn screening in Spain. Our preliminary data shows that genetic testing could be a valid and useful strategy to bypass confirmatory biochemical tests. This could lead to a faster and more accurate diagnosis which will help provide faster treatment to patients.

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EPIGALLOCATECHIN GALLATE EFFECT ON A WILLIAMS-BEUREN SYNDROME MOUSE MODEL

ABSTRACT N° C004_2016 / PATHOPHYSIOLOGY

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Introduction: Williams-Beuren Syndrome (WBS) is a rare neurodevelopmental disorder caused by a heterozygous deletion of 26-28 genes on chromosome band 7q11.23. Patients display a characteristic cognitive and behavioral profile including intellectual disability, increased general anxiety, overfriendly personality and visuospatial deficits. The complete deletion (CD) mouse model carries the same deletion found in WBS patients and it recapitulates most of the neurocognitive phenotype, including low levels of Bdnf and alterations in the PI3K signaling in hippocampus, particularly dysregulation of the regulatory subunit of PI3K (Pik3r1). Therefore, it is a useful tool to evaluate novel therapeutic approaches. Epigallocatechin gallate (EGCG) is the major polyphenolic compound found in green tea. It is associated with various neurological benefits, including cognitive improvement. Although the exact mechanism is unknown, it has been related to the PI3K signaling pathway. In addition, EGCG treatment in a mouse model of Down syndrome restored abnormal levels of Bdnf, an important synaptic plasticity marker. Objective: We hypothesized that EGCG treatment could improve the neurocognitive deficits observed in these mice. Animals were fed either with EGCG or water during one month. We compared the effect of these diets using some behavioral tests, RNA expression studies and neuroarchitecture analysis in hippocampus. Results: Although mRNA levels of Pi3kr1 were not normalized, levels of Bdnf in hippocampus of CD mice were completely restored after the treatment. However, CD mice fed with EGCG presented the same behavioral alterations than control CD mice, including hypersociability, abnormal levels of anxiety-like behavior and impaired working memory. In addition, neuroanatomical findings such as alteration in spine density and dendrite length of hippocampal CA1 neurons were not normalized after the treatment. Discussion: Although EGCG was able to normalize the levels of Bdnf in CD mice, we could not appreciate any effect on behavioral or neuroanatomical aspects. This could be due to: 1) Duration of the treatment or the behavioral tests used was not appropriate, or 2) The alterations seen in CD mice are not exclusively dependent on normalization of mRNA levels of Bdnf and other mechanisms might be involved. Therefore, further analyses are needed to determine the specific effect of EGCG on WBS.

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NEW TOOLS FOR MAPPING MOLECULAR PATHWAYS ALTERED IN KINDLER SYNDROME

ABSTRACT N° C005_2016 / PATHOPHYSIOLOGY

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Kindler Syndrome (KS) (OMIM 173650) is an autosomal recessive skin disorder caused by mutations in FERMT 1 and characterized by skin blistering, photosensitivity, premature aging and skin cancer predisposition. However, the known functions of FERMT1, involved in cell adhesion, do not suffice to fully understand the pleiotropic nature and clinical variability of this genodermatosis. Oxidative stress and mitochondrial disfunction have been recently related to this disease by our group. The complexity underlying this pathology pushes up the development of new tools in order to deeply understand Kindler Syndrome, for this reason our group has developed a skin humanized mouse model that fully recapitulates the histological phenotype of KS patients and we have also performed expression analysis arrays that allow the screening of the potential genes that are altered in KS keratinocytes and get a further understanding about the pathogenesis of the disease.

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CHALLENGES AND EXPERIENCES OF CONDUCTING A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL FOR A RARE GENETIC DISORDER: INTRANASAL INSULIN IN PHELAN-MCDERMID SYNDROME

Abstract n° D003_2016 / Bringing Treatments to the Clinic

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Phelan-McDermid syndrome (PMS) is a rare neurodevelopmental disorder caused by a 22q13.3 deletion. Patients have a moderate to severe developmental delay, often accompanied by behavioural problems. An exploratory study by Schmidt et al. in 2009, suggested a beneficial effect of intranasal insulin on development and behaviour in six children with PMS. From March 2013 to June 2015, we conducted a randomized, double-blind, placebo-controlled trial in 25 children with PMS to validate this possible positive effect. Setting up a clinical trial for this rare chromosomal disorder was challenging, but also rewarding for various reasons. First of all, the biological effects and local distribution of intranasal insulin were not yet known so we had to rely on previous studies in animal models and patients with other disorders. Secondly, at the preparations of the trial, Dutch patients with a 22q13.3 deletion were scattered across the country and only few patients had been diagnosed at our department, so a recruitment strategy had to be developed. Thirdly, we had to choose a study design that would be able to both allow all patients to benefit from the potential treatment and simultaneously detect effects in a small study group. Fortunately, our efforts and strategies have resulted in a good collaboration between Dutch departments of clinical genetics, an excellent relation with and commitment from our parents and a growing number of new referrals to our centre. Moreover, this has contributed to an increased knowledge about this rare disorder and has lead to new research projects. The results of our clinical trial show a promising and clinically relevant improvement of developmental functioning with intranasal insulin, but results did not reach statistical significance for most items in this small study group. We would like to share our experiences in setting up a clinical trial for a rare genetic disorder as PMS. We will also discuss the role of the clinical geneticist and project group in this process, and the importance of staying connected with parents.

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ORPHANDEV, A FRENCH NATIONAL PLATFORM DEDICATED TO RARE DISEASES CLINICAL TRIALS

ABSTRACT N° D004_2016 / BRINGING TREATMENTS TO THE CLINIC

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Less than 100 orphan drugs are available in Europe in 2016, for more than 7000 rare diseases. Despite the implementation of incentives and the involvement of research teams and health industries in rare diseases, the number of therapeutics available for patients remains inadequate. Furthermore, these incentives remain unfamiliar in the academic sector while it is often at the origin of the proof of concept and the creation of start-ups or SMEs. The development of orphan drugs remains a challenge, the barrier of the therapeutic evaluation being one of the main difficulties to overcome. Specific constraints of rare diseases (small number of patients, heterogeneity of patients, etiology poorly documented, lack of previous clinical trials …) are added to the usual constraints of clinical trials. OrphanDev is a unique academic structure in France and in Europe completely dedicated to rare diseases, able to support health industries, researchers and physicians in the elaboration and the conduction of clinical trials. Created in 2009, this platform is labeled by FCRIN (French Clinical Research Infrastructure Network) since 2012, the French component of ECRIN. OrphanDev offers a set of custom services, adapted to the issues of each project. • Regulatory support for orphan designation applications and protocol assistance, an important step in the development of drug candidates, bringing them to the clinic in the best conditions. • Recruitment of patients in clinical trials is a key point and represents a real challenge in rare diseases. OrphanDev, after an analysis of the constraints and objectives of the clinical trial, offers a global recruitment strategy of the patients to anticipate and overcome this difficulty (choice of inclusion criteria, constraints of study, methodological choices, early involvement of patients' organizations…). We develop communication tools and prescreening tools to decrease the screen-failure and optimize the recruitment. • OrphanDev also proposes information tools (newsletters, « OrphanDoc » educational sheet), and organizes training courses: - « Orphan Drug & Rare Disease Seminar », a European meeting destined to health professionals, - « Explain-me clinical trials », aiming to better understand the development of drugs, especially the clinical trials, destined to representatives of patients' organizations with rare and chronic diseases.

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CHRONIC NON BACTERIAL OSTEITIS: IL-ß DYSREGULATION AND EQ5D-5L VALIDATION OF HEALTH OUTCOME STATUS

ABSTRACT N° D005_2016 / BRINGING TREATMENTS TO THE CLINIC

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Introduction Chronic non bacterial Osteitis (CRMO) (OMIM-259680), a rare disease of autoinflammatory spectrum of the bone marrow of unknown etiology. The term autoinflammatory syndrome was introduced by Kastner to include disorders that did not fit into classical groups of immune diseases. The main difference with autoimmune diseases is that neither auto antigens nor autoantibodies are involved. Objective 1. Elucidation of Iyer et al criteria with radiographic and immunohematological diagnosis as for CRMO case . 2. Immunomapping status of gene loci Chromosome 18q21.3 and pstspip2 mutation in CRMO murine model . Methodology Study design: A longitudinal case study with conversion to a double blinded Randomized control trial Study setting: Multicentric trial with Trivandrum Medical College & Advanced Centre for Training education and Research on Cancer, Tata Memorial Centre . Study period: 5 year period (2011 - ongoing) Patient registry : Patient registered with EUROFEVER Project & E-RARE - Pediatric International Trial Organization (PRINTO) . Result The female child of 9 as per Iyer et al criteria for CRMO gave bone biopsy revealing chronic inflammatory infiltrate with predominant monocytes gave sterile culture and negative mycobacterial-RT-PCR . Right-shoulder PDFS & T2WI MRI shows hypointense rim was suggestive of sclerosis with contrast enhancement suggestive of subperiosteal infection. Negative HLA-B27, negative ANA-profile for screening of autoimmune disorders, negative CRP and ESR showed elevation. EQ5D-5L(European Quality of Life) index value as generic health outcome assessment is 0.722. Transgenic CRMO Murine Model The mouse Lupo (I282N) mutation in PSTPIP2 gene leads to reduced expression of PSTPIP2 associated with a macrophage-mediated disease CRMO. Data pooling allowed to map PSTPIP2 mutation & crmo mice having high levels of macrophage inflammatory protein 1-α and IL-6. In CRMO monocytes the effect of attenuated TLR4/MAPK signalling & IL-10 polymorphism with reduced Sp1 recruitment & attenuated H3S10 phosphorylation contributes to central pathophysiology. TPMT assay is withheld considering financial condition of patient. Treatment protocol with anti-TNFα inhibitors & immunomodulatory therapy is initiated for severe disease with low heath outcome. Immunomapping of Ch.18q21.3, an assessment of 1L10, TNFα, IL-1β, and, TNSALP gene mutation (metabolic defect with hypophosphatasia involving the NLRP3 inflammasome) were evidence based optional cytogentic tests Gene Marker : Next generation sequencing technique with D18S60 marker of rare alle. Conclusion Iyer et al criteria sufficiently can aid in starting Immunomodulatory therapy for CRMO, after gene sequencing and immunohematological studies with suceptability gene loci of Chromosome 18q21.3 . Murine model do suggest association of PSTPSI2 mutation but was found unrelated in human CRMO subject.

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GENERATION OF TOOLS FOR DISEASE MODELLING OF PRIMARY HYPEROXALURIA BY CELL REPROGRAMMING

ABSTRACT N° D006_2016 / BRINGING TREATMENTS TO THE CLINIC

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Disease models are essential to understand the molecular mechanisms that drive pathogenesis and enable the development of novel therapies. In particular, cell reprogramming offers a valuable tool to develop patient-specific disease models that after subsequent differentiation into the cell type of interest, allows the study of diseases that were previously inaccessible. In this work we describe two different strategies to develop in vitro disease models of type 1 primary hyperoxaluria (PH1) by cell reprogramming, one generating patientspecific induced pluripotent stem cells (iPSCs) and a second one by direct transdifferentiation. In particular we show the generation and characterization of the first iPSC lines derived from peripheral blood mononuclear cells (PBMCs) and dermal fibroblasts of a PH1 patient homozygous for the p.I244T mutation, which is highly prevalent in Canary Islands due to founder effect. On the other hand, direct reprogramming has been described as a potential source for the generation of hepatocytes from non-hepatic cell sources. We have developed a system to obtain hepatocyte-like cells from human fibroblasts using hepatocyte specific transcription factors and a hepatocyte defined culture media. We have applied this procedure to PH1 fibroblasts and we have obtained PH1 deficient cells expressing hepatocyte markers. Cells obtained from either strategy are being used to develop an E-Rare 3 funded project (ERAdicatPH) which aims the generation of disease models for PH1 that allow the development of synergistic novel therapeutic approaches.

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NEEDS AND OPPORTUNITIES FROM CONGENITAL DISORDERS OF GLYCOSYLATION (CDG): RESULTS FROM THE FIRST WORLD THINK TANKS

ABSTRACT N° D008_2016 / BRINGING TREATMENTS TO THE CLINIC

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CDG are a rapidly growing family of rare genetic life-limiting diseases with about 70 and 110 types identified since the first clinical description in 1980. Despite the rapid expansion of our understanding of the genome, regulatory incentives, and advances in the development of new therapeutic modalities for most CDG types, there are still no treatment options for the disease. Consequently, children and adults are patients for life. This unique and innovative study aims to elicit the expert views of patients, families and practitioners to explore, and gain an understanding of, the main needs of the CDG community. Solutions to overcome these needs are also discussed. The study resorts to a think tank methodology used, for the first time with the CDG community, at the Second World Conference on CDG in Lyon, France, in August 2015. This study revealed that some of the most common unmet needs faced by CDG are: (1) late or missed diagnosis; (2) limited access to reliable information; (3) limited awareness of professionals and lack of access to specialist expertise and knowledge; (3) differences in the availability to diagnostic techniques across countries; (4) differences on the care delivered within and between countries and (5) psychological distress. The study highlights the need to coordinate resources and deliver information and care in a patient-friendly manner. Online platforms were proposed as beneficial for CDG. Overall, these findings help delineate the factors impacting negatively on the development of one of the most urgent needs expressed by CDG families: a medication that could bring hope for children and adults with CDG. Our findings have important policy and practice implications. It is recommended that clinicians and policy decision-makers place greater emphasis on the wide range of needs experienced by the CDG community and the solutions proposed by this population to overcome them.

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DECIPHERING IMMUNOLOGICAL ASPECTS OF CONGENITAL DISORDERS OF GLYCOSYLATION (CDG): A MODEL FOR COMMON DISEASES

ABSTRACT N° D010_2016 / BRINGING TREATMENTS TO THE CLINIC

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Glycosylation is the creation of antennas formed by sugars (glycans) to proteins and others glycoconjugates.Congenital Disorders of Glycosylation (CDG) are a group of serious life- altering disorders caused by the incorrect or absence synthesis of sugar antennas (glycans). Glycosylation of cell surface proteins has a key role in all interactions between cells and between cells and their environment. Since the immune response lays on innumerable contacts between cells and molecules, there is a great probability that glycans or glycopeptides may have a significant role in a variety of more common diseases like cancer, inflammation, Alzheimer's disease and diabetes, and so forth. The immune deficiency aspects of CDG still remains unknown. CDG has a childhood mortality of 15-25% in the first two years of life due to severe infections or organ failure. Under the scope of the first worldwide established CDG Professionals and Patient Associations Working Group (CDG-PPAWG), our current research project aims at (1) boosting patient centered CDG research, (2) uniting expertise from and liaising different laboratories and patient advocacy groups to increase knowledge in the field of glycoimmunology for CDG and related human glycosylation diseases and (3) collecting through literature review using Pubmed as source of information the existing clinical evidence about the impairment of the immune response reported in Congenital Disorders of Glycosylation (CDG). Our results show that immunological dysfunction is a minor or a major part of the phenotype in a minority of CDG. CDG with major immunological involvement are ALG12-CDG, MAGT1-CDG, MOGS-CDG, SLC35C1-CDG, COG6-CDG and PGM3-CDG. Overall, our results about the immunological aspects of CDG, will help us to understand and treat these pathologies and other more common diseases.

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ER AND POST-ER QUALITY CONTROL OF MLC1 BY THE ADHESION MOLECULE GLIALCAM AND THE UBIQUITIN LIGASES CHIP AND UBR1

ABSTRACT N° E002_2016 / NEUROLOGICAL DISEASES

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Megalencephalic leukoencephalopathy with subcortical cysts (MLC) is a rare leukodystrophy, which is caused by mutations in the gene encoding the glia/astrocyte specific MLC1 molecule, an integral plasma membrane (PM) protein, or the adhesion molecule, GlialCAM. Although the exact function of MLC1 remains unknown, it has been postulated to be involved in cellular/endosomal ion homeostasis and cell-volume regulation. In this study we investigated membrane trafficking and ubiquitination of the wild-type MLC1 and its disease associated mutations in relation to GlialCAM at multiple cellular locations, using HeLa and U251N glial cells as heterologous expression systems. Unexpectedly, we found that GlialCAM association with both native and mutant MLC1 can enhance the forward trafficking from the endoplasmic reticulum (ER). This was attributed to the permissive role of GlialCAM in MLC1 biosynthetic maturation at the ER. Depletion of GlialCAM expression induced rapid degradation of MLC1 in the ER via the ubiquitin proteasome system, providing a plausible explanation for the MLC1 cellular phenotype in GlialCAM deficiency. At the PM, GlialCAM restricts the lateral diffusion of WT and mutant MLC1, without influencing the preferential ubiquitination and rapid ESCRT -dependent turnover of mutant MLC1s. We show that the non-native MLC1 represents a substrate for CHIP and Ubr1 dependent ubiquitination in concert with molecular chaperone recognition. Depletion of CHIP was able to partially revert the rapid lysosomal targeting of MLC mutants. The loss in Ubr1 expression was also accompanied by reduction of mutant MLC1 ubiquitination at the PM/endosomes, hence decreasing the consequential lysosomal targeting. The Ubr1 role in the peripheral quality control of MLC1 is supported by its endosomal localization, demonstrated by immunocolocalization. These observations, jointly, demonstrate novel insights into the molecular regulation of MLC1 trafficking. The adhesion molecule GlialCAM first positively regulates MLC1 biosynthetic secretion by enhancing its escape from the ER QC, followed by restricting its diffusion at the plasma membrane to subdomains, where peripheral protein quality control removed non-native MLC1 relying on CHIP and Ubr1 E3 ubiquitin ligases activity.

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MITOCHONDRIAL HAPLOGROUP ANALYSIS IN AUTISM SPECTRUM DISORDERS

ABSTRACT N° E004_2016 / NEUROLOGICAL DISEASES

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Autism spectrum disorders (ASD) is known in patients younger than 3 years. The most important signs of these diseases: impairment in social interactions and verbal and nonverbal behaviors, Failure to develop Relationships and respond to normal teaching methods, repetitive behaviors, pragmatic language impairment and severely limited activities. ASD is kind of neurodevelopmental disorders. Diseases such Asperger's syndrome, Rett syndrome, Pervasive developmental disorder not otherwise specified (PDD-NOS) or, Childhood disintegrative disorder (CDD), Tourette syndrome and Down Syndrome diagnosis by autistic behaviors. A mitochondrial haplogroup is a cluster of phylogenetically related mitochondrial genotypes (haplotypes). These haplogroups are defined by ancient mutations. These changes appeared and survived; therefore, they could not be deleterious mutations. Most of them probably did not have a phenotypic effect and were neutral. Some of them had a beneficial effect and were positively selected. However, this positive effect was related to a particular environment and nowadays, in other environmental conditions, may have different effects on the phenotype. To investigate the involvement of mitochondrial DNA (mtDNA) haplogroups in determining susceptibility to ASD, we sequenced the mtDNA HVS-I of 30 Iranian ASD patients. We examined the relationship between ASD and each of 9 major mitochondrial haplogroups in Iranian ASD patients. In this study we found a significant association of haplogroup H with ASD in Iranian patients so our finding suggests that mitochondrial genetic background plays a role in modifying an individual's risk for ASD.

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PREVALENCE OF RARE HEREDITARY NEURODEGENERATIVE AND NEUROMUSCULAR DISORDERS IN POLAND

ABSTRACT N° E005_2016 / NEUROLOGICAL DISEASES

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Hereditary neurodegenerative and neuromuscular disorders represent a large group of diseases heterogenic in terms of transmission, molecular aetiology and phenotype. Although rare, they are also characterized by diverse frequencies in different populations. The study concerns disorders caused by dynamic mutations: several types of spinocerebellar ataxias (SCAs), Huntington's disease (HD) and muscular dystrophies type 1 and type 2 (DM1 and DM2) and congenital Thomsen/Becker myotonia (CM) resulting from point mutations and microrearrangements. The aim was to assess the relative prevalence of some rare hereditary movement disorders molecularly confirmed in Poland. During 20 years of the molecular investigation 2317 mutation carriers belonging to 1452 pedigrees were identified in 4276 patients suspected of HD or at risk individuals. Testing for SCAs resulting from dynamic mutations revealed pathogenic expansions in 632 subjects amongst 3102 individuals. Identified SCA mutations carriers belong to: 200 SCA1, 38 SCA2, 1 SCA3 (of German origin), 2 SCA7, 51 SCA8, 3 SCA17 and 7 SCA36 pedigrees. The Institute of Psychiatry and Neurology is involved in cooperation with the Polish HD Association and Association of Families with Spinocerebellar Ataxia. Over 10 years of molecular analyses for myotonic dystrophies type 1 and type 2 performed in 1370 individuals resulted in identification of 278 DM1 pedigrees with 476 mutation carriers, and 203 DM2 pedigrees with 276 mutation positive subjects. The latest molecular investigation on CM - corresponding with testing for DMs - has been carried so far for 80 probands with DM1 and DM2 previously excluded. The preliminary data obtained for 8 patients revealed 5 heterozygotic and 2 homozygotic deletions (14 bp c.1437_1450) within the 13 exon of the CLCN1 gene, and in one subject the same heterozygotic deletion in the 13 exon and two point mutations in the exon 5 c.[568G>T; 569G>C] were found. The clinical diagnosis of CM has been confirmed up till now for 3 patients: two cases of recessive Becker myotonia and one patient with dominant Thomsen myotonia. Contrary to the highest worldwide SCA3 frequency, SCA1 is the commonest genetic type of SCA in Poland with relative frequency of 66% (among all genetically confirmed SCAs). The tentative data of congenital myotonia investigation revealed presence of relatively frequent (10%) recurrent deletion within the 13 exon of the CLCN1 gene.

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MONITORING NUCLEOLAR ACTIVITY AS A MARKER OF DISEASE PROGRESSION IN MODELS OF HUNTINGTON´S DISEASE

ABSTRACT N° E006_2016 / NEUROLOGICAL DISEASES

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Inhibition of rRNA synthesis and consequent disruption of nucleolar integrity - nucleolar stress - is an emerging mechanism in neurodegenerative disorders, including Huntington´s disease (HD). The expansion of CAG repeats in the mutant huntingtin protein impairs, among other fundamental cellular functions, the transcription of rRNA genes causing nucleolar stress. To dissect its contribution to the onset and progression of HD, we mimicked for the first time nucleolar stress in striatal medium spiny neurons (MSNs) in mutant mice. This was achieved by conditional ablation of the nucleolar transcription factor TIF-IA gene, crucial for the recruitment of the RNA polymerase I to the rRNA promoters. By this strategy we could specifically induce nucleolar stress-dependent responses showing that is triggers pathophysiological and molecular similarities with HD. These results suggested an important role of nucleolar stress in HD. Hence we performed a systematic analysis of nucleolar activity and integrity in cell and mouse models of HD at different stages and in different brain regions to establish whether nucleolar activity is a marker of disease progression. To this end we optimized molecular and histological methods to measure nucleolar activity in distinct cells and in tissue sections. In parallel, to dissect the function of nucleolar stress in disease progression, we induced nucleolar stress in a slowly progressive mouse model of HD and investigated its impact on neuropathology at early stages. Concomitantly, we showed that the phosphatase PTEN is upregulated upon nucleolar stress and in a cellular model of HD expressing mutant huntingtin, playing a potential neuroprotective role. The results allow to better understand mechanisms of HD and indicate a novel approach to identify disease modifiers linked to altered nucleolar activity also in other disorders.

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THERAPEUTIC POTENTIAL OF THYROID HORMONE ANALOGS TRIAC AND DITPA IN ALLAN-HERNDON-DUDLEY SYNDROME

ABSTRACT N° E009_2016 / NEUROLOGICAL DISEASES

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Allan-Herndon-Dudley syndrome (AHDS) represents a rare form of psychomotor retardation characterized by severe intellectual deficits, pronounced neuromuscular impairments and abnormal thyroid hormone (TH) concentrations in the circulation. This syndrome is caused by inactivating mutations in the X-linked SLC16A2 gene that encodes the monocarboxylate transporter 8 (MCT8), a highly specific TH transporter. Since TH is essential for proper brain development, MCT8 deficiency leads to insufficient neural TH supply and, consequently, to abnormal neural differentiation. However, up to date the exact pathogenic mechanisms underlying AHDS remain largely unknown. Worse still, there is currently no treatment for AHDS patients. We have recently established a mouse model for AHDS namely the 'Mct8/Oatp1c1 dko mice' that fully replicates both the endocrinel abnormalities and neurological phenotypes of the patients. By taking advantage of these mice, two TH analogs, Triac and Ditpa, both of which are not transported by MCT8 but are able to activate TH receptors, were tested to evaluate their therapeutic potential for treating AHDS patients. Animal were injected with these substances during the first three postnatal weeks and neurodevelopment was followed by immunohistochemistry and by performing locomotor tests. In addition, thyroidal state of peripheral tissues was analysed in order to assess any thyrotoxic side effects of this treatment. Our data provided experimental evidence that postnatal application of Triac (400 ng/g bw) was sufficient to normalize three key processes that are compromised in AHDS patients and in Mct8/Oatp1c1 dko mice: (i) cerebellar development, (ii) myelination and (iii) differentiation of GABAergic interneurons in the cerebral cortex. Moreover, only Mct8/Oatp1c1 dko mice treated with Triac displayed normal locomotor function while Ditpa treatment was less effective. Finally, Triac treatment efficiently suppressed endogenous TH production by downregulating hypothalamic TRH and pituitary TSH expression. Overall, our data suggest that Triac may represent a promising therapeutic option for patients with MCT8 mutations particularly if treatment is initiated early in life. This work was conducted as part of the E-RARE project THYRONERVE and funded by the BMBF.

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GENERATION OF IPSC MODELS TO STUDY THE NEURODEVELOPMENTAL DISORDERS CAUSED BY RECIPROCAL 7Q11.23 REARRANGEMENTS: WILLIAMS-BEUREN SYNDROME AND AUTISM SPECTRUM DISORDERS.

ABSTRACT N° E011_2016 / NEUROLOGICAL DISEASES

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The main limitation in the study of human neurodevelopmental diseases is the inability to analyze the brain in detail, the organ directly involved. Despite knowing the genetic cause of many diseases with neurological dysfunction, it is difficult to study the mechanisms whose alterations cause abnormal brain function, and therefore the pathogenesis of the disease. This lack of knowledge limits the possibilities for diagnosis, prevention and treatment for these diseases. The recent research advances in induced pluripotent stem cells (iPSC) have opened new perspectives for modeling human disease "in vivo" generating patient-specific iPSCs and differentiating them into the cell type of interest, neural progenitors in the case of neurodevelopmental disorders. Williams-Beuren Syndrome (WBS) and Autism Spectrum Disorder (ASD) are two neurodevelopmental diseases with opposite phenotypic features in the areas of communication and sociability. WBS is caused by a hemizygous deletion of 26-28 contiguous genes in the region 7q11.23 while the reciprocal duplication of the same locus causes a syndrome commonly associated with ASD. Initially, we generated iPSC cells from those reciprocal genetic models from skin fibroblast of 2 patients with 7q11.23 deletion and 2 patients with 7q11.23 duplication. Next, we derived these iPSCs to neural progenitor cells (NPC) and differentiated them to dopaminergic neurons, using a serum-free neuronal induction medium. We evaluated the efficiency of the neuronal differentiation process by quantitative RT-PCR analyses (panel including Nurr1, TH and FOXA2 expression) and qualitative immunocytochemistry studies using neuronal markers (TH, TUJ1 y FOXA2). Phenotypic evaluation of dopaminergic differentiation process followed by time-lapse microscopy pointed up some divergences between models, including the number and the morphology of neuron-interactions. Transcriptional analyses (GeneChip® Human Gene 2.0 ST Array) of the entire differentiation process were carried out in order to understand the pathophysiology of such genetic diseases, and also to determine appropriate therapeutic targets and biomarkers. Currently, we are generating iPSCs from 4 additional patients to replicate the initial results, and to determine the model specificity of the alterations observed. As a final point, all these generated models will be used as an "in vivo" cellular model to test new therapeutic strategies.

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DRUG RESISTANT EPILEPSY IN A YOUNG MALE WITH CAT EYE SYNDROME

ABSTRACT N° E012_2016 / NEUROLOGICAL DISEASES

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The 22q11 region is susceptible to chromosomal rearrangements, leading to various types of congenital malformation and intellectual disability. Several genomic disorders have been described, including Cat Eye syndrome (CES) caused by extra copies of the most proximal region, DiGeorge/Velocardiofacial Syndrome due to deletion of 22q11.21, 22q11.2 duplication syndrome and distal 22q11.2 microdeletion/microduplication syndrome. We present a clinical observation of a 28 yrs old male with a tetrasomy of the region q11.1q11.21 of the chromosome 22, corresponding to the CES region. Methods The patient was evaluated with clinical,neurophysiological and neuroradiological instruments Laboratory studies included array-CGH, conventional cytogenetic and FISH analysis. Results M, 29 years old, born from non consanguineous parents after a normal pregnancy. Weight at birth: 3350g. At birth a cardiac total anomalous pulmonary venous connection was diagnosed and a surgical correction has been applied. Developmental milestones severe delayed: first steps without help after 3 years, no development of language . A nasal fistula was corrected surgically during infancy. Since two years the patients developed daily atypical seizures, characterized by loss of contact and motor stereotypies, which are refractory to treatment. Seizures become more and more frequent with ageing (up to one/two episodes a day). Clinical examination: turricephaly, spastic tetraparesis more marked on the right side. MRI brain: thinning of the corpus callosum, hypomielination of the oval centers. 24 hours EEG: spikes and polispikes and wave more marked on the left side during sleep. Cognitive phenotype: severe learning disabilities and specific language impairment. IQ at WAIS was undetectable for severity. Behavioural phenotype: presence of ritualistic and stereotyped behaviours, letargy and lack of ocular contact. Array-CGH detected the tetrasomy of about 1,55 Mb on chromosome 22q11.1q11.21, due to the presence of a bisatellited small dicentric supernumerary chromosome, as demonstrated by kariotype and FISH analysis. Concliusion Although seizure characterization is lacking in CES, in the present case, epilepsy emerged as a main disturbance in the clinical picture of CES.

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A NEW GENERATION OF POTENT TRANSTHYRETIN AMYLOID INHIBITORS

ABSTRACT N° E013_2016 / NEUROLOGICAL DISEASES

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The aggregation of proteins into insoluble amyloid fibrils is the hallmark of many, highly debilitating, human pathologies such as Alzheimer's and Parkinson's diseases, or rare neurodegenerative diseases like Familial Amyloid Polyneuropathy (FAP). FAP is an amyloid disease caused by mutations in the protein transthyretin (TTR) and characterized by progressive peripheral and autonomic polyneuropathy, starting with loss of temperature and pain sensation on the lower limbs and evolving to severe autonomic dysfunction, usually resulting, if untreated, in the death of patients 10 to 15 years after the onset of the first symptoms. TTR is a homotetrameric protein found in the plasma, cerebral-spinal fluid and the eye and synthesiszed in the liver, choroid plexus and retina, respectively. Liver transplantation (LT) was the standard treatment option for FAP for nearly two decades. In recent years, tafamidis meglumine was introduced in the European and Japanese markets, demonstrating improvement of symptoms in approximately 60% of FAP patients enrolled in an 18-month phase-III clinical trial. The need for more efficacious solutions to the treatment of FAP, and principally of non-responsive FAP patients, as well as, the need to provide therapeutic solutions for FAP associated co-morbidities of the central nervous system (CNS) and the eye, and other TTR-associated amyloidoses, is of the utmost importance. Here, we report on successful efforts to discover new chemical entities (NCEs) with high amyloid inhibitor profiles in vitro and high TTR stabilization activity ex vivo, in particular, in plasma of carriers of the most common amyloidogenic TTR mutation.

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THE POWER OF SOCIAL MEDIA FOR KARYOTYPE-PHENOTYPE ANALYSIS OF RARE CHROMOSOME DISORDERS

ABSTRACT N° F003_2016 / PATIENTS AND RESEARCH

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This presentation is the direct result of a study that was performed on request of a Facebook Group of parents of children with a chromosome 6 disorder. The successful use of social media in this study demonstrates how eager parents are to give and receive information about the condition of their child. In our study we initially focused on isolated 6q deletions. Through social media including Facebook and Twitter, we were able to collect within a short period of time more and more detailed information then available in literature. This allowed for a better description of the three main groups of 6q deletions: proximal (6q11-q16), intermediate (6q15-q25), and distal (6q25-qter). Moreover, smaller deletions could be further characterised and smallest regions of interest defined. For example a Noonan-like phenotype could be assigned to deletions 6q25.1. All patients with deletions of this region had a highly resembling appearance and shared many clinical features, including short stature and heart defects, predominantly involving the cardiac valves. A detailed analysis of all 6q data allowed the confirmation or identification of candidate genes for specific features, e.g. congenital heart defects. The results of our social media pilot, prompted us to initiate the development of an interactive online database system based on the intelligent collection, combining and presentation of information for chromosome 6, in collaboration with the Chromosome 6 Facebook Group, Unique, ECARUCA and Cartagenia. The online database system will consist of a multilingual patient questionnaire that is currently being validated, an automated data interpretation program, for which the prototype is ready, a program that allows to combine the database information with data available form other sources, and an interactive query and information program suitable for families, primary care-takers and professionals. Eventually, the system can be applied to all chromosome disorders.

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TELETHON FOUNDATION FIGHTING RARE DISEASES ALONGSIDE PATIENTS

ABSTRACT N° F004_2016 / PATIENTS AND RESEARCH

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The Telethon foundation is an Italian charity funding biomedical research towards the cure of rare genetic diseases (www.telethon.it). All its funding decisions are made by an international scientific committee through a peer review-based selection system. After 25 years of activity, the results achieved by Telethon-funded research are globally acknowledged; the Foundation has placed itself among the main players in the world in the field of biomedical research for rare genetic diseases (Hum Gene Ther. 2015 Apr;26(4):183-5). Telethon-funded research, tackling the challenge of genetic diseases from diagnosis to basic and clinical science, is constantly moving forward toward the development of therapies for an increasing number of pathologies including metabolic, hematological and neuromuscular disorders. The Telethon research portfolio includes intramural research led by the three Telethon Institutes TIGET (San Raffaele Telethon Institute for Gene Therapy, in Milan), TIGEM (Telethon Institute of Genetics and Medicine, in Pozzuoli, Naples) and DTI (Dulbecco Telethon Institute, a career program) and extramural research, funded through several funding programs. Telethon participates in several national and international collaborations and alliances, such as the european RD-connect project, the International Rare Diseases Research Consortium (IRDiRC), the European NeuroMuscular Centre (ENMC), and coordinates the EuroBioBank Network. The close relationship with many Patient organizations is at the basis of the Telethon strategic plan and has led, over the course of years, to the implementation of several initiatives: the Telethon-Uildm Call for clinical neuromuscular research; the Telethon Network of Genetic Biobanks (TNGB, http://biobanknetwork.telethon.it/); the Call for Exploratory Projects and the fledgling Undiagnosed Diseased Program. Moreover, to provide patients with information on research on their genetic diseases, Telethon joined Europe PubMed Central as a funder to offer open access to the results of the Telethon-funded research, and has set up activities such as the "Filo diretto" and the network of the "Italian Patients Associations Friends of Telethon" and has promoted patient empowerment on research topics through the organization of several meetings.

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DETECTABLE CLONAL MOSAICISM IN BLOOD DNA AS EARLY MARKER OF CANCER IN FANCONI ANEMIA PATIENTS

ABSTRACT N° F005_2016 / PATIENTS AND RESEARCH

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Introduction. Mosaicism, the coexistence of cells with different genetic composition within an individual, has been associated with aging and cancer. Mosaicism for chromosomal events >500kb affecting ≥10% of cells can be detected using SNP array of DNA from whatever tissue. Fanconi anemia (FA) is a genetic disorder characterized by congenital defects, bone marrow (BM) failure and cancer susceptibility, caused by poor repairing of inter-strand DNA crosslinking (ICL). Due to the high risk for hematological and mucosal cancers, a strict follow-up protocol is recommended including, among other exams, periodic BM testing. We have studied the prevalence of clonal mosaicism in young FA patients blood DNA and whether mosaicism could be used as an early marker for cancer. Methods. Blood DNA samples of 129 FA patients (0-50yo), obtained for diagnostic purposes, were analyzed by SNP array (Illumina 1M or Infinium HumanCore). Copy number and copy neutral chromosomal mosaic events were detected with the MAD software and experimentally validated by microsatellite and MLPA analyses. DNA from an anal squamous cell carcinoma (SCC) sample from one FA patient was also studied. Results. We detected 45 mosaic events in blood of 14/129 FA patients (10.8%), and validated 94.7% of them by microsatellite and/or MLPA analysis. Compared to 11944 age-matched controls, FA subjects under 18yo had a 220X rate while young adults (18-50yo) had a 109X rate of detectable mosaicism (4.39%/0.02% p=2,2x10-7 and 29.4%/0.27%, p=4.1x10-17). Considering events, there was a 243X increase in FA patients, with an average of 0.34 mosaic events/patient and 0.0014 events/control. The risk of developing cancer 0-10 years after DNA extraction was 5.2X increased in FA patients with mosaicism with respect to FA patients without mosaicism (85.7%/16.5%, p=5,7x10-7). An uniparental disomy of 6p was detected both in blood and the SCC of FA013 diagnosed 10y after, suggesting an early embryonic origin of the mosaicism. Conclusions. We have shown that SNP arrays can detect mosaicism for chromosomal rearrangements in an important proportion of FA patients, and that mosaicism detection is associated with higher risk of hematological and solid cancer. Although further studies are required to establish the sensitivity and specificity of the method, detection of clonal mosaicism in SNP arrays from blood (and/or buccal) DNA could be used as early markers for cancer risk in these chromosomal instability disorders.

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NEW PROJECT FOR A CURE: A DUCHENNE PARENT STRATEGY

ABSTRACT N° F008_2016 / PATIENTS AND RESEARCH

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Rare diseases have a limited access to research and drug discovery. Moreover, these type of diseases have a limited number of patients for companies to invest in developing treatments. Duchenne Muscular Dystrophy (DMD) is the best-known muscular dystrophy caused by a mutation in a gene on the X chromosome that prevents the production of dystrophin, a normal protein in muscle. Duchenne Parent Project Spain was created in 2008 by an active group of parents for identifying a cure for DMD. The main objective has three points: 1. To promote investigation to ameliorate disease symptoms, 2. To reach a big, international patient registry, and 3. To identify a cure. Here, we show the key areas and our mission of removing barriers to get an important role in research by patients' organization in order to accelerate the development of effective treatments

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DEVELOPMENT OF REMOTE DATA ENTRY SYSTEM FOR NATIONAL NAMBYO (INTRACTABLE RARE DISEASE) REGISTRY IN JAPAN

ABSTRACT N° F009_2016 / PATIENTS AND RESEARCH

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Purpose: National registry of Nambyo is based on reimbursement of medical expense by the patient by application. Number of application is about 1 million per year. Current paper based registration system results in errors, hard to perform data entry at local government, and so much effort required for data cleanup. To have accurate registration to the rare disease registry for the welfare and research purpose, confident data entry system is important. Method: We have created an application on PC so that physician can put in data easily with initial filter for each element. Data will be uploaded to the server after encryption in the application software. Data elements can be edited for each disease easily by the standardized data element management system. Results: First version was planned using web based data entry with intranet between nationwide hospitals. Our application enables data entry of Japanese Nambyo registry easily directly from the physician. This way, data will be curated automatically initially so that doctor can put in accurate information. Data will be uploaded to the server after automatic encryption, so patient information is secured. After moving to the local system, data will be de-encrypted and stored for analysis. Conclusion: Data entry should be done directly by the physician, and secure uploading system is the key for data transfer.

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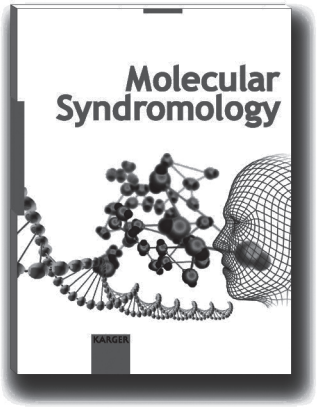

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Selected contributions

- Connecting the *CNTNAP2* Networks with Neurodevelopmental Disorders: **Poot, M.** (Utrecht)
- Clinical and Molecular Heterogeneity in Brazilian Patients with Sotos Syndrome: **Vieira, G.H.** (Greenwood, S.C./Botucatu); **Cook, M.M.** (Greenwood, S.C.); **Ferreira De Lima, R.L.** (Salvador); **Frigério Domingues, C.E.; de Carvalho, D.R.** (Botucatu); **Soares de Paiva, I.** (Rio de Janeiro); **Moretti-Ferreira, D.** (Botucatu); **Srivastava, A.K.** (Greenwood, S.C./Clemson, S.C.)
- Common Somatic Alterations Identified in Maffucci Syndrome by Molecular Karyotyping: **Amyere, M.** (Brussels); **Dompmartin, A.** (Caen); **Wouters, V.** (Brussels); **Enjolras, O.** (Paris); **Kaitila, I.** (Helsinki); **Docquier, P.-L.; Godfraind, C.** (Brussels); **Mulliken, J.B.** (Boston, Mass.); **Boon, L.M.; Vikkula, M.** (Brussels)
- Novel Deletion of *SERPINF1* Causes Autosomal Recessive Osteogenesis Imperfecta Type VI in Two Brazilian Families: **Moldenhauer Minillo, R.** (São Paulo); **Sobreira, N.** (Baltimore, Md.); **de Fatima de Faria Soares, M.** (São Paulo); **Jurgens, J.; Ling, H.; Hetrick, K.N.; Doheny, K.F.; Valle, D.** (Baltimore, Md.); **Brunoni, D.; Alvarez Perez, A.B.** (São Paulo)
- A Mouse Splice-Site Mutant and Individuals with Atypical Chromosome 22q11.2 Deletions Demonstrate the Crucial Role for *Crkl* in Craniofacial and Pharyngeal Development: **Miller, K.A.; Tan, T.Y.; Welfare, M.F.; White, S.M.; Stark, Z.; Savarirayan, R.; Burgess, T.; Heggie, A.A.** (Parkville, Vic.); **Caruana, G.; Bertram, J.F.** (Clayton, Vic.); **Bateman, J.F.; Farlie, P.G.** (Parkville, Vic.)

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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.

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E-RARE ERA-NET FOR RESEARCH PROGRAMMES ON RARE DISEASES

The E-Rare consortium was built to link responsible funding organizations and ministries that combine the scarce resources for rare disease research and thus enable the participation of many researchers to transnational projects via Joint Transnational Calls (JTCs). The E-Rare Consortium gathers twenty-five funding organizations from 17 European, Associated and non-European countries (Canada).

Since 2007 E-Rare has become one of the major contributors to transnational rare diseases research funding. The EC supports the coordination costs among the funding agencies. However, each national funding agency participating in the call funds the research carried out in their own countries once the projects have been selected. The E-Rare Consortium has launched 7 joint transnational calls for collaborative multidisciplinary research projects open for any rare disease (except rare cancers and rare infectious diseases), with a wide range of possible topics and approaches. A total of 1013 multinational applications involving more than 4200 research groups from European and associated countries were submitted to the 7 calls. Two focused calls were dedicated to young, independent investigators (JTC 2012) and development of innovative therapeutic approaches for rare diseases (JTC 2014), respectively. Importantly, the 7th Joint Transnational Call, opened in December 2014, was launched jointly with the European Commission under the ERA-Net Co-fund mechanism. Within this call 19 research projects were recommended for funding for a total of 19.35 M€.

The highly competitive nature of the Joint Transnational Calls resulted in funding of very high quality projects. A large proportion of submitting researchers have outstanding track records with publications in the best-ranking journals. The assessment of the E-Rare funding programme achievements based on the analysis of the final project reports confirmed also that E-Rare funded projects largely contribute to reducing fragmentation of resources and achieving critical mass of data and samples for research projects. All funded consortia initiated new infrastructures (databases, registries and biobanks) with which they achieved the critical mass of samples/data necessary for the development of the project. ERare funding facilitated the academic training of a substantial number of young researchers (MSc and PhD students). Finally, ERare was recognized as a catalyst for new collaborations but also for cooperation sustainability. 77 % of consortia established new collaborations thanks to the E-Rare funding and more than half of them succeeded in obtaining subsequent funding for their project. The importance of E-Rare as a collaboration "stimulator" was also confirmed by an inquiry in Spring 2013 among researchers that applied to E-Rare calls JTC2007 up to JTC2012 but did not succeed to obtain funds. The response rate to this survey was more than 20%. Despite the fact that these applicants were not funded by E-Rare, 50% of the responders confirmed that applying to the E-Rare calls triggered the establishment of new collaborations and most of them pursued this collaboration even without E-Rare funding.

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