



IRDIRC

INTERNATIONAL
RARE DISEASES RESEARCH
CONSORTIUM

3rd International Rare Diseases Research Consortium Conference

Conference Center University Pierre et Marie Curie
Paris, France
February 8-9, 2017

CONFERENCE BOOK

IRDIRC

www.irdirc.org



International Rare Diseases Research Consortium

The International Rare Diseases Research Consortium (IRDiRC) brings together members that share common goals and principles and have agreed to work in a collaborative manner within a multinational consortium. IRDiRC teams up researchers and organizations investing in rare diseases research to achieve two main objectives by the year 2020, namely to deliver 200 new therapies for rare diseases and the means to diagnose most rare diseases.

3rd International Rare Diseases Research Consortium Conference

Paris, France - February 8-9, 2017

Conference Partners	Page 2
Message from the Chair	Page 3
Conference Planning Committee	Page 4
Program-at-a-Glance	Page 5
Detailed Program and Speakers	Page 6-11
Invited Speakers	Page 12-24
Selected Abstracts	Page 25-28
Poster Abstracts	Page 29-50
Practical Information	Page 51
Conference Venue and Floor Plan	Page 52
General Information	Page 53
Notes	Page 54

3rd International Rare Diseases Research Consortium Conference

Paris, France - February 8-9, 2017

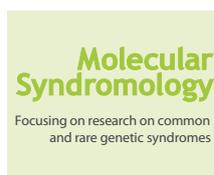
This meeting would not be possible without the support of:



Co-Funded by the
European Union



Media Partners:



3rd International Rare Diseases Research Consortium Conference

Paris, France - February 8-9, 2017

Message from the Chair

It is with great pleasure that I welcome you all to the 3rd International Rare Diseases Research Consortium Conference. This meeting provides the unique opportunity for all stakeholders – including funding agencies, academic researchers, industry members, regulatory agencies, patient advocacy groups, policy makers, opinion leaders, and researchers early in their careers – active in rare diseases from across the globe to reflect on amazing progress made, and chart a bold and ambitious course to build on these successes, to dramatically increase the pace of progress in the understanding, diagnosis, and treatment of rare diseases.

At this Conference, we will hear from world leaders in rare disease research policy and funding, esteemed scientists who have been led the breakthrough discoveries of the last decade, emerging investigators and companies who are leading the way to the future, and thought leaders who will help us understand where the rare disease world will be five years from now.

Five years have passed since the launch of IRDiRC in 2011, and the initial goals enunciated by the Consortium have already been realized. Thus throughout this Conference, new IRDiRC goals for the next decade will be debated, with contributions from all of you. Thank you for taking part in this important visioning process. We aim to leave Paris two days from now informed, invigorated, and empowered to work together to bring prompt diagnosis, effective treatment, and, I hope we can begin to say – cure – to all patients living with rare diseases.

Lastly, I would like to express my deepest gratitude to Support-IRDiRC and the Conference Planning Committee for all their hard work and dedication that made this conference a reality.



Christopher P. Austin, M.D.

Chair, IRDiRC Consortium Assembly

Conference Planning Committee

▶ **Dr Christopher Austin (Chair)**

NIH / National Center for Advancing Translational Sciences (NCATS), USA

▶ **Prof Kym Boycott**

Children's Hospital of Eastern Ontario (CHEO), Canada

▶ **Prof Hugh Dawkins**

Western Australia Department of Health, Australia

▶ **Dr Ruxandra Draghia-Akli**

European Commission / DG Research, Belgium

▶ **Dr Carlo Incerti**

Sanofi-Genzyme, USA

▶ **Dr Daria Julkowska**

E-Rare, France

▶ **Mr Yann Le Cam**

Rare Diseases Europe - EURORDIS, France/ Belgium

▶ **Prof Hanns Lochmüller**

University of Newcastle, UK

▶ **Dr Makoto Suematsu**

Japan Agency for Medical Research and Development (AMED), Japan

▶ **Dr Ana Rath**

Orphanet, France

▶ **Dr Jeffery Schloss**

NIH / National Human Genome Research Institute (NHGRI), USA

▶ **Ms Sharon Terry**

Genetic Alliance, USA

▶ **Dr Lu Wang**

NIH / National Human Genome Research Institute (NHGRI), USA

This Committee is supported by:

▶ **Dr Takeya Adachi**

Japan Agency for Medical Research and Development (AMED), Japan

▶ **Ms Christine Cutillo**

NIH / National Center for Advancing Translational Sciences (NCATS), USA

▶ **Dr Iiro Eerola**

DG Research and Innovation (DG RTD), Belgium

▶ **Dr Anneliene Jonker**

IRDiRC Scientific Secretariat, France

▶ **Dr Lilian Lau**

IRDiRC Scientific Secretariat, France

▶ **Dr Irene Norstedt**

DG Research and Innovation (DG RTD), Belgium

Program-at-a-Glance

February 8, 2017

09:00 – 10:30	Plenary Session 1: Opening Session – IRDiRC History and Achievements		
	Auditorium		
10:30 – 11:00	Coffee break		
	Reception Hall		
11:00 – 12:40	Plenary Session 2: Rare Diseases Research in 2017 – A Global View		
	Auditorium		
12:40 – 14:00	Lunch break		
	Reception Hall		
14:00 – 15:30	Plenary Session 3: State of Foundational, Diagnostics and Therapeutics Research		
	Auditorium		
15:30 – 16:00	Coffee break		
	Reception Hall		
16:00 – 18:00	Parallel Session 1: Diagnostics, Foundational and Therapeutics Research in 2017		
	<i>Diagnostics Track</i>	<i>Foundational Track</i>	<i>Therapeutics Track</i>
	Auditorium	Room 106	Room 108
18:00 – 20:00	Poster session, cocktail reception		
	Reception Hall		

February 9, 2017

09:00 – 10:40	Parallel Session 2: New Approaches to Rare Diseases		
	<i>Diagnostics Track</i>	<i>Foundational Track</i>	<i>Therapeutics Track</i>
	Auditorium	Room 106	Room 108
10:40 – 11:10	Coffee break		
	Reception Hall		
11:10 – 12:40	Parallel Session 3: Trends in the Field		
	<i>Trends in Regulatory & Access</i>	<i>Trends in Patient Advocacy</i>	<i>Trends in Companies</i>
	Auditorium	Room 106	Room 108
12:40 – 14:00	Lunch break		
	Reception Hall		
14:00 – 16:30	Plenary Session 4: Transforming Rare Diseases Research – IRDiRC Goals 2017-2027		
	Auditorium		
16:30 – 17:00	Continued discussion over coffee and refreshments		
17:00	End of conference		

Detailed Program and Speakers

February 8, 2017

09:00 – 10:30 <i>Auditorium</i>	Plenary Session 1: Opening Session – IRDiRC History and Achievements <i>Chair: Lucia Monaco</i>
	IRDiRC: Stepping Stones towards Success Ruxandra Draghia-Akli, DG Research and Innovation, European Commission, Belgium Francis Collins, National Institutes of Health (NIH), USA
	IRDiRC: A Review of its Achievements in its First Six Years Paul Lasko, McGill University, Canada
	IRDiRC: Current State and Future Prospects Christopher Austin, National Center for Advancing Translational Sciences (NCATS), USA
	Panel Q&A Ruxandra Draghia-Akli, Paul Lasko, Christopher Austin
10:30 – 11:00 <i>Reception Hall</i>	Coffee break
11:00 – 12:40 <i>Auditorium</i>	Plenary Session 2: Rare Diseases Research in 2017 – A Global View <i>Chair: Stephen Graft</i>
	AMED Challenges Data Sharing for Undiagnosed Patients Makoto Suematsu, Japan Agency for Medical Research and Development (AMED), Japan
	A European Rare Disease Overview Irene Norstedt, DG Research and Innovation, European Commission, Belgium Caroline Hager, DG Health and Food Safety, European Commission, Belgium
	Office of Rare Diseases Research: Perspective on North American Rare Diseases Research Petra Kaufmann, National Center for Advancing Translational Sciences (NCATS), USA
	From Research Translation to Transformation in a Public Health System Hugh Dawkins, Western Australia Department of Health, Australia
	UN NGO Committee for Rare Diseases (CfRD) Anders Olauson, Ågrenska Foundation, Sweden
12:40 – 14:00 <i>Reception Hall</i>	Lunch break
14:00 – 15:30 <i>Auditorium</i>	Plenary Session 3: State of Foundational, Diagnostics, Therapeutics Research <i>Chair: Makoto Suematsu</i>
	Cross-Cutting Bottlenecks and Solutions in Rare Diseases Research Hanns Lochmüller, Newcastle University, UK
	International Cooperation to Enable the Diagnosis of Most Rare Genetic Diseases by 2020 Kym Boycott, Children's Hospital Eastern Ontario, Canada
	200 Rare Disease Therapies Scored in 2017 – New Objective: 500 in 2027 Diego Ardigò, Chiesi Farmaceutici S.p.A., Italy Yann Le Cam, Rare Diseases Europe-EURORDIS, France/Belgium
15:30 – 16:00 <i>Reception Hall</i>	Coffee break

16:00 – 18:00

Parallel Session 1: Diagnostics, Foundational and Therapeutics Research in 2017

Auditorium

Track 1: Diagnostics Research in 2017

Chair: Kym Boycott

Mendelian Disease and the Centers for Mendelian Genomics: Progress, Challenges and Opportunities

David Valle, Johns Hopkins University School of Medicine, USA

The Matchmaker Exchange, a Global Effort to Identify Novel Disease Genes

Ada Hamosh, Johns Hopkins University School of Medicine, USA

Interpretation of the Disease Liability of Genomic Variants in Rare Diseases: Multi-Disciplinary and International Locus Specific Collaborative Initiatives (CFTR2.org)

Milan Macek, Charles University, Czech Republic

Undiagnosed Disease Programs and Networks

Gareth Baynam, University of Western Australia, Australia

Enabling Neonatal Precision Medicine by Rapid Genome Sequencing

Stephen Kingsmore, Rady Children's San Diego, USA

Panel Q&A

With all speakers of the session

Room 106

Track 2: Foundational Research in 2017

Chair: Hanns Lochmüller

How to Promote Data Sharing in Rare Disease while Protecting Privacy

Mats Hansson, Uppsala University, Sweden

The Impactt Study: Experiences from Performing a Clinical Multicenter Study in Collaboration with CF Patient Organizations

Anders Larsson, Uppsala University, Sweden

Global Phenotypic Data Sharing Standards to Maximize Diagnostics and Mechanism Discovery

Melissa Haendel, Monarch Initiative and Oregon Health & Science University, USA

Precision Medicine in Rare Diseases Across Continents and Disciplines

Matthias Kretzler, NEPTUNE, EuRenOmics and University of Michigan, USA

European Perspective on Sharing –Omics Data for Personalized Medicine in Rare Diseases

Ivo Gut, Centro Nacional de Análisis Genómico (CNAG), Spain

Panel Q&A

With all speakers of the session

Track 3: Therapeutics Research in 2017
<i>Room 108</i> <i>Chair: Diego Ardigo</i>
<p>Ex-Vivo Stem Cell Gene Therapy: Approved Treatment for ADA-SCID Claudio Bordignon, MolMed S.p.A., Italy</p> <p>Approval of a Stem Cell Therapy for Corneal Disease, Holoclar® Graziella Pellegrini, University of Modena and Reggio Emilia, Italy</p> <p>Gene Therapy for Neurological Disorders: A Promising Novel Treatment for AADC Deficiency Jodi Cook, Agilis Biotherapeutics LLC, USA</p> <p>Development of Therapy for GNE Myopathy Ichizo Nishino, National Center of Neurology and Psychiatry, Japan</p> <p>Patient Engagement in Therapeutics Development Sangeeta Jethwa, Roche Innovation Centre, Switzerland</p> <p>Panel Q&A With all speakers of the session</p>
18:00 – 20:00 Poster session, cocktail reception <i>Reception Hall</i>

February 9, 2017

09:00 – 10:40	Parallel Session 2: New Approaches to Rare Diseases
<i>Auditorium</i>	Track 1: New Approaches to Rare Diseases – Diagnostics <i>Chair: Gareth Baynam</i>
<p>Identification of Two New Disease Entities Through the Undiagnosed Disease Program at our Institution Toshiki Takenouchi, Keio University, Japan</p> <p>High Throughput Screening Toward Precision Medicine in Congenital Myasthenic Syndromes Sophie Nicole, Université Pierre et Marie Curie, France</p> <p>More than Meets the Eye: Solving an Evolutionary Riddle Using Rare Disease Robert Hufnagel, National Eye Institute (NEI), USA</p> <p>Development of Therapeutic Strategies for Patients with Allan-Herndon-Dudley Syndrome Edward Visser, Erasmus Medical Center, The Netherlands</p> <p><i>Selected abstract</i> Solving the Lonely Exome: International Connectivity to Enable Discovery Taila Hartley, CHEO, University of Ottawa, Canada</p> <p><i>Selected abstract</i> Variant Data from Patients with Rare Diseases Semantically Linked and Enriched with Gene and Variant Data from Public Data Sources Filip Pattyn, ONTOFORCE, Belgium</p>	

Track 2: New Approaches to Rare Diseases – Foundational <i>Chair: Daria Julkowska</i>	
Room 106	<p>Leveraging Standing Human Variation to Improve Missense Variant Interpretation Slavé Petrovski, University of Melbourne, Australia</p> <p>Eugene Devic European Network (EDEN): Establishment and Use of an European Database and Biobanks for Research and Treatment in Neuromyelitis Optica Romain Marignier, CHU de Lyon, France</p> <p>From Genetics to Therapeutics in Prion Disease Sonia Vallabh & Eric Minikel, Broad Institute, USA</p> <p>A Novel Subtype of Congenital Scoliosis: TBX6-Associated Congenital Scoliosis Nan Wu, Peking Union Medical College Hospital, China</p> <p><i>Selected abstract</i> Status of Rare Diseases Ecosystem in India – Progress and Lessons for Rest of the World Harsha Rajasimha, Organization for Rare Diseases India and George Mason University, USA</p> <p><i>Selected abstract</i> Boosting Health Care and Life Science Research on Rare Diseases by Creating a Robust Infrastructure of Independently FAIR Biobanks, Registries, and Molecular Data Resources Marco Roos, Leiden University Medical Centre, The Netherlands</p>
Track 3: New Approaches to Rare Diseases - Therapeutics <i>Chair: Michela Gabaldo</i>	
Room 108	<p>Translating AAV-Based in vivo Gene Therapies to the Clinic Federico Mingozi, Genethon, France</p> <p>Developing New Therapies for Rare Diseases: Beyond Cystic Fibrosis Stuart Hughes, Vertex Pharmaceuticals Inc., UK</p> <p>Developing Therapies for Inborn Errors of Metabolism Marc Martinell, Minoryx Therapeutics, Spain</p> <p>Disrupting Discovery Efficiency: Combining the Best of Biology, Automation and Artificial Intelligence to Identify 100 Rare Disease Treatments in 10 years Christopher Gibson, Recursion Pharmaceuticals Inc., USA</p> <p><i>Selected abstract</i> IDeAI Designing a Clinical Trial – a Case Study Ralf-Dieter Hilgers, Department of Medical Statistics, RWTH University Aachen, Germany</p> <p><i>Selected abstract</i> Translating Natural History into Clinical Trial Design – Lessons from Duchenne Muscular Dystrophy Susan Ward, collaborative Trajectory Analysis Group (cTAP), Cambridge, USA</p>
10:40 – 11:10 <i>Reception Hall</i>	Coffee break

11:10 – 12:40

Parallel Session 3: Trends in the Field

Auditorium

Track 1: Trends in Regulatory and Access

Chair: Irene Norstedt

Regulatory Trends Including Expanded Access

Jonathan Goldsmith, US Food and Drug Administration (FDA), USA

Regulatory/Scientific Support for Rare Disease Product Development in Japan – Orphan Product Designation System

Hideyuki Kondo, Pharmaceuticals and Medical Devices Agency (PMDA), Japan

Challenges in Reimbursing Orphan Medicinal Products: Evaluating Benefit, Determining a Fair Price and Optimizing Access

Anna Bucsecs, University of Vienna and MoCA, Austria

Managed Access for Ultra Orphan Drugs in England

Edmund Jessop, National Health Service (NHS) England, UK

Panel Q&A

With all speakers of the session

Room 106

Track 2: Trends in Patient Advocacy

Chair: Katherine Beaverson

Perspective on Patient Engagement in Research, Product Life Cycle and Healthcare in Europe

Yann Le Cam, Rare Diseases Europe-EURORDIS, France/Belgium

The Algorithm for Precision Medicine

Matt Might, University of Utah, USA

Recent Japanese NANBYO Situation – How Japanese Patient Groups Contribute to Further the Research Field

Yukiko Nishimura, ASrid, Japan

Management of Patients with Rare Diseases in African Context: The Contribution of Fitima

Hawa Dramé, Fitima Foundation, Burkina Faso

Panel Q&A

With all speakers of the session

Room 108

Track 3: Trends in Companies

Chair: Sangeeta Jethwa

Current Status and Future Trends in Orphan Diseases: A Company Perspective

Carlo Incerti, Sanofi Genzyme, USA

The DNA of Successful Rare Disease Biotechs

Kiran Reddy, Clarus Ventures, USA

The Economics of Rare Diseases from the Venture Capital Perspective

Alain Huriez, Advent Life Sciences, France

Trends in Orphan Development: What can be Extracted from a Regulator's Database

Kristina Larsson, European Medicines Agency (EMA), UK

Panel Q&A

With all speakers of the session

12:40 – 14:00

Lunch break

Reception Hall

14:00 – 17:00 <i>Auditorium</i>	Plenary Session 4: Transforming Rare Diseases Research – IRDiRC Goals 2017-2027 <i>Co-Chairs: Christopher Austin and Hugh Dawkins</i>
14:00 – 14:30	IRDiRC Goal-Setting Process, to Date Christopher Austin, Chair of IRDiRC Consortium Assembly
14:30 – 16:30	Panel Discussion and Selection of IRDiRC Goals for 2017-2027 Moderator: Hugh Dawkins Panellists: Representatives of IRDiRC Consortium Assembly, Constituent Committees and Scientific Committees
16:30 – 17:00 <i>Reception Hall</i>	Continued discussion over coffee and refreshments
17:00	End of conference

Invited Speakers

Diego Ardigo

Diego Ardigo is currently R&D Project Leader for Advanced Therapies at Chiesi Farmaceutici S.p.A. He received his degree in Medicine and the specialization in Internal Medicine at the University of Parma (Italy). After a post-doctoral fellowship at Stanford University (California, US) he obtained a PhD degree in Cardiovascular Pathophysiology at the University of Parma. He is author of more than 40 indexed papers. He joined Chiesi in 2010 where he acted as Clinical Lead in the development and registration of the first stem cell therapy in the EU and led a cross-company team achieving the treatment of the first patient with a commercial gene therapy in EU (in alliance with uniQure BV). He is Chair of the Therapies Scientific Committee of IRDiRC (International Rare Diseases Research Consortium) and a member of the EBE-EFPIA ATMP Working Group.



Christopher Austin

Christopher Austin is Director of the National Center for Advancing Translational Sciences (NCATS) at the U.S. National Institutes of Health (NIH). He leads the Center's work to improve the translation of observations in the laboratory, clinic and community into interventions that reach and benefit patients from diagnostics and therapeutics to medical procedures and behavioral changes. Under his direction, NCATS researchers and collaborators are developing new technologies, resources and collaborative research models; demonstrating their usefulness; and disseminating the data, analysis and methodologies for use by the worldwide research community. Prior to joining NIH, he worked at the pharmaceutical company Merck, where he directed programs on genome-based discovery of novel targets and drugs, with a particular focus on schizophrenia and Alzheimer's disease. He is trained as a clinician and geneticist. In 2016, Dr. Austin was elected Chair of the International Rare Diseases Research Consortium (IRDiRC).



Gareth Baynam

Gareth Baynam is a Clinical Geneticist at the Genetic Services of Western Australia; an Adjunct Policy Advisor on Clinical Genomics at the WA Department of Health; Director of the Undiagnosed Diseases Program- WA, and Head of the Western Australian Register of Developmental Anomalies. He is a Clinical Associate Professor at the School of Paediatrics and Child Health - University of Western Australia, the Institute for Immunology and Infectious Diseases - Murdoch University, and at Spatial Sciences - Curtin University. He is an Honorary research fellow at Telethon Kids Institute. His PhD was in genetic modifiers of vaccine response in children and he leads a 3D facial analysis research team. He is Co-Chair of the Diagnostics Scientific Committee of the International Rare Diseases Research Consortium. He is a member of the Orphanet Australia National Advisory Body and of the Rare Voices Australia Scientific and Medical Advisory Committee. He is a Founding Member of the Board of Directors of the Undiagnosed Diseases Network - International.



Claudio Bordignon

Claudio Bordignon is Chairman of MolMed S.p.A., a biotech company dedicated to the development of new anti-cancer molecular treatments, to which he contributed to its foundation in 1996. Previously, he worked at the San Raffaele Scientific Institute where he established the Program of Hematology and Bone Marrow Transplantation and became the Director of the Research Units of Experimental Hematology and Gene Therapy. In this field, his team quickly became the European leader and one of the most important players in the international scientific community. He led the group that performed the first worldwide experience of gene therapy in hematopoietic stem cells for hereditary diseases. In 2002 this work led to the publication of the first successful gene therapy treatment of adenosine deaminase-deficient SCID. He expanded this experience to stem cell gene therapy of other genetic diseases and AIDS, and to immuno-gene therapy of cancer. Prof. Bordignon has been President of European Society of Genetic Therapy and member of major scientific committees. He founded in 1995 and directed until 2000 the Telethon Institute for Gene Therapy of Genetic Diseases (TIGET).



Kym Boycott

Kym Boycott is a Medical Geneticist at the Children's Hospital of Eastern Ontario (CHEO), Senior Scientist at the CHEO Research Institute, and Professor of Pediatrics at the University of Ottawa. Her research program in rare diseases bridges clinical medicine to basic research and is focused on understanding the molecular pathogenesis of these disorders, enabling the design of new therapies to ultimately benefit patients and their families. She is the principal investigator of Canada's national genome-wide sequencing platform for rare disease, Care4Rare Canada, and of the Rare Diseases: Models & Mechanisms Network, established to catalyze connections between clinical investigators discovering new genes in patients with rare diseases and basic scientists who can analyze equivalent genes and pathways in model organisms. She moves the international rare disease agenda forward through her role as Chair of the Diagnostics Scientific Committee of the International Rare Diseases Research Consortium, and as Co-Lead of Matchmaker Exchange.



Anna Bucsics

Anna Bucsics received her medical degree from the Karl-Franzens-University of Graz, Austria, where she also did her postgraduate research at the Department of Experimental and Clinical Pharmacology. In 1991 she moved to Vienna where she worked as auditor for pharmaceutical expenditures at the Viennese Social Health Insurance, and at the Main Association of Austrian Social Insurance Institutions, where she was Head of the Department of Pharmaceutical Affairs until the end of 2013. She is advisor to the MoCA (Mechanism of Coordinated Access to Orphan Medicinal Products) project, and to the MEDEV Committee (an informal group of experts from public organizations responsible for pharmaceutical reimbursement), whose speaker she was from 2001 to 2005. She has participated in European projects such as EUnetHTA, the Pharmaceutical Forum, and the Platform on Access to Medicines in Europe. She is an instructor at the Department of Finance, University of Vienna, a member of the European Commission Experts Group on Rare Diseases as well as Judicial Advisor (Beisitzer) at the Federal Administrative Court of Austria.



Francis Collins

Francis S. Collins is the Director of the National Institutes of Health (NIH). In that role he oversees the work of the largest supporter of biomedical research in the world, spanning the spectrum from basic to clinical research. He is a physician-geneticist noted for his landmark discoveries of disease genes and his leadership of the international Human Genome Project, which culminated in April 2003 with the completion of a finished sequence of the human DNA instruction book. He served as director of the National Human Genome Research Institute at NIH from 1993-2008. Before coming to NIH, Dr. Collins was a Howard Hughes Medical Institute investigator at the University of Michigan. He is an elected member of the Institute of Medicine and the National Academy of Sciences, was awarded the Presidential Medal of Freedom in November 2007, and received the National Medal of Science in 2009.



Jodi Cook

Jodi Cook is the Chief Operating Officer for Agilis Biotherapeutics, a gene therapeutics company focused on treatments for rare genetic diseases of the central nervous system. She has more than 20 years of senior executive experience in the life-sciences industry, in a broad range of Companies, from advanced technology start-ups to a Fortune 500 corporation. Her experience includes clinical practice, academic research, and corporate management, giving her a unique perspective and understanding of all key stakeholders. Previously, she was Vice President, Clinical Research and Professional Relations for InSound Medical, a venture-backed company acquired by an industry leader. She has vast translational experience and has been instrumental in the successful global launch of innovative medical products. She counts among her accomplishments the development and execution of sound clinical and regulatory strategy and leadership for corporate medical and professional affairs. She earned her Ph.D. in Auditory Science at Arizona State University, and completed a fellowship at Johns Hopkins School of Medicine.



Hugh Dawkins

Hugh Dawkins is the Director of the Office of Population Health Genomics (OPHG). OPHG is leading the Australian efforts in the development of a National Framework for Rare Disease, and is responsible for implementing the Western Australian Rare Diseases Strategic Framework. OPHG is also currently leading the development of a national framework for newborn (bloodspot) screening; implementing with the Genetic Services of WA the genetic and undiagnosed disease service which includes integrating enabling phenotyping tools; and developing a national approach to the incorporation of massively parallel sequencing into clinical diagnostic services. Professor Dawkins is the nominated Australian contact for Orphanet and Vice Chair of the International Rare Diseases Research Consortium (IRDiRC). He is also leading the Australian partnership in a European Commission FP7 programs, RD-CONNECT; concerted action project RARE-BestPractice; and EC Joint Action program RD-ACTION.



Ruxandra Draghia-Akli

Ruxandra Draghia-Akli is Deputy Director-General for Research & Innovation (DG RTD) at the European Commission, responsible for the Research Programmes. She serves as the Commission representative in the Governing Boards of most Joint Technology Initiatives of the EU with different industrial sectors. Dr Draghia-Akli joined the European Commission in 2009 as Director for Health Research in DG RTD. She has contributed considerably during these past years to the successes of the 'Health' Programme. She holds a MD degree and a PhD degree in human genetics from the University Carol Davilla, Romania and has participated in a fellowship programme in Genetics and Metabolic Pathology Department in René Descartes University in France, and a post-doctoral training in molecular biology at Baylor College of Medicine, USA. Before joining the Commission, she worked in biotechnology companies, as Vice-President managing research programmes in the area of gene therapy and DNA vaccination.



Hawa Dramé

Hawa Dramé, is a founder of FITIMA, dedicated to the rehabilitation and education of children with disabilities, rare diseases and women rights. A biochemist by training, she previously worked in the field of rare diseases for AFM (French Neuromuscular Association), Alliance des Maladies Rares (Collective of French associations fighting against rare diseases) and Rare Diseases Europe-EURORDIS as therapeutic development coordinator for the orphan drugs program and expert at the COMP. She is a consultant in the field of health strategy for several international organizations (UNICEF and WHO). She is also involved in the implementation and coordination of ROAMY «West African Organization against Myopathies» and CAIRE «Help Center for Women» in Guinea.



Christopher Gibson

Christopher Gibson is the Co-Founder and CEO of Recursion Pharmaceuticals, a biotech company leveraging the intersection of the latest automation, computation and biological tools to do drug discovery at scale. He developed the technology and approach underlying Recursion as part of his graduate work in the MD/Ph.D. program at the University of Utah in the lab of Co-Founder, Dr. Dean Li. He took a leave of absence from medical school in order to transform this technology into the rapidly growing company it is today. He comes from a family of entrepreneurs, is a graduate of Rice University with degrees in bioengineering and managerial studies, and was finally compelled to change his career from medicine to entrepreneurship through an intense course in entrepreneurship at Stanford GSB. Chris is also a Board Member of CureHHT, a patient advocacy group for Hereditary Hemorrhagic Telangiectasia. He enjoys cycling on both the road and the trails that cut through Utah's great wilderness, as well as spending precious time with his family.



Jonathan Goldsmith

Jonathan Goldsmith started his career with the FDA in 2005 as Deputy Director of the Center for Biologics Evaluation and Research's Office of Blood Research and Review. From 2008 to 2014, he was Deputy Branch Chief of the Division of Blood Diseases and Resources at the National Institutes of Health's National Heart, Lung, and Blood Institute. In 2014, he returned to FDA and has since served as the Associate Director of the Rare Diseases Program in the Center for Drug Evaluation and Research's Office of New Drugs. Dr. Goldsmith earned his medical degree from New York University School of Medicine, received his post-graduate training in Internal Medicine at Vanderbilt University Hospitals, and completed specialty training in Hematology and Blood Coagulation at the University of North Carolina. Prior to his federal service, he had an extensive career in academia as a tenured professor, in regulated industry where he focused on clinical drug development and safety of biopharmaceutical products, and with orphan disease foundations.



Ivo Gut

Ivo Gut is Director of the Centro Nacional de Análisis Genómico (CNAG-CRG), the second largest genome sequencing center in Europe, which he established in 2010. His research interests are genomics, genetics, high-throughput nucleic acid analysis methods, proteomics, implementation of -omics methods, omics technologies, automation bioinformatics, data analysis, disease gene identification, cancer genomics and agrogenomics. He received his PhD in Physical Chemistry from the University of Basel in 1990. After his appointments as Research Fellow at Harvard Medical School and Imperial Cancer Research Foundation of London, he led a group in the Department for Vertebrate Genomics at Max-Planck-Institute for Molecular Genetics. He is author of more than 350 research papers, 11 reviews and 12 book chapters, cited over 27 000 times, inventor of 25 patents or patent applications, founder of 4 biotech start-ups, and serves on numerous international advisory boards.



Melissa Anne Haendel

Melissa Haendel is an Associate Professor at the Oregon Health & Science University and she is the Director of the Ontology Development Group, also at the Oregon Health and Science University, Library and Department of Medical Informatics and Epidemiology. Her research is focused on developing and testing ontologies for classifying and querying biological data and ontological methods for making data interoperable. Ontology-based search allows one to exploit the logical definitions and relations between entities and thereby infer additional information. She is particularly interested in using anatomy ontologies for translational research to link human diseases to model organism data. Furthermore, she is a member of various advisory boards and committees, such as the Vice President Joe Biden Cancer Moonshot Blue Ribbon panel on Open Data sharing and the Global Alliance for Genomics and Health (GA4GH) Data and Clinical working group.



Caroline Hager

Caroline Hager has more than 25 years' experience working on a wide range of EU policy issues - internal market, employment, environment and health - for European and British business organisations as well a UK government agency as its EU and international relations manager. She joined the European Commission in 2001, and since 2011 has been working in the field of health policy in the Directorate General for Health and Food Safety. Caroline is responsible in taking forward the Action Plan for the EU health workforce which fosters European cooperation in the areas of health workforce planning and forecasting, skills and continuous professional development as well as recruitment and retention of health professionals.



Ada Hamosh

Ada Hamosh is Dr. Frank V. Sutland Professor of Pediatric Genetics at the McKusick-Nathans Institute of Genetic Medicine (IGM), and a professor in the Department of Epidemiology at Johns Hopkins Bloomberg School of Public Health. Since 2002, she has served as clinical director of the IGM and Scientific Director of the Online Mendelian Inheritance in Man® (OMIM), a catalog of more than 12,000 human genes and genetic disorders created by Dr. Victor A. McKusick. Her research centers the molecular basis of Mendelian disorders, the integration of genetics into clinical practice and the diagnosis and management of inborn errors of metabolism. She is member of various professional associations and advisory committees including the American Society of Human Genetics, the Society for Pediatric Research, and a fellowship at the American College of Medical Genetics.



Mats Hansson

Mats Hansson is Professor of Biomedical Ethics and Director of The Centre for Research Ethics & Bioethics (CRB) at Uppsala University. The Centre is a multi-disciplinary unit awarded for international excellence with long experience of managing large international projects, currently leading research on risk conceptualisation and communication. This 25-person team of researchers is combined with social scientists, psychologists and risk communication experts as well as ethicists for assessment of individual preferences and public health needs and front line research in different disease areas. Philosophers, medical doctors, nurses and lawyers are also part of the team. Prof. Hansson is coordinating the project Mind the Risk, a project with a multi-disciplinary research program representing strong academic centres in Europe providing a rich philosophical and conceptual framework that together with historical and socio-cultural analyses of concerns about risk information, empirical investigations of risk perceptions and preferences and ethical analyses may guide regulation and management of risk information in various settings.



Robert Hufnagel

Robert Hufnagel is a Clinical Molecular Genetics Fellow, at the Medical Genetics Branch at the National Human Genome Research Institute, at the National Institutes of Health (NIH). He is also an Ophthalmic Genetics Fellow at the Ophthalmic Genetics and Visual Function Branch, at the National Eye Institute, at the NIH. The goal of his research program is to apply the scientific approaches of developmental biology and molecular genetics to hereditary ophthalmic diseases to improve diagnosis and ultimately vision for these patients. As a physician-scientist, he has developed a translational research program wherein biospecimens from carefully phenotyped patients are evaluated by genomic sequencing to identify disease etiologies for study in human and animal models to discover novel disease genes and molecular targets for therapeutic trials.



Stuart Hughes

Stuart Hughes is Director and Head of Pharmacology at Vertex Pharmaceuticals Europe Ltd. Following the award of a PhD in Cellular and Molecular Neuroscience from Cardiff University in 1999 he spent several years as a postdoctoral scientist studying the mechanisms that underlie a host of physiological and pathological brain rhythms. In 2006 he was awarded a Wellcome Research Fellowship to continue this work and made important contributions to the understanding of the cellular events that lead to the slow waves of deep sleep as well as the neural mechanisms that shape the so-called alpha rhythm of relaxed wakefulness. In 2008, he took up a position as a group leader in CNS research at Eli Lilly and Company, pursuing a range of ion channel targets for treating a variety of neurological and psychiatric disorders. In 2013, he moved to Vertex Pharmaceuticals to lead the UK in vivo pharmacology group where his main areas of focus have been on orphan diseases, cancer and neurodegeneration.



Alain Huriez

Alain Huriez is Partner at Advent Life Sciences, which he joined in 2012. He has 25 years of experience in the life sciences sector, including CEO of TcLand-Effimune and Neovacs, Associate Partner at Truffle Capital and Vice President at Quintiles International. His experience includes private equity financing, tech transfer & scouting, business development and general management in the areas of vaccines, antibodies, molecular diagnostics, devices & technology platforms. By training, he is a Medical Doctor and holds an MBA and a Masters of Pharmaco-Economics from Paris La Sorbonne University. Prior to joining the industry, he was head of the Emergency Room in a large hospital and practiced as a General Practitioner for two years. Alain has been responsible for several lobby initiatives at the European level (EMA, EC, and Parliament) in the area of personalised medicine through his work as chairman of EPEMED, the European Personalised Medicine Association www.epemed.org, which he founded in 2009.



Carlo Incerti

Carlo Incerti is the Head of Global Medical Affairs at Sanofi Genzyme. He oversees the Global Medical Affairs in the 4 Therapeutic Areas of Sanofi Genzyme, a Global Business Unit of Sanofi Corporation: Oncology, Immunology, Multiple Sclerosis and Rare Diseases. He is a Board Certified Endocrinologist, who started his career in the medical profession as a staff member and then as Associate Professor at the Department of Endocrinology of Modena University Hospital in Italy. He joined Genzyme in 1992 and in his tenure, which covers more than two decades, he has been responsible for the development of all of the Genzyme products, including the ones in the rare disease field, with specific focus on Lysosomal Storage Disorders. These development activities started with the successful approval in Europe of what is considered the first pre-orphan drug (Cerezyme for Gaucher disease) and in the first officially approved orphan drug (Fabrazyme for Fabry disease).



Edmund Jessop

Edmund Jessop has been practicing public health for the NHS in England since 1981 in various jobs at district, regional and national levels. Since 2002, he has been medical adviser to the team which plans, funds and monitors services for patients with very rare disease. This has included decision making, and more recently close liaison with NICE, on the so-called «ultra-orphan» drugs as well as other highly specialized technologies. Edmund is UK representative to the EU Expert Group on Rare Disease. He was Vice President of the UK Faculty of Public Health (FPH) from 2011 to 2014 and Editor of the Journal of Public Health 1998 - 2007. He has taught courses on public health including health economics and health technology assessment for over 15 years.



Sangeeta Jethwa

Sangeeta Jethwa holds a Medical degree from the University of Wales, College of Medicine, with specialty training in Anesthesia and Intensive Care Medicine. She is also board certified in Pharmaceutical Medicine with Fellowship of the Faculty of Pharmaceutical Medicine. After several years of clinical practice, she joined the pharmaceutical industry 14 years ago as a Medical Advisor and held roles of increasing responsibilities in oncology medical affairs, at local, European and then global level. Her current role is Head of Patient Partnership within the Rare Disease R&D unit at Roche in Basel, Switzerland. Her role is to drive patient-centricity generally in early R&D and specifically in Rare Diseases, advancing science together with patients. She is a member of the EURORDIS Company Round Table and the IRDiRC Consortium Assembly.



Petra Kaufmann

Petra Kaufmann is Director of both the Office of Rare Diseases Research and the Division of Clinical Innovation. Her work includes overseeing NCATS' Rare Diseases Clinical Research Network, Genetic and Rare Diseases Information Center, and Clinical and Translational Science Awards Program as well as the NIH/NCATS Global Rare Diseases Patient Registry Data Repository/GRDR®' program. She focuses on engaging a broad range of stakeholders to accelerate translation from discovery to health benefits through use of innovative methods and tools in translational research and training. She has served on scientific advisory committees for many rare disease organizations and is a member of the American Academy of Neurology Science Committee, the International Rare Diseases Research Consortium Interdisciplinary Scientific Committee and the Clinical Trial Transformation Initiative Steering Committee.



Stephen Kingsmore

Stephen Kingsmore is President and CEO of Rady Children' Institute for Genomic Medicine at Rady Children's Hospital, San Diego, which is implementing pediatric genomic/precision medicine at unprecedented scale. Previously he was the Dee Lyons/Missouri Endowed Chair in Genomic Medicine at the University of Missouri-Kansas City School of Medicine and Director of the Center for Pediatric Genomic Medicine at Children's Mercy Hospital, Kansas City. He trained in clinical immunology in Northern Ireland and did his residency in internal medicine and fellowship at Duke University Medical Center. He is a fellow of the Royal College of Pathologists. TIME magazine ranked his rapid genome diagnosis one of the top 10 medical breakthroughs of 2012. In March 2015, Dr. Kingsmore surpassed his previous record in genetic sequencing by reducing the process to 26 hours which was recognized in April 2016 by Guinness World Record as the fastest genetic sequencing in the world.



Hideyuki Kondo

Hideyuki Kondo is Deputy Director of the Office of International Programs, at the Japan Pharmaceutical and Medical Devices Agency. For more than 10 years, he has been working at the Ministry of Health, Labour and Welfare, Japan, in several positions in the field of pharmaceutical and medical device regulations, including those related to pre-market review policies, GMP/QMS inspections, post-market safety measures and R&D promotion. He started the current position as a Deputy Director from March 2016, aiming at advancing international cooperative activities, especially between EU and Japan. He received the Bachelor of Pharmaceutical Sciences from Kyoto University in Japan, and the Master of Business Administration with a focus on of Health Sector Management from Fuqua School of Business, Duke University in the USA.



Matthias Kretzler

Matthias Kretzler is Warner-Lambert/Parke-Davis Professor of Internal Medicine/Nephrology and a Research Professor of Computational Medicine and Biology at the University of Michigan. His research interests is defining the molecular pathophysiology of glomerular disease for function based disease management in international, multidisciplinary research networks. To reach this goal he has developed a translational research pipeline centered on integrated systems biology analysis of renal disease. He leads the Nephrotic Syndrome Research Network (Neptune) in the Rare Disease Clinical Research Network II, the Coordinating center of the CureGN research network, and is Director of the Applied Systems Biology Core at the Michigan Kidney Center and in the NIH Acceleration of Medicine (AMP) program in autoimmunity.



Anders Larsson

Anders Larsson is Professor of Biomedical Laboratory Science with emphasis on health economics at the Department of Medical Sciences, Uppsala University, and also senior consultant at the Department of Clinical Chemistry and Pharmacology, Akademiska Hospital, Uppsala, Sweden. He heads a research group focusing on assay development and the use of avian antibodies. He has published over 600 scientific articles. He has been working with avian antibodies for more than 30 years and been involved in Swedish human treatment studies with egg antibodies for the prevention of pseudomonas infections in cystic fibrosis patients for more than 20 years. Professor Larsson is the Project Coordinator for the IMPACTT project (IMPACTT.eu). The core of IMPACTT is a randomized placebo controlled multicenter study performed in 9 European countries. The aim of the Phase III study is to document the efficacy and safety of oral treatment with yolk anti-pseudomonas antibodies for the prevention of pseudomonas infections in cystic fibrosis patients.



Kristina Larsson

Kristina Larsson joined the Orphan Team of the EMA as the Head of Office in July 2014. Prior to that, she spent 8 years as a Scientific Officer in the Scientific Advice Team of the EMA, mostly focusing on oncology, inborn errors of metabolism and biosimilar monoclonal antibodies. Before joining the agency, she worked for three years in clinical research for AstraZeneca in Mölndal, Sweden. She has a Master of Medicine in Pharmaceutical Bioscience from the University of Gothenburg.



Paul Lasko

Paul Lasko is Professor at the Department of Biology, McGill University. He received his B.A. from Harvard and his Ph. D. from the Massachusetts Institute of Technology, and joined McGill in 1990 after a postdoctoral period at the University of Cambridge. He has authored over 100 research papers in genetics and developmental biology. Since 2010, he has served as Scientific Director of the CIHR Institute of Genetics. He oversees the Institute's strategic research funding initiatives, many of which involve fostering international partnerships. In the past, Dr. Lasko worked extensively for the Human Frontiers of Science Program Organization (HFSPO), and also served as President of the Genetics Society of Canada. Dr. Lasko recently completed a three-year term as Chair of the Executive Committee of the International Rare Diseases Research Consortium.



Yann Le Cam

Yann Le Cam is the CEO and Co-Founder of Rare Diseases Europe-EURORDIS. He has dedicated 25 years of professional and personal commitment to health and medical research non-governmental organizations in France, Europe and the United States in the fields of cancer, HIV/AIDS and rare diseases. He has been more than instrumental in the formulation of rare diseases as a public health concept and meaningful public policy instrument, which has been crucial for the promotion of patient representatives as active participants to decision making process. He was one of the first patient representatives appointed to the Committee for Orphan Medicinal Products (COMP) at the European Medicines Agency (EMA) and has recently been elected to the EMA's Management Board. Yann Le Cam is also a member of and former Chair of the Therapies Scientific Committee of the International Rare Diseases Research Consortium.



Hanns Lochmüller

Hanns Lochmüller is Professor of Experimental Myology at the Institute of Genetic Medicine at Newcastle University. He has a long-standing interest in the molecular genetics of the inherited myopathies and neuromuscular junction disorders, and his research focuses on the further study of animal models of these disorders as a means to understand their pathophysiology, as well as to develop the means to monitor disease progression and therapeutic interventions. His research encompasses multiple model systems such as zebrafish and mouse *in vivo* models, cell culture models and clinical studies involving patients. Hanns is current Chair of the Interdisciplinary Scientific Committee of the International Rare Diseases Research Consortium, Coordinator of the RD-Connect project and former Chair of the Executive Committee of the TREAT-NMD Alliance.



Milan Macek

Milan Macek is Professor at Charles University in Prague Chairman of the Department of Biology and Medical Genetics and Co-Chair of the National Cystic Fibrosis Centre. He is also the past President of the European Society of Human Genetics and past-board member of the European Cystic Fibrosis Society. He was member of the EUCERD.eu committee, and currently serves as an EC-appointed expert at the Commission Expert Group on Rare Diseases. His department was designated by the Czech Ministry of Health as a National Coordination centre for rare diseases and serves as a «clearing centre» for dissemination of knowledge in rare disease-related genetics gathered within various international European projects related to cystic fibrosis. He did his postdoctoral studies at Humboldt University Berlin, then at the McKusick-Nathans Centre for Genetic Medicine, Johns Hopkins University in Baltimore. During that time he was also a fellow at Harvard School of Medicine in Boston. His main research and clinical interest is molecular genetics/genomics in rare diseases, and how to bring genetics knowledge to the bedside. Prof. Macek is also the Czech National Coordinator of Orphanet and member of the Diagnostic Committee of the International Rare Disease Research Consortium.



Romain Marignier

Romain Marignier is neurologist and Assistant-Professor in the Neurological Hospital of Lyon, France. His field of expertise is the neuro-inflammatory disorders of the central nervous system with a specific interest on a rare but severe disease, namely neuromyelitis optica (NMO). He is the Coordinator of the French nationwide NMO cohort and biobank, NOMADMUS, set up in 2010 that includes all the French clinical experts in neuro-inflammatory disorders. He was also the Project Coordinator of the European Network EDEN «establishment and use of a European database and biological bank for research and treatment in acute neuromyelitis optica and related disorders», funded by ERANet ERARE 2 from 2012 to 2015. Dr Marignier is also the Head of Neurobiotec, part of the biological resource centre of the Lyon University Hospital. The goals of Neurobiotec are to provide facilities necessary to set up a biocollection and ensure storage security of human biological samples and to make available to public or private research teams these samples.



Marc Martinell

Marc Martinell obtained his PhD in Chemistry from the University of Barcelona. He has broad experience in drug discovery and biotechnology through his participation at companies such as Crystax Pharmaceuticals and Oryzon Genomics, where he managed several research projects and led the team in charge of target selection, structural biology, computational chemistry and hit ID through a fragment-based approach. At Oryzon, he actively contributed to the identification of the first-in-class inhibitors for the epigenetic target LSD1 currently in clinical studies and licensed to Roche. In 2011, he co-founded Minoryx Therapeutics, a clinical stage biotech company focused on the development of new drugs for a group of rare diseases known as Inborn Errors of Metabolism. He is co-author of several patents and publications.



Matt Might

Matt Might is Associate Professor at the School of Computing of the University of Utah, and a Visiting Professor in Biomedical Informatics at the Harvard Medical School. He is deeply committed to supporting people with rare diseases, including his own son, Bertrand, who was the first person diagnosed with NGLY1 deficiency. His work on rare diseases propelled him to the White House: he is a strategist in the Executive Office of the President to accelerate the implementation of the Precision Medicine Initiative. He is also the author of several highly-read essays about the process of scientific discovery in rare diseases, and the diagnostic odyssey for Bertrand.



Federico Mingozi

Federico Mingozi is Research Director at INSERM, and Associate Professor at University Pierre et Marie Curie, Paris. He is a team leader at the Immunology and Liver Gene Transfer Unit of Genethon, in Evry, France. The research activities in his laboratory are mostly focused on the development of gene therapies based on adeno-associated virus (AAV) vectors and on the study of immune responses in gene transfer. Previously, he was a Director of Translational Research in the Center for Cellular and Molecular Therapeutics at the Children's Hospital of Philadelphia. Furthermore, he is a member of different scientific societies, including the American Society of Gene and Cell Therapy and the European Society of Gene and Cell Therapy.



Sophie Nicole

Sophie Nicole is the Co-Leader of the "Neurogenetics and Physiology" team at the brain and spinal cord institute (ICM, Paris, France) since January 2014. She received her PhD in Human Genetics in 1999 at the Pierre et Marie Curie University (UPMC, Paris, France) before obtaining a research associate position at Inserm in 2002. She got the highest French academic degree (habilitation to direct research) in 2009 from UPMC and received the Research Senior Prize from the « association pour la recherche sur des pathologies pédiatriques » the same year. Sophie Nicole and her team focus on understanding the mechanisms that regulate the neuromuscular excitability from genetics to tissue excitability, and lead to rare human disorders (peripheral synaptopathies, channelopathies) when deficient using cell and animal (zebrafish, mouse, human) models. The translational part of their research projects is done in close collaboration with two clinical reference centers (Neurology Department and Myology Institute, Pitié-Salpêtrière hospital) for the benefit of individuals with these rare diseases.



Yukiko Nishimura

Yukiko Nishimura is President and Founder of NPO ASrid (Advocacy Service for Rare and Intractable Diseases' stakeholders in Japan). ASrid is committed to providing valuable service/system for connecting and creating with/among multi-stakeholders related to its field, as an intermediate organization. Based on her effort, ASrid and JPA (Japan Patients Association) have set up cooperation about research promotion and drug development area, and also collaborated with the Pediatric NANBYO network, the biggest Pediatric Rare Diseases Network in Japan. She has worked/collaborated with patients/patients' families and the stakeholders in rare and intractable diseases and orphan drug field for about 10 years. She has been a board member of the ICORD committee since 2010, has worked as a Chief Secretariat of International Relations at JPA, and as an Assistant Professor of Research Center for Advanced Science and Technology, University of Tokyo.



Ichizo Nishino

Ichizo Nishino is Director of Department of Neuromuscular Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry (NCNP), Japan. He is also Director of Departments of Medical Genome Development and Clinical Genome Analysis, Medical Genome Center, NCNP, Guest Professor at Faculty of Science and Engineering, Waseda University and Faculty of Medicine, University of Yamanashi. He obtained his M.D. from Kyoto University Faculty of Medicine, Japan. After 5 years of training in clinical neurology, he started muscular disease research in NCNP, which led him to obtain Ph.D. from Kyoto University. He was appointed Section Chief at Department of Ultrastructural Research at NCNP before he moved to his current position in 2001. Prof. Nishino is an Executive Board member for several academic societies including World Muscle Society, TREAT-NMD, Asian-Oceanian Myology Center (Secretary) and Japanese Muscle Society (Trustee), and has been serving as an Editorial Board member for more than 10 international journals.



Irene Norstedt

Irene Norstedt is Head of Unit for the Innovative and Personalised Medicine Unit in the Health Research Directorate in DG Research and Innovation. This Unit focuses on personalised medicine and supports research in -omics, diagnostics, rare diseases and various aspects of personalised medicine including piloting personalised medicine in health care. She has been working with European life sciences research aspects at the European Commission since 1996. In 2015, she was also Acting Executive Director for the Innovative Medicines Initiative (IMI), a public private partnership between the EC and the Pharmaceutical industry. Her previous responsibilities at the EC have primarily focussed on small and medium size enterprises and industry aspects of biotechnology and health research at European level. Before starting her position in Brussels she worked for Biacore AB in Uppsala, Sweden. She has also worked as Assistant Technical Attaché at the Swedish Embassy in London.



Anders Olauson

Anders Olauson is the Chairman of the Ågrenska Centre, and was involved in its founding in 1989. In his role, he is responsible for establishing The Ågrenska Virtual International Academy, a research centre for rare disorders. He is particularly concerned with the impact of rare conditions on children and their families. His work involves contact with both national and regional legislative bodies on the subject of rare disorders. He is also in contact with representatives of hospitals, education and labor unions as well as other key players in the field of rare diseases. Previously, he has been a member of the board of EURORDIS, a member of the board of the European Patients' Forum (EPF) and a member of the advisory group for Health Research within DG Research. Together with EURORDIS, Ågrenska started the NGO Committee for Rare Diseases (United Nations, New York), a substantive committee established under the umbrella of the Conference of NGOs in Consultative Relationship with the United Nations.



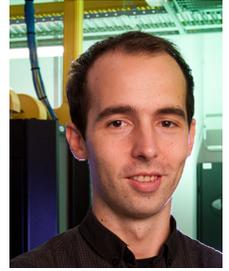
Graziella Pellegrini

Graziella Pellegrini is Professor at the University of Modena and Reggio Emilia, Director of the Cell Therapy Program at the Centre for Regenerative Medicine «Stefano Ferrari». She is also co-founder, R&D Director and Qualified Person at Holostem Terapie Avanzate S.r.l. She was awarded for her research on central nervous system, on ocular pathology and on urethra. Author of 6 patents, book chapters and more than 70 peer reviewed publications in the major international journals, she was invited speaker or chairman in almost two hundreds major international meetings on Stem Cells and Regenerative Medicine. She is one of the inventors of the technology for culture and transplantation of limbal stem cells for treatment of blindness due to corneal stem cell deficiency, and she made a significant contribution to its orphan drug designation and European registration of the therapy. She developed other translational medicine protocols for treatment of third degree burns, depigmentation, gene therapy of epidermolysis bullosa and is currently working on oral mucosa, urethra and airway epithelium.



Slavé Petrovski

Slavé Petrovski is a Senior Research Fellow and Group Leader in Computational Genomics, at the Department of Medicine, University of Melbourne. Throughout his early career he contributed to the discovery of new Mendelian and complex disorder disease genes. Besides his interest in disease gene discovery, his passion continues to be in facilitating the interpretation of human genomics data. This includes development of novel conceptual frameworks to facilitate interpreting individual genomes, such as: the residual variation intolerance score (RVIS), parental-mosaic transmission screen, trio-analysis frameworks for severe undiagnosed genetic disorders, and development of novel analytical frameworks. He is currently involved in numerous collaborative projects with international institutions and industry partners.



Kiran Reddy

Kiran Reddy is a Venture Partner at Clarus Ventures where he focuses on new company formation, venture investments, and risk sharing partnerships with pharmaceutical companies. He is also the President & CEO of a Praxis Precision Medicines, a new biotech company focused on precision medicine in genetically defined autism and neurodevelopmental disorders. Prior to Clarus, he was at Biogen as part of the Corporate Strategy leadership team and an Associate Partner at Third Rock Ventures. He supported and managed various portfolio companies in addition to focusing on new company formation and new investments. He was part of the founding team and interim Chief Business Officer for SAGE Therapeutics through its IPO, and co-inventor of SAGE-547 the Phase 3 program for the rare epilepsy disorder refractory status epilepticus. Kiran was part of the team that launched Foundation Medicine, and he has served as a Board Observer for Alnara pharmaceuticals, Rhythm pharmaceuticals, and PanOptica pharmaceuticals.



Makoto Suematsu

Makoto Suematsu is the Founding President of the Japan Agency for Medical Research and Development (AMED). He is a Research Director at the Japan Science and Technology Agency, working on the Suematsu Gas Biology Project, which aims for a comprehensive explanation of the acceptance, transportation, and decomposition mechanisms of the gas molecules produced and utilized in the body and applying the results to medicine. He is also Dean of the School of Medicine at Keio University. Furthermore, he is member of various scientific organizations, such as the Heads of International Research Organization (HIROs), the Global Alliance of Chronic Diseases (GACD)' and the International Rare Diseases Research Consortium (IRDiRC).



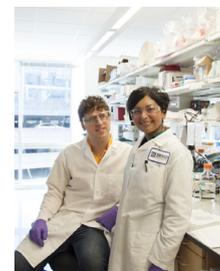
Toshiki Takenouchi

Toshiki Takenouchi is an instructor in Pediatrics at Keio University Hospital, Tokyo, Japan. He is a Principal Investigator at Keio University Hospital, working on the mechanisms of a new syndromic form of thrombocytopenia. He previously worked as a Pediatric Neurologist at Weill Cornell Medical College in New York. His work has led him to receive several honorary awards, both in Japan and the USA. He has successfully led various research projects and published more than 50 research peer-reviewed papers.



Sonia Vallabh and Eric Minikel

Sonia Vallabh watched her 52 year old mother die of a rapid, mysterious, undiagnosed neurodegenerative disease in 2010. One year later, she learned that her mother had died of genetic prion disease, and that she herself had inherited the causal mutation, making it very likely she would suffer the same fate in 20 years time. There was no prevention, treatment, or cure available. Despite having no prior training in biology, Sonia and her husband, Eric Minikel, set out to re-train themselves as scientists and devote their lives to searching for a treatment or cure for her disease. They quit their jobs in consulting, started a scientific blog, began taking night classes and attending conferences, found new jobs in research labs, and eventually enrolled as PhD students in biology at Harvard Medical School. They are now based in Stuart Schreiber's laboratory at the Broad Institute of MIT and Harvard, and have launched a new therapeutic initiative to discover drugs for her disease.



David Valle

David Valle is a Professor and Director at the McKusick-Nathans Institute of Genetic Medicine, Pediatrics, with joint appointments in Molecular Biology and Genetics, Ophthalmology and Biology, in John Hopkins School of Medicine. His research interests include understanding all aspects of the contribution of genetic variation to human health and disease. In particular, his studies involve clinical, biochemical, molecular and therapeutic aspects of specific human genetic diseases as well as more global studies on the network interactions and consequences of variation in the genes and proteins implicated in human disease. He has previously been President of the American Society of Human Genetics, and a member of the Institute of Medicine of the National Academy of Sciences. He is an author of over 250 scientific articles and various book chapters.



Edward Visser

Edward Visser is a clinical endocrinologist at the Erasmus Medical Centre (Erasmus MC, Rotterdam, The Netherlands). He had his clinical training at the Erasmus MC and the Addenbrookes hospital (University of Cambridge, Cambridge, UK). He did his PhD at the Erasmus MC and a postdoctoral fellowship at the Institute of Metabolic Science (Cambridge, UK). His major focus of research is the role of local thyroid hormone signaling in health and disease. His academic interests include studies in rare thyroid diseases, in particular thyroid hormone resistance (RTH) syndromes such as patients with mutations in the thyroid hormone transporter MCT8. The main focus is on identification of novel RTH syndromes, as well as exploring underlying mechanisms and treatment options of known syndromes. An important translational research line is the Triac Trial, in which more than 50 AHDS patients worldwide are treated with the T3 analogue Triac. He is member of the Taskforce of the European Thyroid Association to formulate a guideline on diagnosis and management of RTH syndromes and is a chair of the group 'Thyroid hormone signaling disorders' in the European Reference Network – ENDO



Nan Wu

Nan Wu is an attending orthopedic surgeon at the Department of Orthopedic Surgery at Beijing Union Medical College Hospital, Beijing Union Medical College and the Chinese Academy of Sciences. He is also attached to Beijing Key Laboratory for Genetic Research Skeletal Deformity, where his research direction is in clinical genetics. He carries out a series of genetic studies of bone and joint disease especially in vertebral malformations. He has established a large cohort of congenital vertebral malformations patients with epidemiological data, clinical documents, imaging data and biological samples. He has successfully led various research projects and published more than 20 research peer-reviewed papers.



Abstracts

Selected Talk Abstracts

Foundational:

- | | |
|------------------|--|
| Harsha Rajasimha | Status of Rare Disease Ecosystem in India – Progress and lessons for rest of the world |
| Marco Roos | Boosting health care and life science research on rare diseases by creating a robust infrastructure of independently Findable, Accessible, Interoperable, and Reusable (FAIR) biobanks, registries, and molecular data resources |

Diagnostics:

- | | |
|---------------|--|
| Taila Hartley | Solving the Lonely Exome: International Connectivity to Enable Discovery |
| Filip Pattyn | Variant data from patients with rare diseases semantically linked and enriched with gene and variant data from public data sources |

Therapeutics:

- | | |
|---------------------|---|
| Ralf-Dieter Hilgers | IDeAI designing a clinical trial – a case study. |
| Susan Ward | Translating Natural History into Clinical Trial Design – lessons from Duchenne Muscular Dystrophy |

Abstracts

Selected Talk Abstracts: Foundational

Status of Rare Disease Ecosystem in India – Progress and lessons for rest of the world

Harsha Rajasimha, Prasanna Shirol, Sangeeta Barde

Organization for Rare Diseases India and George Mason University

Just 4 years ago, there was no active umbrella organization to advocate for patients with rare diseases in India. The best we had was an organization supporting the needs of patients with lysosomal storage disorders and a few disease specific patient advocacy groups such as retinaindia, pompe foundation, hemophilia foundation, thalassemia society, inborn errors in metabolism, muscular dystrophy foundations, etc.

The founding of the Organization for Rare Diseases India (ORDI; Rajasimha et al., Genetics Research, 2014) has significantly accelerated the progress and served as an umbrella organization supporting the needs of patients with rare diseases in India. With focus on awareness (www.racefor7.com), care coordination (rare disease care coordination centers of excellence) model programs with private and government hospitals, 100s of volunteers with varied backgrounds, funding from government and industry sponsorship for these programs have spurred great hope for patients and opportunity for all stakeholders involved. We will discuss these programs and policy advocacy efforts in detail, lessons we borrowed from USA ODA and EU rare disease policies, and how India could serve as a model country for rest of the world.

ORDI has organized tens of continuing medical education programs, engaged with all recognized medical genetics departments across India and facilitated international collaborations to foster clinical research involving rare diseases. The organization also supports drug discovery and clinical trial programs by matching the right patients from our registry. With our partnership with rare genomics institute, USA, we refer patients and parents for sponsored genome sequencing programs for discovery of genetic mutations causing yet undiagnosed diseases.

The change in the attitude of high courts in India in the last couple years with verdicts favoring a no-cost treatment for patients with lysosomal storage disorders is seen as a major breakthrough supporting our mission. We look forward to more global collaborators in future.

Boosting health care and life science research on rare diseases by creating a robust infrastructure of independently Findable, Accessible, Interoperable, and Reusable (FAIR) biobanks, registries, and molecular data resources

David van Enckevort¹, Rachel Thompson², Claudio Carta³, Mark Wilkinson⁴, Marco Roos⁵

1.University Medical Centre Groningen, The Netherlands
2.Newcastle University, UK
3.Istituto Superiore di Sanita, Rome, Italy
4.Universidad Politécnica de Madrid, Spain
5.Leiden University Medical Centre, The Netherlands (co-lead Elixir rare disease use case)

Purpose: Aiding the rare disease community in developing robust infrastructure that supports data integration needs to take into account that there are over 6000 rare diseases with multiple types of resources (biobanks, registries, omics) across countries. Researchers should be able to combine data from these resources, because of the relative sparsity of the data. Maintaining a centralized warehouse at this scale, and with this kind of sensitive data, is neither feasible nor ethically or legally acceptable. We need to provide solutions that can scale-up to be adopted by thousands of resources 'at the source' and facilitate cross-resource analytics at the level of the data itself. This mitigates the high costs of researchers spending too much time reconciling data ambiguities, while previous reconciliation efforts can not be reused.

Methodology: We present a 'rare disease data linkage plan' written and endorsed by stakeholders in the rare disease community and infrastructure experts. They have committed to making rare disease resources findable, accessible, interoperable, and reusable by humans and computers (FAIR) at the source. It is supported by RD-Connect, Elixir, CORBEL, BBMRI, FAIRDict, and ODEX4All, and rare disease patient organisations have shown strong willingness to co-invest. At least seven biobanks/registries will be made FAIR, and making molecular data resources FAIR is investigated. The plan provides recommendations for data annotation and exchange, and tooling.

Results: Early design decisions include using the FAIR data API, ontologies, and linked data to enable cross-resource analysis. The project incrementally provides ontology recommendations, starting with the HPO for phenotypes and ORDO for diseases. Case-based ontological models ('semantic archetypes') will be shared and incorporated into tooling. Harmonizing how data are encoded by ontologies can compensate lack of agreement on common data elements. We report on Elixir-supported Bring Your Own Data Workshops that drive the data linkage plan.

Abstracts

Selected Talk Abstracts: Diagnostics

Solving the Lonely Exome: International Connectivity to Enable Discovery

Taila Hartley¹, Martine Tetreault², Orion Buske³, Mike Brudno³, Kym Boycott¹ on behalf of the Care4Rare Canada Consortium⁴

1. Children's Hospital of Eastern Ontario Research Institute, University of Ottawa, Ottawa, Ontario, Canada; 2. Department of Human Genetics, McGill University, Montréal, Québec, Canada; 3. Department of Computer Science, University of Toronto, Toronto, Canada; 4. www.care4rare.ca

Despite recent advances in genome-wide sequencing up to 75% of patients remain unsolved after the analysis of known disease genes. We have shown that a significant proportion (23%) of unsolved patients can ultimately be explained by mutations in novel disease genes. Discovery of these genes requires finding additional unrelated patients with a deleterious-appearing variant in the same gene and overlapping phenotype. We have therefore been an early adopter of international 'matchmaking' efforts, investing in hypothesis-driven matching, where one or both sides have a candidate gene.

For two-sided hypothesis matching, we have entered 110 single-surviving candidate genes into various nodes of the Matchmaker exchange, an API that functions to connect PhenomeCentral, GeneMatcher, DECIPHER, and MyGene2. We have had 172 matches representing 76 genes. Of these matches, 26.3% (45/172) had at least partial phenotypic overlap prompting further investigation. Thus far, three novel genes (UNC80, TRIT1, EXTL3) have been published with 13 international collaborators. For single-sided hypothesis matching, we have manually searched for our own candidate genes within PhenomeCentral's 'Similar Patient' portal and available cohort databases (Geno2MP, DECIPHER, Genesis, RD-Connect). These searches have prompted the investigation of four novel genes in which participants have been found with overlapping phenotypes. We have also established an in-house matchmaking tool that can be queried for variants in candidate genes identified by collaborators. We have received 302 queries, from which four (1.3%) successful matches have been made (ADNP, TBCK, TRIT1, RSPRY1) and an additional three genes are currently being studied.

Our results demonstrate the utility of both two-sided and single-sided hypothesis matching; further they show that the false positive rate of single-sided hypothesis matching is significantly less than two-sided. Given the additional information available to the querier in single-sided hypothesis matching (phenotypic features, variant, zygosity), it is unsurprising that this approach has a higher specificity.

Variant data from patients with rare diseases semantically linked and enriched with gene and variant data from public data sources

Filip Pattyn, Kenny Knecht, Peter Verrykt, Hans Constandt

ONTOFORCE, Ottergemsesteenweg-Zuid 808, 9000 Gent, Belgium

The technological advancements in high-throughput sequencing have moved genetic testing to a new level. Sequencing technology has matured and crosses the bridge from research to common clinical practice. Clinical interpretation of variant data implies trustworthy information about the functional effects of genetic variants and the subsequent clinical consequences related to diseases. This information is scattered over many databases. Rare diseases are mainly studied and diagnosed in specialized centers, which has led to the emergence of many gene variant databases focused on a small set of genes or diseases(1). It's a challenge to link this data with more centralized initiatives like dbSNP(2) , ClinVar(3) , SwissVar(4) , DisGeNet(5) etc.

We have developed DISCOVER(6) , a public platform for fast and efficient searching across 110+ public life science related data sources. The data is processed through an automatic update pipeline, semantically interlinked and organized in different data types, such as: variant, gene, protein, disease, pathway, clinical trial, publication, patent etc. Users can quickly search what is known in different databases about a specific variant, or they can quickly see which genes and variants are associated with a certain disease. By applying the specific filters per data type and following the relationships linking the data types, users can create a search path and share this with others. Moreover, for every individual data point the originating data source can be traced back to allow a critical assessment at any stage.

Local patient data can be integrated on an internal secure DISCOVER platform and combined with a data federation system to enrich this data with all the available data on the public DISCOVER platform.

The DISCOVER platform is a centralized search system for information about gene variants in rare diseases.

1 <http://www.lovd.nl>

2 <https://www.ncbi.nlm.nih.gov/SNP/>

3 <https://www.ncbi.nlm.nih.gov/clinvar/>

4 <http://swissvar.expasy.org>

5 <http://www.disgenet.org>

6 <http://www.discover.com>

Abstracts

Selected talk abstracts: Therapeutics

IDeAI designing a clinical trial – a case study

Ralf-Dieter Hilgers, Geert Molenberghs

Department of Medical Statistics, RWTH University Aachen / I-BioStat, Universiteit Hasselt

Purpose: In rare diseases the sample size of patients that could be enrolled in a clinical trial is limited. The purpose of the paper is to show the potential gain by rigorous use of tailored design and analysis aspects, which are developed within the IDeAI project.

Methodology: IDeAI is a currently EU funded project developing new integrated statistical design and analysis methods for clinical trials in small populations. Among various tools developed, here some specific design and analysis findings are presented related to rigorous use of longitudinal data modeling. This is illustrated by using the recently published two year data on Friedreich's Ataxia patients (Reetz, 2016).

Results: A brief overview of the IDeAI project, the aims and the results are given. Then it is shown that the sample size needed to detect a fictive 50% reduced effect in a clinical trial with a two arm parallel group design could be dramatically reduced by consistently use of longitudinal data models. Hereby the dependency of the sample size on the number of measurements over time is shown, when the data are analysed by linear mixed effects models. This is illustrated using the 2 year data from the Friedreich Ataxia register, where the total sample size could be reduced under specific assumptions by almost 50%. Other design aspects may be considered, like change of the endpoints to surrogate endpoints, selection of a randomization procedure which protects best against bias. These aspects should be combined to analysis methods like randomization based inference of the longitudinal data or nonlinear mixed effects modelling.

Conclusions: The presented methods indicate, that sample size considerations strongly depend on design aspects as well as analysis aspects. Reasonable sample sizes may result from rigor application of newest statistical methods which will be discussed with regulators next march.

Translating Natural History into Clinical Trial Design – lessons from Duchenne Muscular Dystrophy

E Mercuri, N Goemans, J Signorovitch, and S.J Ward, on behalf of the collaborative Trajectory Analysis Group (cTAP).

Catholic University, Rome, Italy; University Hospitals, Leuven, Belgium; Analysis Group, Boston USA, cTAP, Cambridge USA

Although the criticality of establishing natural history in support of drug development is widely understood, and an unprecedented number of rare disease communities are now collecting natural history data, translating natural history into clinical trial design presents new challenges. Drug development in Duchenne Muscular Dystrophy exemplifies both the regulatory challenges in applying natural history to trial design as well as a unique collaborative approach to identifying solutions.

The Duchenne community was prescient in collecting natural history before drugs reached clinical trials. Despite such foresight, the majority of clinical trials in Duchenne have failed to meet their primary statistical endpoints, raising key questions on trial design: Was it the right endpoint? Tested over the right time frame? Is the biomarker adequate? Did our drug not 'work'? Furthermore, the relative wealth of Duchenne natural history itself has led regulators to surface new concerns: Is natural history the same in different countries, and across multiple centers? Have changes in medical practice impacted observed natural history? How does clinical practice differ from clinical trial protocols – and does it matter?

cTAP is a consortium established to address these challenges. Forging a dynamic alliance between clinical experts, patient advocates and a growing number of drug developers in Duchenne, cTAP helped leading academics pioneer data-sharing to access advanced data science, collaboratively.

Results: With de-identified longitudinal disease trajectories of 1300+ patients from 10,000+ clinic visits – the largest and most comprehensively studied data-set in Duchenne, cTAP has halved the unexplained variance impacting clinical trials and developed prognostic on-line tools to assist drug developers in trial design. This unprecedented level of collaboration has also provided clinical experts with the 'apples to apples' statistical comparisons of their data necessary to address regulator questions on consistency of Natural history.

Abstracts

Poster abstracts

- 1 Anna Ambrosini Fondazione Telethon's Strategies to Build up and Support the Italian Neuromuscular Clinical Platform
- 2 Rosaleen Anderson Improving the Treatment of Cystinosis
- 3 Corrado Angelini Clinical and imaging phenotypes of trasportinopathy (limb-girdle muscular dystrophy type 1F)
- 4 Heather Ascani Precision medicine in diabetic complications: using Nephroseq and tranSMART data-exploration tools to define diabetic kidney disease
- 5 Dorota Badowska RD-Connect: data sharing and analysis for rare disease research within the integrated platform and through GA4GH Beacon and Matchmaker Exchange
- 6 Gianluca Baldanzi Repurposing Existing Drugs for X-Linked Lymphoproliferative Disease 1 Therapy
- 7 Terence Beghyn Desirable "Individualized Medicine": from concept to reality
- 8 Virginie Bros-Facer International Joint Recommendations to address specific needs of Undiagnosed Rare Disease Patients
- 9 Salvador Capella-Gutierrez The RD-Connect Central Authentication Service: components and deployment
- 10 Monica Carmosino Functional characterization of Lamin A mutants to identify targeted therapies for cardiolaminopathies
- 11 Chiara Ciriminna Swan #RAREvolution: the use of digital communication to support rare disease research
- 12 Jeanine D'Armiento Tumorigenic Cells of Lymphangioliomyomatosis are of a Neural Crest Origin and Susceptible to Tyrosine Kinase Inhibitors
- 13 Angel del Pozo TAT:CF: Novel therapeutic approaches for the treatment of cystic fibrosis based on small molecule transmembrane anion transporters through open innovation
- 14 Sander Dijkstra Conventional primary central chondrosarcoma of pelvic bone: prognostic factors and outcome of surgical treatment in 162 patients
- 15 Nicolas Doulet Imagine Institute, a translational research institute wholly-dedicated to genetics diseases
- 16 Michela Gabaldo Bringing an effective gene therapy to ADA-SCID patients: StrimvelisTM as a successful example of a collaborative effort involving a charity, a research hospital and a pharmaceutical company
- 17 Anne Galy Net4CGD: advancing gene therapy for a rare primary immune deficiency
- 18 Ritchie Head ODAK: the Orphan Drug for Acanthamoeba Keratitis
- 19 Kristina Hettne Pathway analysis on the metabolome of dystrophin deficient mice and humans
- 20 Tunc Lacin Effect of diaphragm pacing on quality of life and respiration in patients with Amyotrophic Lateral Sclerosis: Preliminary Study

21	Stefan Maeser	Clinical Diagnostics of Neuronal Ceroid Lipofuscinoses on Dry Blood spots: Development of New Cathepsin Substrates for Mass Spectrometric Determination
22	Eduardo López-Granados	TRANSPLANT-CHILD-ERN, an European strategy to attend “the secondary rare disease” induced by Paediatric Transplantation
23	Lucia Monaco	Developing an international network of rare diseases biobanks within the EuroBioBank/RD-Connect platform
24	Hanayuki Okura	In situ differentiated adipose tissue-derived multi-lineage progenitor cells could be remedy for rare diseases with liver dysfunction
25	Christina Olsen	VISION-DMD: Advancing clinical development of the innovative orphan drug Vamorolone for DMD
26	Manuel Posada	RD-Connect platform: A useful tool for the undiagnosed rare diseases program SpainUDP
27	Giuseppe Procino	X-linked nephrogenic Diabetes Insipidus: Potential Novel Strategies for Treatment
28	Michael Przybylski	Molecular characterization of antibody epitopes for repositioning immune reactivity in enzyme replacement therapy of lysosomal storage diseases
29	Roberto Quesada	Facilitated transmembrane transport, a viable therapeutic approach for channelopathies?
30	Ana Rath	Orphanet and the Orphanet Rare Disease Ontology: Facilitating the interoperability of data in the field of rare diseases
31	Dorianna Sandonà	Novel therapeutic perspectives for sarcoglycanopathy: rescue of folding-defective mutants by means of protein folding correctors
32	Pedro Sernadela	Current challenges on the creation of european-wide rare diseases cohorts
33	Gabriele Siciliano	NMR voxel-based morphometry and functional analysis as neural correlates of neuropsychological dysfunction in DM1
34	Rumen Stefanov	Moving Forward Health Technology Assessment and Appraisal of Orphan Drugs
35	Daisuke Sugiyama	International cooperation of the Center for Clinical and Translational Research, Kyushu University
36	Domenica Taruscio	RD-Connect ID-Cards of biobanks and registries: making RD data Findable, Accessible, Interoperable and Reusable
37	Thomas Vaccari	Modeling of rare diseases in <i>Drosophila melanogaster</i> : opportunities and challenges
38	Nathalie Vandeveldde	Propositions of new financing modalities for analyses of medical biology specific for the diagnosis and follow-up of rare diseases
39	Shuyang Zhang	A Briefing of the National Rare Diseases Registry System of China (NRDRS)

Anna Ambrosini and Lucia Monaco

Fondazione Telethon, Milan, Italy

Fondazione Telethon (FT) was founded in 1990 by the patient association «Italian Union against Muscular Dystrophy»; therefore, promoting research on genetic neuromuscular diseases (NMD) has always been a relevant part of its mission. In 2002, FT launched a specific call to support clinical studies on NMD, aimed at improving care and quality of life for subjects with a neuromuscular condition. Several actions were put in place to make this effort valuable, including methodological support and coordination support to manage ongoing multicenter projects.

With an overall investment of about 10 M€ and 54 approved projects (48 multicenter ones), major outcomes are: i) over 6,000 patients involved in clinical studies; ii) development of an Italian clinical network specialized in myology and peripheral neuropathy; iii) genetic and clinical characterization of large patient cohorts and development of research registries; iv) development and validation of new outcome measures; v) direct involvement of patients in quality of life surveys.

Overall, this investment proved to be highly relevant. Benefits to patients include being connected with specialists who provide diagnosis and genetic counseling, best standards of care and information regarding upcoming trials, while clinical investigators are facilitated in the collection of accurate data for prospective studies on natural history, rehabilitation and palliative care. The initiative was very effective also to promote trial readiness, contributing relevant information at international level (more than 200 peer-reviewed publications and Italian experts' participation in international working groups), and facilitating the inclusion of Italian patients in therapeutic clinical studies.

FT also contributed to the creation of and continues support to neuromuscular multispecialty clinical centres in Italy and participates in international partnerships, such as the European Neuromuscular Centre consortium and the Treat-NMD program. New strategic plans are under development to consolidate this clinical platform and promote participation of the Italian NMD consortium in international studies.

L Frost, P Hambleton, RJ Anderson

University of Sunderland

The ultra-orphan genetic disease Cystinosis is linked to malfunction of the cystinosin transporter and characterised by lysosomal cystine accumulation in all tissues. Without treatment, Cystinosis patients progressed to renal failure; death before age 10 was the usual outcome.

Although Cystinosis can be treated with cysteamine bitartrate, which significantly delays disease progression, it is difficult for patients to maintain the required dosing regimen due to its frequency and unpleasant side effects. A deeply unpleasant taste and smell cause nausea and vomiting, with frequent reports of gastric and duodenal disturbances, and ulceration. After absorption, up to 90% of the dose is wasted by first pass metabolism, leading to production of dimethylsulfide and methane thiol, for which human olfactory sensitivity is in the ppb range. Cystinosis patients often suffer lack of confidence due to concerns about severe halitosis and body odour. The low bioavailability and short half-life of cysteamine demand high and frequent doses: up to 1g every 6 hours is required to achieve sufficient depletion of cystine. It is not surprising to find that many patients, particularly teenagers and young adults, do not achieve their target dosing schedule, causing kidney, muscle, skeletal and endocrine deterioration over time.

We have developed a new delivery technology for cysteamine to overcome the side effects and metabolism, leading to decreased opportunity for metabolite production and improved bioavailability, with the advantage of twice daily dosing. The pre-clinical candidate CF-10 has appropriate physicochemical properties for oral administration, displays minimal gastric side effects and very low serum concentrations of cysteamine. In the mouse model of Cystinosis, twice daily dosing of CF-10 depleted the accumulated cystine from all tissues evaluated, to a level comparable to that achieved with cysteamine and over a shorter treatment period. We will present the data supporting the development of CF-10 to clinical candidate.

Clinical and imaging phenotypes of transportinopathy (limb-girdle muscular dystrophy type 1F)

Angelini C¹, Fanin M², Cenacchi G³, Pinzan E¹, Pegoraro V¹, Giaretta L.¹, Nigro V⁴

1. Fondazione Ospedale San Camillo IRCCS (Venice, IT); 2. University of Padua (Padua, IT); 3. University of Bologna (Bologna, IT); 4. TIGEM (Naples, IT).

We report muscle histopathological, ultrastructural and radiological features of a large Italian-Spanish family with autosomal dominant LGMD, previously mapped to 7q32.2-32.2 (LGMD1F).

We collected the DNA, clinical history, muscle biopsies histopathology of one LGMD1F kindship. Biopsy of two affected patients mother and daughter was studied (in the daughter two consecutive biopsies at 9 and 28 years and in the mother at 48 years).

In LGMD1F patients the age of onset varied from 2 to 35 years, weakness occurred either in upper or in lower girdle; in 14 cases there was hypotrophy both in proximal upper and lower extremities in calf muscles. Muscles MRI showed hyperintensity in proximal limb muscles. The daughter has a severe clinical course and the fiber atrophy was more prominent in the second biopsy at 28 years. The mother has a relatively compromised histopathology and many small muscle fibers, and autophagic changes by acid-phosphates stain. Immunofluorescence against desmin, myotilin, p62 and LC3 showed accumulation of myofibrils, ubiquitin binding proteins aggregates and autophagosomes. Ultrastructural analysis revealed myofibrillar disarray, vacuolar changes, granular material and dense subsarcolemmal bodies deriving from cytoskeleton-myofibrillar proteins. We hypothesize that the pathogenetic mechanism in LGMD1F might lead to disarrangement of desmin-associated cytoskeletal network.

Transportin-3 (TPNO3), which was found by NGS to be the causative gene in LGMD1F, is suggested to mediate the nuclear import-export. The non-stop mutation identified in this family encodes for a longer protein which is expected to be unable to move to the nucleus. Clinical phenotype penetrance in this family correlates at 92% with mutation presence. MRI imaging is a powerful tool for the follow up in the evolution of this dominant LGMD and demonstrated atrophy of lower girdle.

Precision medicine in diabetic complications: using Nephroseq and tranSMART data-exploration tools to define diabetic kidney disease

Heather Ascani, Colleen Kincaid-Beal, Becky Steck, Ross Patterson, Rachel Dull, Christopher M. Gates, Viji Nair, Felix H. Eichinger, Wenjun Ju, Matthias Kretzler

The University of Michigan – Ann Arbor, Michigan USA

Precision Medicine, identifying the right treatment for the right patient at the right time, must be applied in glomerular diseases to advance the field beyond the current “one size fits all” approach. Comprehensive genetic data from patient cohorts and animal model systems are presently generated for many disorders, including those of the glomerulus. The challenge of precision medicine, however, is designing an “informational commons”; a virtual space for researchers to share and explore large-scale datasets.

One of the goals pursued by the Applied Systems Biology Core is to establish an effective way for scientists to interrogate molecular data without requiring specific expertise in bioinformatics or statistics. To this end, Nephromine was developed as a web-based, systems-biology search engine, focused on renal gene-expression datasets. The next generation, Nephroseq, was released in early 2016. Nephroseq has an intuitive interface, accessing all publicly-available, human, renal gene-expression datasets and a growing number of model-system expression datasets. It allows exploration of differentially-regulated transcripts using predefined cohorts and datasets with an extensive suite of systems-biology tools.

The data exploration platform TranSMART goes beyond preset analyses and allows user-specified exploration of cohort-study datasets along the entire genotype-to-phenotype continuum. Researchers define cohort strata and, using a simple drag-and-drop function, explore interactions in data from cohort study participants; these can range from prospective clinical phenotypes, histological descriptors, genotypic information, gene and protein expression profiles to environmental exposures. TranSMART instances, using shared data ontologies, are currently deployed for multiple renal disease cohorts with complex phenotypes and associated genetic and molecular data sets. Within these networks, TranSMART serves as an outreach tool for ancillary study investigators, enabling dynamic access to complex datasets from cohort studies.

Future goals for Nephroseq and TranSMART are to further facilitate integration of glomerular disease datasets and to empower geographically-distributed research networks to jointly implement precision

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

S. Beltran^{1,2}, D. Piscia^{1,2}, S. Laurie^{1,2}, J. Protasio^{1,2}, A. Cañada^{3,14}, J.M. Fernández^{3,14}, R. Kaliyaperumal⁶, S. Lair⁷, P. Sernadela⁸, M. Girdea⁹, R. Thompson¹⁰, H. Lochmüller¹⁰, D. Badowska¹⁰, V. Straub¹⁰, M. Roos⁶, P.A.C. 't Hoen⁶, A. Valencia^{3,14}, D. Salgado^{4,5}, C. Bérout^{4,5,13}, I. Gut^{1,2} and the RD-Connect Consortium

Affiliation: 1Centro Nacional de Análisis Genómico (CNAG-CRG), Center for Genomic Regulation, Barcelona Institute of Science and Technology (BIST), Barcelona, Spain 2Universitat Pompeu Fabra (UPF), Barcelona, Spain 3Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid, Spain 4Aix-Marseille Université, Marseille, France 5Inserm, UMR_S 910, Marseille, France 6Department of Human Genetics, Leiden University Medical Center, Leiden, The Netherlands 7Interactive Biosoftware, Rouen, France 8DETI/IEETA, University of Aveiro, Portugal 9Centre for Computational Medicine, Hospital for Sick Children and University of Toronto, Toronto, ON, Canada 10John Walton Muscular Dystrophy Research Centre, Institute of Genetic Medicine, MRC Centre for Neuromuscular Diseases, Newcastle University, UK 11Centre for Comparative Genomics, Murdoch University, Perth, Western Australia 12APHM, Hôpital TIMONE Enfants, Laboratoire de Génétique Moléculaire, Marseille, France 14Instituto Nacional de Bioinformática (INB), Spain

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

Repurposing Existing Drugs for X-Linked Lymphoproliferative Disease 1 Therapy

Suresh Velnati, Alberto Massarotti, Elisa Ruffo, Giancesare Tron, Andrew Snow, Kim E. Nichols, Andrea Graziani, Gianluca Baldanzi

1Department of Translational Medicine and Institute for Research and Cure of Autoimmune Diseases, University of Piemonte Orientale, 28100 Novara, Italy – 2Department of Pharmacology and Molecular Therapeutics, Uniformed Services University of the Health Sciences, Bethesda, MD 20814, USA – 3Department of Oncology, St. Jude Children's Research Hospital, Memphis, TN 38105 USA -10School of Medicine, University Vita e Salute San Raffaele, Milan, Italy

Introduction: XLP1 is a primary immunodeficiency due to mutations in the SH2D1a gene, encoding the SAP protein. As SAP deficiency results in a constitutive DGK alpha activity1 that impairs CD8+ T cell homeostasis, pharmacological inhibition of DGK alpha in XLP1 animal models limits CD8+ T cell expansion and disease progression2. Those data support the use of DGK alpha inhibitors for XLP1 therapy.

Methods: We intend to develop new inhibitors of DGK alpha suitable for clinical trials in XLP1. We screened a series of 150 compounds (100µM) on DGK alpha overexpressing homogenates, using the two commercial inhibitors as positive controls. Active compounds were tested at least three times at 0.1/1/10/100 µM in order to determine the IC50. For selected compounds, an assay with purified DGK alpha was also carried out at 10µM.

Results: In the primary screen 18 compounds inhibit DGK alpha at least by 25%. Of those, compound1 and Ritanserin showed a potency superior to the two commercial inhibitors. In the purified enzyme assay, 5 compounds showed an activity comparable to the two commercial inhibitors: Ritanserin, Risperidone, SKI-II, Aripiprazole, and Ebastine. Ritanserin, a specific and long acting serotonin S2-antagonist presently in clinical trials, is the most active compound with and IC50 of 5.1±0.8µM in homogenate assay.

Conclusion: We found new compounds actively inhibiting DGK alpha of those Ritanserin is a very promising drug candidate as it was safe for human use. Our results suggest the possibility of repurposing Ritanserin for the treatment of XLP1. We are validating those compounds into in vitro and in vivo models of XLP1 to provide preclinical data supporting future clinical trials.

References

- 1: Baldanzi G. SAP-mediated inhibition of DGK alpha regulates TCR-induced DAG signalling. J Immunol. 2011 Dec 1; 187(11):5941-51.
- 2: Ruffo E, Malacarne V. Inhibition of DGK alpha restores restimulation-induced cell death and reduces immunopathology in XLP-1. Sci Transl Med. 2016 Jan 13; 8(321):321ra7.

Desirable “Individualized Medicine”: from concept to reality

Terence Beghyn¹, Benoit Deprez¹, Dries Dobbelaere²

1: APTEEUS 2: Jeanne de Flandre, CHRU Lille France

A large number of rare diseases are monogenetic. Although a causal relationship is often established between the mutation in the target gene and the disease, the nature of the mutation is key to the function lost or acquired, to the clinical manifestations and to their response to a treatment. It is thus challenging to find a cure that will meet the medical need of a whole population of patients suffering from the same disease. This is well illustrated by the recent development of mutation-specific CF drugs.

From a theoretical point of view, the ideal solution would be to run one research program for each individual. Obviously, this approach cannot find economic viability if research programs are run according to the current pharmaceutical paradigm, which aims at serving large patient populations.

The question we try to address is: How could we be fast and efficient enough to meet individual medical needs?

Apteeus answers the question by engaging patient early and individually in its discovery process. This new process brings high throughput drug discovery tools from bench to patient bedside to test all marketed drugs in disease-specific screening assays performed on unmodified primary cells obtained from the patient. In a couple of months, APIs restoring the compromised pathway specifically in the donor cells can be identified. These drugs are immediately available candidates to treat the donor, who benefits directly from the technology. Eventually the new drug candidate can enter a development in the new indication for the population of patient subsequently screened and found responder to the drug.

We will disclose the process of individualized discovery that has been put into practice for a young boy suffering from an ultra-orphan peroxisomopathy. The young boy is currently benefiting from the treatment identified using Apteeus technology under an expanded use protocol.

International Joint Recommendations to address specific needs of Undiagnosed Rare Disease Patients

Virginie Bros-Facer¹, Nick Meade², Helen Cederroth³, Nicole Mills⁴, Durhane Wong-Rieger⁵, Yukiko Nishimura⁶ and Paul Melmeyer⁷

EURORDIS (1), Genetic Alliance UK (2), Wilhelm Foundation (3), Rare Voices Australia (4), Canadian Organization for Rare Diseases (5), the Advocacy Service for Rare and Intractable Diseases' stakeholders in Japan (6) and National Organization for Rare Disorders (7)

EURORDIS (Rare Diseases Europe), together with SWAN UK (the support group run by Genetic Alliance UK), the Wilhelm Foundation, Rare Voices Australia (RVA), the Canadian Organization for Rare Disorders (CORD), the Advocacy Service for Rare and Intractable Diseases' stakeholders in Japan (ASrid) and the National Organization for Rare Disorders (NORD) jointly submit a list of recommendations to address the specific needs of patients without a diagnosis urging all stakeholders to recognise undiagnosed patients as a specific population within the rare disease community.

Undiagnosed rare disease patients require the availability of a complete health and social care pathway in advance of receiving a diagnosis. Such care should promote their chances of receiving an accurate diagnosis in as efficient and timely way as possible, while ensuring that, until a diagnosis is made, they nevertheless receive the best possible health and social care. These recommendations also highlight the importance of promoting ethical and responsible international data sharing to help inform a clinical diagnosis, accelerate research into novel conditions and provide insights into disease mechanisms. Furthermore, knowledge and information sharing among all stakeholders should be optimally coordinated and fostered so that patients can access appropriate resources in a timely and efficient manner.

The RD-Connect Central Authentication Service: components and deployment

Fernández, José María,^{1,2} Cañada, Andrés,^{1,2} Piscia, Davide,³ Protasio, Joan,³ Beltrán, Sergi,³ Capella-Gutierrez, Salvador,^{1,2}. Valencia, Alfonso,^{1,2}

(1) Spanish National Cancer Research Institute (CNIO), Madrid, Spain. (2) Spanish National Bioinformatics Institute (INB), Spain. (3) Centro Nacional de Análisis Genómico (CNAG-CRG), Center for Genomic Regulation, Barcelona, Spain.

The RD-Connect platform connects and integrates sensible data, rare disease developments and knowledge, like medical records from several registries, sample metadata from biobanks, experiments databases, pipeline analysis databases and clinical bioinformatics tools. All these resources have their own web platforms, and most of them have some kind of access control mechanism in order to restrict the access to sensible information. These control mechanisms are managed independently, so a mechanism which allows creating a web of trust among them is mandatory in order to use them in RD-Connect platform. The RD-Connect Central Authentication Service (CAS) has been setup and deployed to play this role, providing a single sign-on facility trusted by all these distributed resources. Moreover, we are working to integrate the ELIXIR AAI as part of a coordinated effort in the context of the ELIXIR-EXCELERATE project. ELIXIR AAI will facilitate the access to additional data and service resources making possible further analyses in a transparent manner for users, as long as they have the appropriate permissions.

Functional characterization of Lamin A mutants to identify targeted therapies for cardiomyopathies

Monica Carmosino¹, Andrea Gerbino², Cinzia Forleo³, Sandro Sorrentino³, Giorgia Schena¹, Maria Grazia Mola², Giuseppe Procino², Stefano Favale³ and Maria Svelto².

1 Department of Sciences, University of Basilicata, Potenza IT; 2 Department of Biosciences Biotechnologies and Biopharmaceutics, University of Bari, Bari, IT; 3 Cardiology Unit, Department of Emergency and Organ Transplantation, University of Bari, Bari, IT

Mutations in the LMNA gene, encoding nuclear proteins Lamin A, have been associated with severe cardiac disease named 'cardiomyopathy' associated with a high risk of sudden death. The implant of a cardioverter defibrillator is to date the only effective intervention. Of note, understanding the molecular mechanism by which a single mutation in LMNA gene alters protein function provides the basis for mutation-specific pharmacological strategies.

Genetic screening performed in family members affected by severe forms of cardiomyopathies with frequent history of sudden death, led to the identified of new pathogenetic mutations in LMNA gene. The resulting Lamin A mutants were expressed in cardiomyocytes and functionally characterized. Here we provided findings from two representative mutants. The LMNA gene mutation c.418_438dup consists of a duplication of 21 nucleotides in exon 2 of the LMNA gene, resulting in the 'in frame' duplication of seven amino acids from position 140 to position 146, in the Lamin A protein (LMNA DUP). When expressed in cardiomyocytes LMNA DUP forms aggregates of different sizes in the nuclear envelope of dysmorphic nuclei. Moreover, its expression significantly increases nuclear envelope fragility upon different cellular stresses, such as hypertonic, hypoxic, and oxidative stresses. The second representative LMNA gene mutation is a nonsense mutation that introduces a premature termination codon within the 6th exon of LMNA gene. The resulting mutant version of Lamin A, LMNA R321X, mislocalized in the endoplasmic reticulum (ER) causing a profound impairment of ER homeostasis such as 1- ER stress response, 2- impaired ER Ca²⁺ handling 3- reduced capacitative Ca²⁺ entry at the plasma membrane and 4- abnormal nuclear Ca²⁺ dynamics.

Although the final cellular event upon the expression of both Lamin A mutants is an increase in cardiomyocytes apoptosis rate, the different pathomechanisms triggered by the two mutations suggest different and novel therapeutic venues.

#RAREvolution: the use of digital communication to support rare disease research

Chiara Ciriminna Swan and Olivier Menzel

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

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

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

The BLACKSWAN Foundation is also contributing through the #RAREvolution program to increasing awareness and advocate for rare diseases at global level. A stronger awareness and political implication at international level is fundamental to attract more resources for research on RD and increase prevention, diagnosis and treatments for RD patients. The program includes a digital awareness campaign on RD research and an advocacy action including an online petition that provides guidelines to policy-makers for the establishment of policies on RD research. The aim of the #RAREvolution campaign is to make rare diseases an international public health and research priority (<http://www.blackswanfoundation.ch/en/petition/>)

#RAREvolution: Stand up for scientific research

Tumorigenic Cells of Lymphangioleiomyomatosis are of a Neural Crest Origin and Susceptible to Tyrosine Kinase Inhibitors

Jeanine D'Armiento, Uchenna Unachukwu, Takayuki Shiomi, Jarrod Sonnet, Denzel Woode, Vincent Anguiano, and Kiran Chada

1 Center for LAM and Rare Lung Disease, Department of Anesthesiology, College of Physicians and Surgeons, Columbia University, 630 West 168th Street, New York, NY 10032, USA. 2 Department of Biochemistry, Rutgers-Robert Wood Johnson Medical School, Rutgers University, 675 Hoes Lane, Piscataway, NJ 08854, USA.

Lymphangioleiomyomatosis (LAM) is a rare neoplasm characterized by the proliferation of atypical melanocytic and smooth muscle-like cells (LAM cells) causing cystic destruction in the lungs, and the development of renal angiomyolipomas (AMLs) and lymphangioleiomyomas in the axial lymphatics. LAM occurs mostly in women in a sporadic manner, or as part of the Tuberous Sclerosis Complex (TSC) disorder caused by mutations in the TSC1/2 genes, which activates the mTOR signaling complex. Inhibition of the mTOR pathway temporarily stymies tumorigenesis, however, given disease recurrence upon discontinuation of therapy, there remains no sustainable cure for LAM. Importantly, the source of LAM cells is also not known.

Given the multi-systemic manifestation of the disease using pluripotent lineage cells, we tested the hypothesis that LAM and AML cells are mesenchymal and derive from the neural crest. Using immunohistochemistry, we identified mesenchymal PDGFR beta, melanocytic HMB45 and endothelial CD146 marker expressions on both LAM and AML cells and demonstrated pluripotency by successfully stimulating the differentiation of AML cells into smooth muscle cells, melanocytes, adipocytes and lymphatic endothelial cells. We also defined an alternative therapeutic strategy for LAM by successfully attenuating AML proliferation and diminishing tumor cell viability using a combination of sirolimus and tyrosine kinase inhibitors that target the PDGF pathway. In delineating the pathogenesis of LAM, we propose LAM and AML cells as embryonic migrants of the neural crest, domiciled in various organs and quiescent in activity until environmental triggers stimulate tumorigenesis. An ongoing clinical trial at our center based on these findings is testing the therapeutic efficacy of these agents on the disease.

TAT:CF: Novel therapeutic approaches for the treatment of cystic fibrosis based on small molecule transmembrane anion transporters through open innovation

Angel del Pozo, Marta Pastor, Roberto Quesada, Yolanda Gil, TAT-CF Consortium

Biopraxis Research AIE, University of Burgos, TAT-CF Consortium

Statement of Purpose: TAT-CF is an H2020 funded collaborative project coordinated by the University of Burgos, which has been launched on 1st of January 2016 with a duration of 36 months. Apart from the UB, the consortium is formed by CSIC (Spain), Istituto Giannina Gaslini (Italy) and Istituto di Biofisica, CNR (Italy); Steinbeis Innovation GmbH (Germany) and Bioneer A/S (Denmark) and 2 companies: Biopraxis AEI (Spain) and Avidin Ktf (Hungary). This is an ambitious project with a budget of 4.6 million euros, which covers all aspects of drug discovery, from chemical synthesis to preclinical studies in animal models.

Methodology: TAT-CF will develop an innovative therapeutic approach for the treatment of Cystic Fibrosis (CF). This condition originates from the defective function of the CFTR protein, a chloride and bicarbonate permeable transmembrane channel. This project will evaluate small molecules capable of facilitating the transmembrane transport of anions such as chloride and bicarbonate and will thus enable CF treatment by replacing the missing CFTR anion permeation activity. This represents an unexplored path in the treatment of CF and a paradigm shift with respect to current strategies searching for a cure for CF. Instead of focusing on the development of mutation-specific treatments; we plan to develop a therapy applicable to CF patients, regardless of the type of mutation they harbor. This therapeutic approach overcomes the limitation of current mutation-specific treatments and is applicable to CF patients in general.

Results: To achieve this goal we have set up a comprehensive program to validate a research concept and complete the preclinical development of a new lead compound, making it ready for early clinical development, from the synthesis of new compounds to validation on animal models. Up to a hundred of compounds have been tested in vitro, and progress to in vivo with promising results regarding efficacy.

Conventional primary central chondrosarcoma of pelvic bone: prognostic factors and outcome of surgical treatment in 162 patients

MPA Bus¹, DA Campanacci², JI Albergó³, A Leithner⁴, MAJ van de Sande¹, LC Gaston³, G Caff², J Mettelsiefen⁵, R Capanna², PU Tunn⁵, LM Jeys³, PDS Dijkstra¹

1 Leiden University Medical Center, Department of Orthopaedic Surgery Leiden, The Netherlands 2 Azienda Ospedaliera Universitaria Careggi, Centro Traumatologico Ortopedico Firenze, Italy 3 Royal Orthopaedic Hospital Oncology Service Birmingham, United Kingdom 4 Medical University of Graz, Department of Orthopaedic Surgery Graz, Austria 5 Helios Klinikum Berlin-Buch, Sarcoma Center Berlin-Brandenburg Berlin, Germany

Purpose: Conventional (grade 1-3) primary central chondrosarcoma is a rare tumor, with the pelvis being the preferential localization. Studies focusing on the oncological outcome after treatment of this tumor type in the pelvis are lacking. We conducted this retrospective study at five referral centers to gain insight in the outcome of treatment and to identify risk factors for impaired oncological outcome.

Methodology: 162 consecutive patients (118 males, 73%) who underwent resection of a conventional primary central chondrosarcoma of pelvic bone from 1985-2013 were evaluated. Median age was 51 years (15-78). Median follow-up was 12.6 years (95%CI, 8.4-16.9). There were 30 (19%) grade 1, 93 (57%) grade 2 and 39 (24%) grade 3 lesions. **Results:** Sixty-two patients (38%) experienced local relapse: nine grade 1 (30%), 31 grade 2 (33%) and 22 grade 3 (56%) lesions. Forty-eight patients (30%) developed metastases. The risk of disease-related death was 3% for grade 1 (1/30; this patient had a grade 2 recurrence and died of metastases), 33% (31/93) for grade 2, and 54% (21/39) for grade 3 tumors. Identified risk factors for impaired disease-specific survival were tumor grade (grade 2, hazard ratio [HR] 20.18, p=0.003; grade 3, HR 58.93, p<0.001), resection margins (marginal, HR 3.21, p=0.001; intralesional, HR 3.56, p<0.001) and maximal tumor size (HR 1.08, p=0.026). Deep infection (n=31, 19%) was the predominant complication.

Conclusion: This study offers a standard for survival rates of conventional primary central chondrosarcoma of the pelvis. Survival for grade 1 tumors was excellent. Wide resection margins were associated with a significant survival advantage for higher-grade tumors. Because grade 1 and grade 2/3 cannot be distinguished reliably preoperatively, any central pelvic chondrosarcoma should be treated with en bloc resection with wide margins.

Imagine Institute, a translational research institute wholly-dedicated to genetic diseases

Nicolas Doulet, Imagine Institute

IHU Imagine

Imagine Institute's main strength is to bring together, on a single site, a large number of genetic diseases' specialists, all recognized experts in their fields, whether as researchers or clinicians, with the aim:

- 1) to better understand genetic diseases and pathophysiological pathways, in order to
- 2) better develop innovative treatment and diagnosis solutions.

Its patient-centered organization implements a unique « bench-to-bedside and back » model that acts as a facilitator for the pharmaceutical and biotech industry and brings solutions for critical bottlenecks encountered in the identification of key targets for network medicine and diagnosis, for the establishment of preclinical proof-of-concept on small molecules, antibodies... and the development of gene and cell therapies. Researchers and clinicians are organized into Integrated Care and Research Programs e.g. in immunology, hematology, in kidney disorders, ophthalmology, dermatology...

The key factors of this translational research continuum at Imagine Institute are:

- 26 research teams,
- 10 clinical departments and facilities, including Clinical Investigation Centers and databases,
- 11 Reference Centers,
- Key core facilities, including genomics/NGS, bioinformatics, animal facilities (mouse, zebrafish and drosophila), cell sorting and imaging, a biological resource center, iPS cells and databases.

Bringing an effective gene therapy to ADA-SCID patients: Strimvelis™ as a successful example of a collaborative effort involving a charity, a research hospital and a pharmaceutical company

Michela Gabaldo^{1,2}, Francesca Ferrua^{2,3,4}, Maria Pia Cicalese^{2,3}, Maria Grazia Roncarolo^{2,5} and Alessandro Aiuti^{2,3,4}

- 1 Fondazione Telethon, Milan, Italy
- 2 San Raffaele Telethon Institute for Gene Therapy, San Raffaele Scientific Institute, Milan, Italy
- 3 Pediatric Immunohematology and Bone Marrow Transplantation Unit, San Raffaele Scientific Institute, Milan, Italy
- 4 Vita-Salute San Raffaele University, Milan, Italy
- 5 Stanford University, Stanford, CA.

In May 2016, Strimvelis™ was approved by the European Medicines Agency for the treatment of patients with adenosine deaminase severe combined immunodeficiency (ADA-SCID) for whom no suitable HLA matched related donor is available. Strimvelis is the first ex-vivo, autologous, stem cell gene therapy and represents an example of a product born thanks to a strategic alliance between a non-profit organization, a research hospital and a pharma company.

In 1995 Fondazione Telethon, an Italian charity whose mission is to support excellent research on genetic diseases to the benefit of patients, and Ospedale San Raffaele in Milan created the San Raffaele-Telethon Institute for gene therapy (SR-TIGET), bringing together the skills and human and technological resources to effectively transfer the results of basic research into clinical practice.

The first gene therapy pilot study was initiated in two ADA-SCID patients in 2001 and followed up in 2002 by a phase 1-2 pivotal study involving 12 patients. Following the Protocol Assistance achieved in 2007 from EMA, in 2010 Fondazione Telethon and Ospedale San Raffaele signed an agreement with GlaxoSmithKline, which allowed the deployment of the resources, expertise and infrastructures required to complete research development and achieve pharmaceutical production at the industrial level and encompassed six more genetic diseases in the SR-TIGET clinical pipeline.

The Strimvelis marketing authorisation was based on data from 18 children treated. A 100% survival rate at three years post-treatment was observed for all of them, with overall safety findings in line with those expected in ADA-SCID children who have undergone treatment with low-dose chemotherapy and who are undergoing immune recovery.

The approval marks the culmination of more than 20 years of research and development at SR-Tiget and of many years of collaboration between SR-TIGET and GSK, representing the next step towards bringing life-changing treatment to patients with ADA-SCID and their families.

Net4CGD: advancing gene therapy for a rare primary immune deficiency

A. Galy¹, G. Santilli², S. Stein³, J. Schwaeble⁴, U. Siler⁵, A. Magnani⁶, S. Pouillot⁷, K. Kuehlcke⁸, M. Schmidt⁹, T. Paprotka¹⁰, G. Honnet¹, F. Mavilio¹, M. Grez³, H. Serve⁴, J. Reichenbach⁵, S. Blanche⁶, H.B. Gaspar², M. Cavazzana⁶, A.J. Thrasher².

1. Genethon, Evry, France, 2. University College London, London UK, 3. Chemotherapeutisches Forschungsinstitut Georg-Spreyer-Haus Stiftung, Frankfurt, Germany, 4. Klinikum der Johann Wolfgang Von Goethe Universitaet, Frankfurt, Germany, 5. Universitaet Zuerich, Zurich, Switzerland, 6. Assistance Publique - Hopitaux de Paris, Hopital Necker Enfants-Malades, Paris, France, 7. Genosafe, Evry, France, 8. Eufets, Idar-Oberstein, Germany, 9. Deutsches Krebsforschungszentrum (DKFZ), Heidelberg, Germany, 10. GATC Biotech, Constance, Germany

The Net4CGD European consortium project (FP7) is focused on the clinical development of gene therapy for patients with the X-linked form of chronic granulomatous disease (X-CGD). This debilitating primary immunodeficiency is caused by an absence of NADPH oxidase activity affecting phagocyte function. The disease is marked by elevated susceptibility to bacterial and fungal infections, as well as an excessive inflammatory response leading to granuloma formation. Current treatments of X-CGD are not entirely satisfactory and prior attempts at autologous gene therapy have failed. A new gene therapy strategy has been developed and is based on the use of a lentiviral vector expressing high levels of the gp91phox transgene in myeloid cells. With encouraging preclinical results, an orphan drug designation was obtained.

The Net4CGD consortium aims to develop this new orphan drug by conducting phase I/II trials in eligible patients. The Net4CGD consortium includes 7 scientific and clinical expert centers and SMEs. Since the start of the Net4CGD project, we have manufactured several lots of clinical-grade vector and a European multi-centric gene therapy trial for X-CGD has been successfully initiated. At present, 5 European centers are currently open in 4 countries to recruit adult or pediatric patients. While the clinical studies are ongoing, efforts are ongoing to develop state-of-the-art biological analyses for assessment of hematopoietic stem cell quality and patient biological response monitoring and to ensure high-quality harmonization of products and procedures to facilitate future product registration.

ODAK: the Orphan Drug for Acanthamoeba Keratitis

Ritchie Head², Antonino Asero¹, Vincenzo Papa¹, Christina Olsen², Christa van Kan³, Jolanda Overweel³, Loic Favennec⁴, Julie Gueudry⁴, Silvana Venturella⁵, Michela Salvador⁵, Prof John KG Dart⁶

1SIFI SpA, 95025 Lavinaio-Aci S. Antonio, Catania, Italy; 2Ceratum Ltd, Merseyside, CH48 8AP, UK; 3PSR Group B.V. Hoofddorp, 2132HN, Netherlands; 4University of Rouen Normandy, Rouen, France. 5RTC 00040 Pomezia, Italy. 6Moorfields Eye Hospital London EC1V 2PD.

Acanthamoeba keratitis (AK) is a rare but severe infectious disease caused by Acanthamoeba spp. a ubiquitous free living protozoan. The incidence is uncertain but probably <500 cases/year based on the EU population of about 500 million. In the absence of treatment, the disease progresses to blindness as a result of corneal vascularisation and scarring or corneal perforation. PHMB 0.02% eye drops is an unlicensed product that is empirically used to treat AK.

ODAK is an EU funded FP7 project bringing together a group of experts to develop the first safe and effective approved ophthalmic drug for the treatment of Acanthamoeba keratitis. Initially a retrospective study (Papa et al., 2014) was undertaken to evaluate the clinical outcome of patients affected by AK treated with unlicensed drugs: PHMB 0.02% used as monotherapy was shown to have a good risk to benefit ratio. In follow-up the ODAK Group has produced strong evidence, by in vitro and in vivo tests, that PHMB at concentrations ranging between 0.04% and 0.08% was much more effective than PHMB at 0.02% in treating AK (Asero et al., 2015).

Based on this preliminary data and subsequent safety data for PHMB 0.08% eye drops (Asero et al., 2016) a Phase 1 clinical trial was completed. This has shown that the same concentration is safe in healthy human volunteers (Press Release, 2016). Based on the Phase 1 clinical trial data PHMB 0.08% has been selected as the most appropriate concentration to be tested in Phase III clinical trial. In parallel to clinical development the ODAK project has engaged with patients for input in the drug development pathway, helped establish patient group activities including the rare-connect community, patient workshops, and the development of patient centric information.

Pathway analysis on the metabolome of dystrophin deficient mice and humans

Kristina Hettne¹, Ekrem Sabir¹, Kees Burger¹, Rajaram Kaliyaperumal¹, Alexandre Seye², Jesse Hemerik³, Jan van Klinken¹, Tareq Malas¹, Eleni Mina¹, Mark Thompson¹, Erik Schultes¹, Marco Roos¹, Barend Mons¹, Peter A. C. 't Hoen¹, Jelle Goeman³, Roula Tsonaka³, and Pietro Spitali¹

1) Department of Human and Clinical Genetics, Leiden University Medical Centre, Leiden, The Netherlands. 2) Profilomic, 31 rue d'Aguesseau, 92100 Boulogne Billancourt, France. 3) Department of Medical Statistics and Bioinformatics, Leiden University Medical Center, Leiden, The Netherlands

Duchenne muscular dystrophy (DMD) is a hereditary X-linked disease caused by protein truncating mutations in the DMD gene coding for dystrophin. Dystrophin-deficient mouse models (mdx) were used to study the effects of dystrophin deficiency in detail, and to enable testing of novel treatment options. The mdx model has only a mild phenotype, due to upregulation of utrophin, a dystrophin paralog that can replace dystrophin at the sarcolemma. To generate a more severe model, mice with one functional utrophin allele were generated (mdx/utrn+/-).

This study was performed on human volunteers and murine models. The main goal was to find metabolic biomarkers for disease severity by comparing the metabolome of the mdx with the mdx/utrn+/- mouse model. Additional goals were to determine and compare the effect of dystrophin deficiency on the metabolome between mice and humans, and to identify biomarkers for disease progression in mice.

The Metabolome of single time point human serum, and 5 time points plasma samples from mice were measured using LC-MS. Pathway analysis, using the global test package in R and pathway data from WikiPathways, was performed to uncover affected biological processes.

Significant differences at the pathway level were found between the wildtype and mdx model. No difference was observed between the mdx and mdx/utrn+/- models. We identified 24 similar and 7 differently influenced pathways between mice and humans, among which the well-known DMD-affected creatinine and arginine levels showed opposite changes.

Analysis is ongoing to identify biomarkers for disease progression by modelling metabolite levels over time. Transcriptomics (mice only), proteomics (human only), and lipidomics data were measured in parallel to the metabolomics data. With an integrated analysis of aforementioned datasets, dystrophin deficiency's effects can be studied on a broader molecular level, potentially allowing for the identification of novel biomarkers.

Effect of diaphragm pacing on quality of life and respiration in patients with Amyotrophic Lateral Sclerosis: Preliminary Study

Tunc Lacin¹, Pinar Kahraman Koytak², Canan Cimsit³, Cagatay Cimsit³, Emel Eryuksel⁴, Kayihan Uluc², Sait Karakurt⁴, Berrin Ceyhan⁴, Tulin Tanridag², Mustafa Yuksel¹

1 Department of Thoracic Surgery, 2 Department of Neurology, 3 Department of Radiology, 4 Department of Pulmonary Medicine

Objective: Respiratory insufficiency in amyotrophic lateral sclerosis(ALS) is managed initially by noninvasive measures. Need for other measures have evolved as respiratory related deaths predominate. We aim to detect the efficacy and safety of diaphragm pacing in managing respiratory insufficiency of selected ALS patients.

Methods: Prospectively collected data of seven patients (4 female, median age 57,7 years) with ALS who underwent diaphragmatic pacing between April and October 2014 were reviewed. Preoperative selection criteria for pacing included positive evidence of stimlatable diaphragms tested through diaphragm EMG, ultrasound and one of the four evidence of chronic hypoventilation: FVC<50%, maximal inspiratory pressure<60 cmH₂O, pCO₂>45 mmHg or saturation<%88 for 5 minutes during sleep. Patients underwent 4-port laparoscopic placement of the electrodes. The duration for pacing of each patient was set according to the need.

Results: Six patients had an uneventful course. One had a pneumothorax requiring chest tube placement. The patient who was under 20 hours of BIPAP did not benefit from pacing. She had a cardiac arrest at postoperative 3rd month. Six patients stated that they have a better sleep cycle. The patient who had tracheostomy was off the ventilator at the end of the 3rd month. In four patients, the decrease in diaphragm thickness fraction correlated with increase in symptoms. None of the patients had a pneumonia attack during the follow-up. Five patients who underwent pacing retained their respiration parameters at the end of the 1st year. One patient received tracheostomy at postoperative 8th month for progressive disease.

Conclusion: With the better understanding of the respiration dynamics in patients who underwent pacing, timing of the implantation will be precise. Diaphragm thickness fraction measurement is a reliable tool to assess disease progression. This preliminary study showed that pacing may treat respiration insufficiency in select patients by increasing the thickness of the diaphragms. As the disease progression is heterogeneous and the cohort size is small, it is assertive to state that system may prolong survival by delaying ventilator dependence.

Clinical Diagnostics of Neuronal Ceroid Lipofuscinoses on Dry Blood Spots: Development of New Cathepsin Substrates for Mass Spectrometric Determination

Stefan Maeser¹, Hendrick Rusche¹, Laura Ion^{1,2}, Brindusa-Alina Petre^{1,2}, Thomas Braulke³, Alfried Kohlschütter³, Angela Schulz³, Michael Przybylski¹

1) Steinbeis Centre Biopolymer Analysis and Biomedical Mass Spectrometry, Rüsselsheim, Germany; 2) I. A. Cuza University, Department of Chemistry, Iasi, Romania; 3) University Hospital Hamburg-Eppendorf, Department of Pediatrics, Hamburg, Germany

The loss of enzyme activity is a characteristic feature of lysosomal storage diseases (LSDs), a group of ca. 50 metabolic disorders such as mucopolysaccharidoses, sphingomyelinoses, and neuronal ceroid lipofuscinoses. Reduced enzymatic activity causes substrate accumulation in lysosomes, which can cause to severe disease symptoms and finally death. For several LSDs treatment has become available by enzyme replacement therapy (ERT), however, successful ERT is critical to start early which renders clinical diagnostics of key importance. We have developed new types of substrate derivatives based on alkyl-umbelliferone analogs, that enable fluorimetry and multiplex mass spectrometry (MS-MRM) using the same substrates. Here we describe specific and sensitive diagnostics on dry blood spots (DBS) for neuronal ceroid lipofuscinoses, by simultaneous fluorimetric and MS-MRM analysis.

Neuronal ceroid lipofuscinoses (NCLs) are a group of neurodegenerative disease in childhood, characterized by vision loss, dementia, epilepsy, and physical decline and early death of patients with incidence rate of about 1:30000 live birth.

TRANSPLANT-CHILD-ERN, an European strategy to attend “the secondary rare disease” induced by Paediatric Transplantation

López-Granados E¹, Pérez-Martinez A², Hernandez F³, Santamaria M³ on behalf of ERN-TRANSPLANT-CHILD

1 Clinical Immunology Department, 2 Paediatric Haemato-Oncology Department, 3 Paediatric Surgery Department. University Hospital La Paz, Madrid, Spain

Paediatric Transplantation (PT), solid (SOT) and hematopoietic Stem-cell(HSCT) are extremely rare and high specialized procedures needed to cure several severe rare paediatric diseases. Transplanted children though shift their primary disease to a life-long chronic condition or “secondary rare disease”, mostly imposed by the necessary long-term treatment regimens as immunosuppression to avoid rejection. In addition low case volume is being associated with worse surgical outcomes.

Although each type of transplant requires specific individual training requirements and technical variation, graft tolerance/rejection immune phenomenon, clinical phases(pretransplantation, transplantation and postransplantation) and many clinical events are common. An European Reference Network-(ERN) focus on PT, TRANSPLANT-CHILD-ERN has been created to potentiate the highest quality treatment across Europe by improving experience and knowledge in PT to the most up to date. This ERN will focus on a successful outcome both for the patient, caregivers and his/her family. These new cross-border healthcare structures can improve the quality of care received.

Developing an international network of rare diseases biobanks within the EuroBioBank/RD-Connect platform

Chiuhui Mary Wang¹, David van Enckevort², Roxana Merino-Martinez³, Robert Reihls⁴, Heimo Müller⁴, Estrella Lopez-Martin⁵, Manuel Posada de la Paz⁵, Marina Mora⁶, Petr Holub⁷, Stefano Benvenuti¹, Anna Ambrosini¹, Leopoldo Laricchia Robbio¹, Hanns Lochmüller⁸, Lucia Monaco¹

(1) Fondazione Telethon, Milan, Italy; (2) Department of Genetics, University Medical Center Groningen, Groningen, The Netherlands; (3) Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Solna, Sweden; (4) Institute of Pathology, Medical University of Graz, Graz, Austria; (5) Institute of Rare Diseases Research, IIER, ISCIII & CIBERER, Madrid, Spain; (6) Neuromuscular Diseases and Neuroimmunology Unit, Fondazione Istituto Neurologico C. Besta, Milan, Italy; (7) BBMRI-ERIC, Graz, Austria; (8) University of Newcastle, Newcastle upon Tyne, UK

Purpose: Access to high quality human biological materials is crucial for research in rare diseases (RD). It underpins the understanding of RD pathogenesis, development of diagnostic tools, identification of therapeutic targets and testing of therapeutic response. One goal of the European FP7-funded program RD-Connect is to create a network of RD biobanks and a comprehensive catalogue of high quality biological samples connected to patient registries and databases of -omics data, to facilitate sample access and promote data integration for maximum exploitation of valuable RD biological resources and data.

Methodology: The RD-Connect biobank component engages expertise of IT developers, biobank managers and network coordinators across Europe. Besides the development of the IT infrastructure, emphasis is placed on data privacy and workflows related to biomaterials sharing and clinical information. Collaborations with international partners ensure global interoperability, as well as input from patient representatives for ethical, legal and social issues (ELSI).

Results: At the fourth year of the six-year program, RD biobanks are actively invited to participate via a dedicated interface called RD-Connect ID-Card, and share their sample data via the RD-Connect Sample Catalogue, based on the MIABIS 2.0 standard to share biobank data. In addition to the sample catalogue, the RD-Connect platform offers biobanks streamlined workflows and training materials. EuroBioBank, the first RD biobank network in Europe founded in 2001, recently agreed to act as the de facto biobank network of RD-Connect. This partnership signifies the integration of EuroBioBank's sample catalogue into RD-Connect's, and the development of bilateral synergy via the implementation of workflows, sharing of established biobanking standard operating procedures and compliance to the latest ELSI principles developed and recommended by RD-Connect. The RD-Connect Sample Catalogue promotes interoperability with other networks such as BBMRI-ERIC. A close link is maintained at both network and operational levels to ensure long term sustainability.

In situ differentiated adipose tissue-derived multi-lineage progenitor cells could be remedy for rare diseases with liver dysfunction

Hanayuki Okura, Ph.D, Mitsuko Morita, BS. Maiko Fujita, BS. Kyoko Naba, BS. Nozomi Takada, BS. Akihiro Ichinose, MD.Ph.D, and Akifumi Matsuyama, MD. Ph.D.

National Institutes of Biomedical Innovation, Health and Nutrition. Platform of Therapeutics for Rare Disease

Purpose: We have reported that adipose tissue-derived multi-lineage progenitor cells (ADMPCs) could differentiate into hepatocyte-like clusters in vitro. This differentiation protocol is mimicked the environment of liver parenchyma. We supposed whether ADMPCs should differentiate into hepatocytes in situ and then show feasibility as the novel therapy for rare diseases with liver dysfunction.

Methods: ADMPCs have been obtained as reported previously (Okura et al. Tissue Eng Part C Methods. 2011.). GM1-gangliosidosis model mice as a representative example of lysosomal storage disease or the Watanabe heritable hyperlipidemic (WHHL) rabbit were used as the model for rare disease with liver dysfunction and the animals were transplanted of ADMPCs or GFP-ADMPCs via portal vein. After transplantation, the differentiation in situ of ADMPCs into hepatocyte-like cells were examined with immunohistochemistry. The recoveries of diseased animals were estimated by serum beta-galactosidase levels in GM1-gangliosidosis model mice, and serum cholesterol levels and LDL turnover study in the WHHL rabbits.

Results: The ADMPCs were integrated into the hepatic parenchyma both of mice and rabbits and co-expressed GFP and hepatocyte markers such as albumin, indicating that the cells were reprogrammed into hepatocytes-like cells in situ. In GM1-gangliosidosis model mice, the serum levels of GLB1 were recovered and the results indicated the ADMPCs transplantation could improve GLB1 deficiency. In WHHL rabbit, which is the animal model of familial hypercholesterolemia, transplantation of ADMPCs resulted in a significant reduction of serum total- and LDL-cholesterol levels. 125I-LDL turnover study showed significant improvement in the rate of LDL clearance.

Conclusion: Transplantation of ADMPCs must be one of the useful therapies for FH and lysosomal storage disease, as the representatives of rare diseases with liver dysfunction. In situ differentiation therapy using ADMPCs might be a universal therapeutic agent for many kinds of rare diseases with liver dysfunction including monogenic ones.

VISION-DMD: Advancing clinical development of the innovative orphan drug Vamorolone for DMD

Olsen, C.¹; Guglieri, M.²; Clemens, P.³; Athanasiou, D.⁴; Vroom, E.⁴; Hoffman, E.⁵; Morgenroth, L.⁶; Haberlova, J.⁷; Bushby, K.²; Demotes-Mainard, J.⁸; Davis, R.². Head, R.¹

1 Ceratium Limited, UK; 2 John Walton Muscular Dystrophy Research Centre, UK; 3 University of Pittsburgh School of Medicine and VA Pittsburgh Healthcare System, USA; 4 United Parent Project Muscular Dystrophy, Netherlands; 5 ReveraGen BioPharma, UK/USA 6 TRINDS, USA; 7 Fakultni Nemocnicev Motole; 8 ECRIN, France;

VISION-DMD is an international collaboration aiming to advance clinical development of the orphan drug Vamorolone (also known as VBP15) as a new therapy to revolutionise care for all patients with Duchenne muscular dystrophy (DMD). DMD is an incurable, rare muscle wasting disease; boys progressively weaken, lose ambulation and death occurs by early adulthood. Corticosteroids are widely recognised to increase muscle strength and delay disease progression but global acceptance as standard of care is variable due to severe side effects.

Vamorolone is an innovative steroid-like drug designed to retain or better Corticosteroids efficacy and improve membrane stabilization with reduced or no side effects. Following positive preclinical and Phase 1 results and based on FDA and EMA advice, VISION-DMD will undertake a Phase 2 registration directed clinical programme aimed at an affordable therapy for this disease by 2020.

The Phase 2a study will demonstrate the safety and tolerability of ascending doses of Vamorolone in ambulant DMD boys aged 4 to 7 years old. This study started recruitment in July 2016 and participating countries include US, Canada, UK, Sweden, Israel, and Australia.

The Phase 2b study will demonstrate the efficacy and safety of two doses of Vamorolone in ambulant DMD boys. Phase 2a and 2b studies will be followed by extension studies for long term safety and efficacy data collection.

The study sponsor is Reveragen Biopharma working with a consortium of leading teams in the neuromuscular field including Newcastle University's John Walton Muscular Dystrophy Research Centre (UK), the US based Cooperative International Neuromuscular Research Group (CINRG) and University Hospital Motol (Czech) and clinical trial expertise from the European Research Infrastructure Consortia (ECRIN) in France and the United Parent Projects Muscular Dystrophy (UPPMD) will ensure DMD patient groups involvement. Ceratium Ltd (UK) manage the project and valorisation of project results.

RD-Connect platform: A useful tool for the undiagnosed rare diseases program SpainUDP

Estrella López¹, Steven Laurie², Sergi Beltrán², Eva Bermejo¹, Manuel Hens¹, Beatriz Martínez-Delgado³, Gema Gómez-Mariano³, F. Javier Alonso³, Sara Monzón⁴, Isabel Cuesta⁴, Rachel Thompson⁵, John Dawson⁵, Hanns Lochmuller⁵, Ivo Gut² and Manuel Posada¹

1Institute of Rare Diseases Research, IIER-ISCIII & Centre for Biomedical Network Research on Rare Diseases, CIBERER (Madrid, Spain), 2National Center for Genomic Analysis, CNAG & Centre for Genomic Regulation, CRG (Barcelona, Spain), 3Institute of Rare Diseases Research, IIER-ISCIII (Madrid, Spain), 4Bioinformatics Unit, ISCIII (Madrid, Spain), 5John Walton Muscular Dystrophy Research Centre, Institute of Genetic Medicine, Newcastle University (Newcastle, United Kingdom)

Purpose: Description of the usefulness of the RD-Connect platform for SpainUDP (Spanish Undiagnosed Rare Diseases Program), which has been implemented by the Institute of Rare Diseases Research (IIER) of the Institute of Health Carlos III.

Methods: SpainUDP aims to offer a multidisciplinary approach to those patients who have long sought a diagnosis without any success. As IIER is a full member of RD-Connect, it is contributing with their undiagnosed cases to the platform of this project, fulfilling all the international standards for these purposes. Data from sequencing experiments is processed with a standard pipeline and detailed phenotypic information is connected to genetic information.

Results: In a first phase of the approach, cases sent to SpainUDP are required to provide all clinical information available. All documents are carefully reviewed by the IIER's professionals and a close collaboration with local healthcare services is established. If actions carried out during this phase are not enough to achieve a diagnosis, genetic analyses are performed and genotype-phenotype correlation is managed by using the RD-Connect platform.

Raw genomic data from sequencing experiments is realigned and reprocessed through a standard pipeline and held in the central RD-Connect database. The processed data is available for online analysis through a user-friendly interface and it is combined with phenotypic information by using a HPO-based software solution called PhenoTips. Also, the system allows to push data from PhenoTips to Phenome Central, a central repository that facilitates the matching of cases with similar clinical and genotypic profiles.

Conclusions: RD-Connect platform enables a comparison of patient data from SpainUDP across multiple projects submitting data to the platform, as well as an analysis with sophisticated bioinformatic tools. In addition, the possibility of pushing data to Phenome Central allows to communicate specific case details within larger shared international networks. Furthermore, RD-Connect is participating in the Matchmaker Exchange initiative, a federated platform

X-linked nephrogenic Diabetes Insipidus: Potential Novel Strategies for Treatment

Giuseppe Procino¹, Serena Milano¹, Monica Carmosino², Andrea Gerbino¹, Massimo Dal Monte³, Giorgia Schena², Lisa Mastrofrancesco¹, Piero Portincasa⁴, Paola Bagnoli³, Maria Svelto¹

1Department of Biosciences, Biotechnologies & Biopharmaceutics, University of Bari, Bari, Italy; 2Department of Sciences, University of Basilicata, Potenza, Italy; 3Department of Biology, University of Pisa, Pisa, Italy; 4Clinica "A. Murri", Department of Biomedical Sciences & Human Oncology, University of Bari Medical School, Bari, Italy;

X-linked nephrogenic diabetes insipidus (X-NDI) is a rare disease caused by inactivating mutations of the vasopressin (AVP) type 2 receptor (AVPR2) gene. Loss of AVPR2 function downregulates the water channel AQP2 in the kidney collecting duct (CD), prevents its plasma membrane expression in the presence of circulating AVP and dramatically impairs the kidney concentration ability. In patients this results in severe polyuria and risk of dehydration. At present, no specific pharmacological therapy exists to cure X-NDI.

In the last years we explored a number of strategies to bypass inactivation of the AVPR2 and restore a sufficient amount of AQP2 at the apical plasma membrane of renal cells. These included treatment with the cholesterol-lowering drugs statins and activation of G proteins-coupled receptors (GPCR) activating the cAMP pathway that promotes AQP2 synthesis and plasma membrane expression.

We previously reported that statins improve the symptoms of X-NDI in the animal model of the disease. Moreover, in hypercholesterolemic patients, statins induced a rapid and significant increase of AQP2 at the cell plasma membrane, reduced the urine output and increased urine osmolality. These results indicate that further investigation on the possible role of HMG CoA reductase inhibitors may improve the efficacy of the current X-NDI treatment.

We also found that the GPCR secretin receptor is functionally expressed in the kidney CD cells. In X-NDI mice, chronic infusion with secretin significantly increased AQP2 levels in the CD. Strikingly, combination of secretin and statin greatly reduced the polyuria in these mice.

Recently we found that the GPCR 3-adrenoreceptor (3AR) is expressed in most of the nephron segments that also express the V2R. In X-NDI mice pharmacological stimulation of 3AR promoted water and electrolytes reabsorption in the kidney, thus promoting a potent antidiuretic effect. Taken together, these findings open new perspectives for the pharmacological treatment of X-NDI.

Molecular characterization of antibody epitopes for repositioning immune reactivity in enzyme replacement therapy of lysosomal storage diseases

Stefan Maeser¹, Zdenek Kukacka¹, Filippo Santorelli², Anna Maria Papini³, Michael Przybylski¹

1Steinbeis Centre for Biopolymer Analysis and Biomedical Mass Spectrometry, Rüsselsheim/Germany; 2Fondazione Stella Maris, Pisa/ Italy; 3Department of Peptide Chemistry and Biology, University of Florence /Italy

Enzyme replacement therapy (ERT) has been successfully developed for the treatment of several lysosomal storage diseases (LSDs), such as Gaucher (GD), Fabry (FD) and Pompe (PD) Disease. While effective for a number of LSDs, severe limitations are caused by the formation of neutralizing antibodies, which may be associated with allergic reactions, from mild symptoms to life threatening complications including anaphylactic shock. The formation of antibody-enzyme complexes can prevent the uptake of enzymes into lysosomes and diminish the efficacy of ERT. At present there is poor understanding of the mechanisms of immune reactions and antibodies upon ERT, and there is currently no approach to modulate or prevent immune reactivity and impairment of therapy.

Antibodies formed upon ERT bind to a defined epitope region of the lysosomal enzyme. For molecular identification and affinity determination of epitopes, highly specific and sensitive methods have been developed by the combination of biosensor and mass spectrometry (MS) tools. The SPR-biosensor-MS analysis has been successfully applied to the epitope elucidation and affinity characterization of antibodies against alpha-galactosidase (Fabry), and chemical synthesis of the epitope, aGal(309-322). The epitope (309-322) was obtained by solid phase peptide synthesis (SPPS) and showed high affinity binding to the antibody (ca. 30 nM). The identification of epitope(s) of lysosomal enzymes to an antibody is opening a new concept to hyposensitizing patients from allergic reactions, using synthetic epitope peptides, and to repositioning therapeutic efficiency of ERT.

Facilitated transmembrane transport, a viable therapeutic approach for channelopathies?

Roberto Quesada, Israel Carreira, Marcin Mielczarek, María García-Valverde, Olga Zegarra, Oscar Morán, Angel del Pozo, Laszlo Puskas, Anette Mullertz, Manfred Fey and Daniel Bachiller

Universidad de Burgos

Facilitated transmembrane anion transport is an emerging topic in supramolecular chemistry. Ionophores are small lipophilic molecules capable of facilitating the transmembrane transport of ions.¹ Small molecule anion transporters are able to disturb the normal ionic balance across cell membranes inducing cell death, being this approach useful for killing cells with an abnormal growth, such as tumor cells, or to eliminate harmful microorganisms.² On the other hand, these molecules could have potential in the treatment of conditions derived from the defective regulation of chloride and bicarbonate transport such as Cystic Fibrosis for instance.

In order to be useful as novel therapeutics for Cystic Fibrosis a subtle balance between toxicity and transmembrane transport activity should be achieved. Nevertheless, the knowledge of the requirements for designing effective anion transporters remains poor, and identification of active derivatives is mostly based on trial/error methods. Recently, we have performed a QSAR study of the transmembrane anion transport activity of different anion transporters, aimed to shed light on the structural design requirements to successful anion carriers.³ Our efforts to implement assay to test the usefulness of these compounds as chemotherapeutics for the treatment of channelopathies will be presented.

- 1) Alfonso I.; Quesada, R. *Chem. Sci.*, 2013, 4, 3009.
- 2) V. Soto-Cerrato, P. Manuel-Manresa, E. Hernando, S. Calabuig-Fariñas, A. Martínez-Romero, V. Fernández-Dueñas, K. Sahlholm, T. Knöpfel, M. García-Valverde, A. M. Rodilla, E. Jantus-Lewintre, R. Farrás, F. Ciruela, R. Pérez-Tomás and R. Quesada, *J. Am. Chem. Soc.*, 2015, 137, 15892
- 3) N. J. Knight, E. Hernando, C. J. E. Haynes, N. Busschaert, H. J. Clarke, K. Takimoto, M. García-Valverde, J. G. Frey, R. Quesada, P. A. Gale, P. A. *Chem. Sci.*, 2016, 7, 1600.

Orphanet and the Orphanet Rare Disease Ontology: Facilitating the interoperability of data in the field of rare diseases

A. Olry, M. Hanauer, V. Lanneau, S. Demarest, C. Rodwell and A. Rath

INSERM, US14 – Orphanet, Plateforme Maladies Rares, 96 rue Didot, 75014, Paris, France

Statement of purpose: Many different types of data surround rare diseases, with many different terminologies for each type of data. Data is scattered in different countries, communities and contexts, without a single point of entry. An interoperability backbone integrating genomics, phenomics and functioning data around a standardised nomenclature of rare diseases in a structured, computable way is essential. When integrated with other resources, this will constitute a common language and resource for achieving interoperability.

Methodology: Orphanet is the reference resource for information and data on rare diseases and orphan drugs. Orphanet derives from its knowledge base an ontology of rare diseases (Orphanet Rare Disease Ontology), information on rare diseases (Orphanet website www.orpha.net) and data on rare diseases (www.orphadata.org). Orphanet maintains a unique nomenclature and inventory of rare diseases mapped with resources as OMIM, ICD10, MeSH and UMLS, annotation of diseases with International Classification of Functioning (ICF-CY) derived terms, and a multi-hierarchical classification of diseases elaborated using existing published expert classifications. In the Orphanet nomenclature each entry (group, disorder, subtype) is given a unique, stable ORPHA number (or Orphacode), as well as a preferred term and as many perfect synonyms as necessary. The nomenclature is translated into 9 languages. Rare diseases in Orphanet are also annotated with HPO terms, a description of the phenotypic expression of each RD, together with data on frequency of occurrence of phenotypes in the patient population.

Summary of results: Orphanet, its nomenclature of rare diseases and ontology are key interoperability backbone components for rare diseases. ORDO is the reference ontology in this field, serving to link data, ease interoperability between data sources, and act as an essential pivot between the fields of care and research. Its impact in facilitating data sharing led to Orphanet and ORDO receiving official IRDiRC Recognized Resource status.

Novel therapeutic perspectives for sarcoglycanopathy: rescue of folding-defective mutants by means of protein folding correctors

Dorianna Sandonà¹, Roberta Sacchetto², Elisa Bianchini^{1,3}, Marcello Carotti¹, Chiara Fecchio¹, Chiara Gomiero²

(1) Department of Biomedical Sciences, University of Padova; (2) Department of Comparative Biomedicine and Food Science, University of Padova, (3) Aptuit, Verona, Italy

Sarcoglycans (SG) are glycosylated proteins (alfa-, beta-, gamma- or delta-SG) forming a key structural complex, essential for the sarcolemma integrity of striated muscles during contraction. In sarcoglycanopathies, it is well known that defects in any one of the sarcoglycan genes lead to the strong reduction or even the loss of the SG-complex. Most of the reported cases are due to missense mutations originating a full length but folding-defective proteins. We proved 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 deliver to proteasomal degradation the folding-defective mutants. This results in secondary loss of the wild-type partners. We also demonstrated that many missense mutants retain their function as the entire complex can be properly rescued by reducing the mutant degradation.

These findings opened new perspectives for therapy of this neglected disease allowing to design small molecule-based approaches aimed either to inhibit sarcoglycan mutants degradation, or to help their folding so that, skipping disposal, they can assemble and traffic at the proper site of action. We tested several small molecules known as CFTR correctors which were effective in recovering different mutants of alpha-sarcoglycan in cellular models and, notably, the whole SG-complex in primary myotubes from a patient suffering of alfa-sarcoglycanopathy.

To confirm in vivo this successful strategy we need animal models expressing folding-defective sarcoglycans. As the SG-null mice are unsuitable to our purposes, and considering the large number of reported sarcoglycan missense mutants, our aim is now the generation and characterization of novel alfa-sarcoglycanopathy models by the transduction of the null mice with rAAVs (recombinant adeno associated viruses) expressing different missense mutants of the human alfa-SG. We are confident that, once fully characterized, these animals will become suitable sarcoglycanopathy models to test in vivo our therapeutic strategy.

Current challenges on the creation of european-wide rare diseases cohorts

Pedro Sernadela and José Luis Oliveira

University of Aveiro

Combining rare diseases information resulting from clinical and research resources is a vital process to improve patient treatments, and to build the most suitable tools for personalised medicine. However, produce rare diseases adequate cohorts is hard to achieve. Both phenotypic information and final diagnosis have to be derived from the clinical examination, genetic, histo-pathological, and other laboratory tests and radiological images, among some other specific sources, which are all challenging due to their heterogeneity and complexity. This scenario brings challenges regarding the adoption of common data elements and makes the standardization of the primary sources of information an important issue.

Although there is an overall desire in the European community to increase the harmonisation behind rare diseases resources, it is important to highlight that the translation process from the real patient clinical status to the information storage is a critical point for data quality and reliability. In this way, these translational processes imply some potential risk of introducing some bias information. Currently, several European organizations are publishing common data element models in order to solve the interoperability problem among different databases. Although these efforts ensure interoperability within the selected domain, interoperability across application domain boundaries is not automatically possible. Though, the active translational dialogue among the actors in the clinical and research domains is important to both stimulate the use of standards. Finally, convincing data owners of the true value in sharing their data is a delicate task. In addition to the privacy and security issues, data owners fail to realize the incentives underlying the sharing of their data. To overcome this in the future, financing projects should include clear guidelines to mandate the anonymous sharing of data for research purposes. Including these political policies would shed a new light on the benefits of sharing data to a broader community.

NMR voxel-based morphometry and functional analysis as neural correlates of neuropsychological dysfunction in DM1

Siciliano, G., Baldanzi, S., Cecchi, P., Simoncini, C., Ricci, G., Fabbri, S., Lorio, R., Bevilacqua, F., Cosottini, M., Angelini, C.

University of Pisa Clinical and Experimental Medicine 56126 Italy, University of Pisa Clinical and Experimental Medicine Pisa Italy, Azienda Ospedaliero Universitaria Pisana Neuroradiology Unit Pisa Italy, IRCCS San Camillo Lido Venice Italy, University of Pisa Translational Research and of New Surgical and Med Pisa Italy

The variable phenotypic spectrum of myotonic dystrophy type 1 (DM1) includes central nervous system with mild to severe involvement. Our aim was to investigate grey matter (GM) and white matter (WM) structural alterations, as well as brain functional activation, by nuclear magnetic resonance (NMR) in a sample of adult-onset DM1 patients and to evaluate relationship with clinical and cognitive variables. Thirty DM1 patients underwent neuropsychological investigation and brain 3T-MRI protocol. GM and WM changes were evaluated calculating brain parenchymal fraction (BPF), voxelbased morphometry (VBM), white matter lesion load (LL% and Fazekas scale) and tract based spatial statistical (TBSS).

Patients showed main impairment in executive and amnesic domains with visuospatial involvement, significantly related to BPF. VBM revealed clusters of widespread GM reduction and TBSS revealed areas of decreased fractional anisotropy (FA) and increased radial diffusivity (RD), mean diffusivity (MD) and axial diffusivity (AD) in patients compared to a group of matched healthy controls. Multiple regression analysis showed areas of significant negative relationship between atrophy in the left temporal lobe and verbal memory, and between RD and mnesic and visuo-spatial cognitive domains. Our data show extensive atrophy in DM1 over both cerebral hemispheres. Global atrophy, expressed with BPF, correlated with impaired executive and visuospatial abilities. TBSS results indicate that the involvement of normal appearance WM beyond the signal changes detected with conventional MR imaging (Fazekas scale and LL%), was associated to neuropsychological deficit. Finally, brain functional NMR activation showed fronto-temporal correlates of anosognosia. These data suggest that disrupted complex neuronal networks can underlie cognitive-behavioural dysfunctions in DM1.

Moving Forward Health Technology Assessment and Appraisal of Orphan Drugs

Rumen Stefanov, Georgi Iskrov

Department of Social Medicine and Public Health, Faculty of Public Health, Medical University of Plovdiv, Plovdiv, Bulgaria // Institute for Rare Diseases, Plovdiv, Bulgaria

Reimbursement decision-making on orphan therapies tends to be one of the most complicated health policy tasks nowadays. Classic paradigm of health technology assessment (HTA) seems unable to find a balance between the competing interests of patients, health care providers, payers and industry. There is a strong need for orphan drug-tailored decision support tools that could set the scene for timely and adequate access to newly approved rare disease therapies.

Multi-criteria decision analysis (MCDA) is believed to have a significant potential in value-based reimbursement. MCDA enables exploration of stakeholders' preferences and explicit organisation of a range of criteria on which real-world decisions are made.

We conducted a mixed-method study to create an MCDA model for assessment and appraisal of orphan drugs. Our value assessment model is a result of two stakeholder-representative surveys and a focus group discussion, all held in Bulgaria.

Standard HTA approaches are dominated by clinical and cost effectiveness criteria. We found, however, disease severity and burden to be the most important decision considerations in orphan drug appraisal. Strength of evidence proved to be a crucial criterion as well, as evidence is used not only to shape reimbursement decision-making but also to lend legitimacy to policies pursued.

Progress and innovation in medicine should correspond to a greater value for patients, health-care systems and societies. Research on MCDA feasibility and integration to HTA could efficiently address this problem.

International cooperation of the Center for Clinical and Translational Research, Kyushu University

Daisuke Sugiyama and Yoichi Nakanishi

Center for Clinical and Translational Research, Kyushu University, Japan

The Kyushu University Center for Clinical and Translational Research (CCTR) established the International Cooperation Unit in July 2014. The objective of the unit is to exchange seeds developed by academia both inside and outside of Japan, to import and export the most suitable seeds to meet the needs of each region and to foster a network of international collaborators. There are 4 methods by which we aim to achieve these objectives: 1) To establish an international network through the conduction of site visits with potential collaborators, 2) To bring medical innovators from the Asia Pacific Region through the Japan Medical Innovation tour, 3) To invite teaching staff from high level organizations to educate human resources at Kyushu University, and 4) To establish and foster systems to encourage young scientists to become medical innovators through the EDGE program and other initiatives.

Currently we divided infrastructure of our center into 2 departments; the Department of Clinical Research and the Department of Translational Research. Here, we aim to introduce the strategies implemented at Department of Translational Research at the CCTR with particular attention to international corporation.

RD-Connect ID-Cards of biobanks and registries: making RD data Findable, Accessible, Interoperable and Reusable

Torreri P¹, Gainotti S¹, De Paulis F¹, Kodra Y¹, Carta C¹, Wang M², Monaco L², Reihls R³, Mueller H³, Taruscio D¹

Affiliation: (1) Istituto Superiore di Sanità, Rome, Italy (2) Telethon Foundation, Milan, Italy (3) Medical University of Graz, Graz, Austria

Purpose: Data on RD patients, including registry data and availability of bioresources are collected and stored in different biobanks and databases, and they are usually not easily findable, accessible, interoperable and reusable (FAIR). The RD-Connect ID-Cards aims at concentrating sparse information on RD patients in one unique source by showing the number of samples/cases included in biobanks and registries, providing a first gateway towards more intense data sharing, and increasing the integration of biobanks and registries.

Methods: Each ID-Card consists in a webpage with information on a biobank or registry, including contact information, aggregated data and metadata data such as accessibility and standards for the resources, standard operating procedures, documents for the informed consent, case report form. Importantly, the “disease matrix” (DM) section provides information on the number of patient cases and biological samples held for each RD, with its associated Orphacode, OMIM and ICD10 codes.

Results: Currently RD-Connect ID-Cards is populated with aggregated data for more than 170 registries and 14 biobanks, including more than 834000 cases.

Registries from all countries worldwide are participating, with a strong contribution from USA, followed by Italian, French, German, Spanish and UK registries and most of them belong to a network of registries; National programs or platforms. ID-Cards from EuroBioBank members are included, and their biosample collection data are being imported to the RD-Connect Sample Catalogue.

Interestingly, the most prevalent group of diseases represented in the registries and biobanks is rare neurological disorders.

Modeling of rare diseases in *Drosophila melanogaster*: opportunities and challenges

Victor Alfred, Ilaria Busi, Emiliana Tognon, Elena Morelli and Thomas Vaccari

IFOM, The FIRG Institute of Molecular Oncology via Adamello 16 20139 Milano, Italy

Purpose: Sustainable modeling of rare diseases poses outstanding challenges: Big data approaches, yielding large amounts of sequence data, require fast and effective functional screening of gene variants. Patients are few, limiting chances to functionally characterize newly-identified mutations. Cell and biochemistry based approaches are scalable and inexpensive, but they are not very informative and rely on previous knowledge of gene function, while modeling in mice is slow and expensive. Innovative methods of functional investigation of gene function that are informative, cheap and fast are clearly needed and constitute a current bottleneck in establishing modern personalized medicine approaches for rare diseases.

Methodology and results: We propose the establishment of an innovative pipeline of intervention based on combing large amounts of sequencing and clinical history data from patients with undiagnosed rare diseases to identify those cases where follow up with the production of a model of the disease in *Drosophila melanogaster* might be beneficial. These would be cases in which a clear homolog exists and clinical history offers phenotypic hints. Loss of function mutations and dominant active or negative mutations can be easily modeled using CRISPR/Cas9 and more traditional mis-expression approaches. We will provide examples of 4 disease genes, associated to a congenital disorder, a rare lysosomal storage disease and two neurodegenerations, modeled and functionally characterized in such a way. More advanced CRISPR/Cas9 knock-in and point mutants will be soon implemented in our pipeline, allowing the generation of more precise patient avatars. Importantly, our approach is fast and cheap (<3months and 300€/mutation), easily scalable and amenable to rapidly screening potential existing inhibitors and compounds. Our strategy establishes a solid first line of investigation of selected uncharacterized mutations of undiagnosed rare disease that will complement and speed up existing precision medicine approaches.

Propositions of new financing modalities for analyses of medical biology specific for the diagnosis and follow-up of rare diseases

Vandeveldel N.M., Rare Diseases Working Group of the service of Quality of Medical Laboratories of the WIV-ISP, Van De Walle P.

Scientific Institute of Public Health

Purpose: In the context of the Belgian Plan for Rare Diseases (RD's), we performed an inventory of rare diseases for which the reimbursement of analyses of medical biology remains insufficient and has developed new financing modalities for priority analyses in close collaboration with the Belgian clinical experts and healthcare authorities.

Methodology: The work was based on the 3 main steps of the RAND/UCLA appropriateness method: data collection; exchange of opinions between experts in order to propose new strategies to improve medical care; implementation/evaluation of the new strategies (Fitch et al,2001). For that purpose, clinical data was collected (May-December 2015) from 210 Belgian laboratories of medical biology in order to list the unreimbursed analyses prescribed in Belgium in the context of RD's. Secondly, a working group composed of experts from the Belgian reference centers for RD's was set-up in order to select analyses that should be priority funded and to determine some additional needs required for the realization of some priority analyses. On that basis, cost-benefits studies were performed in order to propose financing modalities for the priority analyses.

Results: 64 unreimbursed priority analyses were identified. They belong to the biochemistry (59.4%), coagulation/hemostasis (23.4%), immuno-hematology/non-infectious serology (7.8%), hematology (4.7%), hormonology (4.7%) domains. These analyses correspond to ~600 ORPHANET diseases codes (mainly rare metabolic diseases). The realization of these analyses is highly centralized (61% of them are performed in ≤ 3 Belgian laboratories). 11% of priority analyses are outsourced abroad (currently unavailable in Belgium). Three types of financing modalities were proposed: reimbursement nomenclature codes (39 analyses; annual budget : 448.500€); financing of Belgian Reference Laboratories (RL's; 18 analyses; annual budget: realization of analyses [53.500€], external quality evaluations [25.000€], accreditation [15.000€], administrative tasks [75.000€], RL's management [23.500€]) and collaborations with ≤ 5 foreign laboratories for analyses unavailable in Belgium (7 analyses; annual budget : 11.500€).

A Briefing of the National Rare Diseases Registry System of China (NRDRS)

Mengchung Gong and Shuyang Zhang

National Rare Diseases Registry System of China (NRDRS)

China has just launched the first nation-wide patient registry system for rare diseases, the National Rare Diseases Registry System of China (NRDRS), as one of the key strategic directions in the development of precision medicine. As an essential platform to promote the rare diseases research in China, NRDRS, led by Professor Zhang Shuyang from Peking Union Medical College Hospital (PUMCH), incorporates the resources from 20 leading medical institutes of China and provides informatics system for more than 50 rare diseases and disease groups. Based on this system and the funding from central government, a group of experts from clinical medicine, genetics, informatics, ethics and policy making made the alliance to build a clinical service system, including on-site care, emergency care, referral and transferal services, to rare diseases patients and a registry system, incorporating epidemiological, clinical, socio-economical, genomics and metabolomics data, for rare diseases patients all over China. From 2016 to 2020, the target is to accomplish registry of 50,000 cases and WES/panel sequencing of no less than 10,000 cases/trios. The reliability and accuracy of the data is guaranteed by the standards of registry and sampling, including LOINC, ICD and Chinese HPO, and a centralized sequencing and interpretation platform. With the integrated phenome-genome database, innovative medical informatics technologies, including phenome-wide association study, will be performed to explore the real-world evidence about rare diseases in Chinese population.

A series of large scale cohort studies, focusing on heart, lung, kidney, the endocrine system, blood, skin, skeleton, the neurological system and those in children, will be carried out on the basis of the registry system to conclude the characteristics of clinical manifestation and pathogenesis in China, and to support healthcare planning, policy making and healthcare economics evaluation systemically. A biobank linked to the clinical database will be built centrally. With the help of biomedical informatics, clinical phenotypic and biological omics data can be integrated to indicate the mechanism of rare diseases, discover the novel diagnostic and prognostic biomarkers, develop the orphan drugs and other therapeutics, leading to the improvement of clinical outcomes and life quality of the patients. As a national strategy for enhancing the development of medical sciences and the improvement of population health in China, NRDRS and its cohort studies will bring improvement in both clinical care and scientific research. This platform is open to domestic and international collaboration and will provide support in communication between experts, organization of patient recruitment, data aggregation and analysis and collaboration on the patient advocacy for rare diseases worldwide. Peking Union Medical College Hospital and NRDRS now welcome cooperation with partners worldwide to improve patient care, escalate medical sciences, innovate diagnostics and therapeutics and impact policy making and, most importantly, promote the beneficence of rare diseases patients.

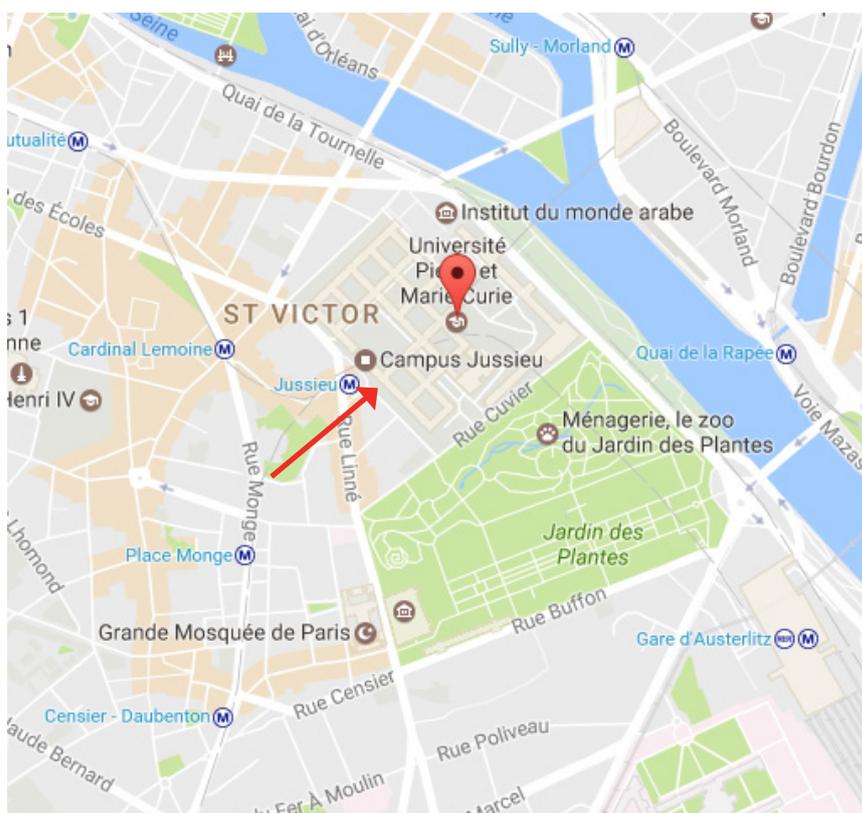
Practical Information

Venue

Conference Center
Université Pierre-et-Marie-Curie (UPMC)
4 place Jussieu
75005 Paris
France
Tel: +33 (0)1 44 27 44 27
www.upmc.fr/

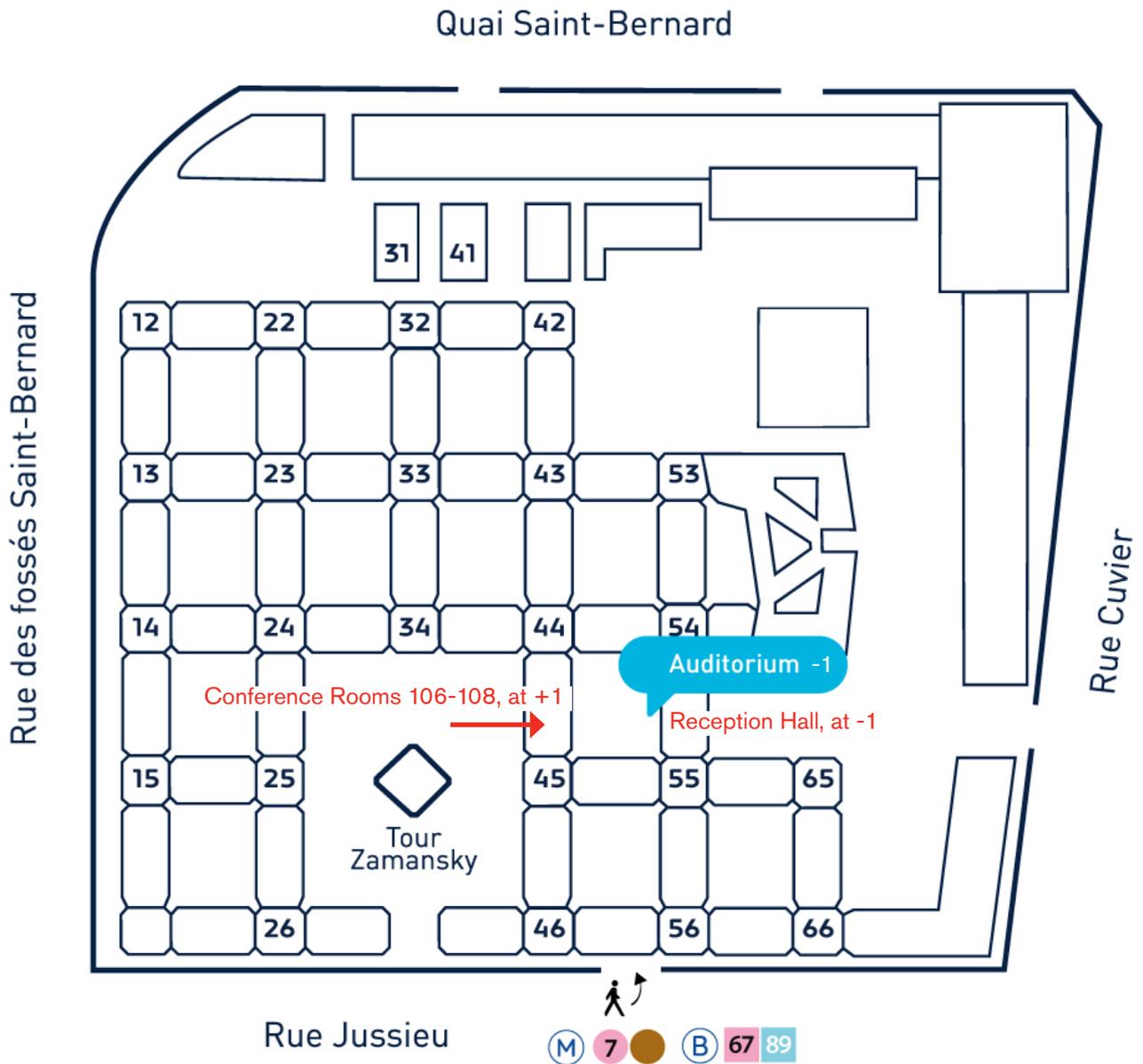


- ▶ The red arrow indicates the main entrance of the conference site.
- ▶ The closest metro station is Jussieu (Lines 7 and 10).



Conference Venue and Floor Plan

- ▶ The Auditorium and Reception Hall are located at Level -1, between poles 54 and 55.
- ▶ The Conference Rooms 106 and 108 are located at Level +1, between poles 44 and 45.
- ▶ The entrance is located at Level 0.



General Information

Plenary Session

Auditorium located at Level -1 (entry via glass box, see image).

Parallel Sessions

Conference Rooms located at Level +1, or in the main auditorium at level -1.

Poster Session / Cocktail Reception

Reception Hall, located at Level -1.

Coffee and Lunch Breaks

Reception Hall, located at Level -1.

Registration Opening Times

The registration desk is located at the Reception Hall of the conference venue. The registration desk will be open during the following times:

Wednesday, February 8	08:00 - 19:00
Thursday, February 9	08:00 - 17:00

On-site Speaker Room

The speaker room is located next to the stage at the main auditorium.

Wi-Fi

Individual Wi-Fi codes will be distributed together with the conference badges.

Follow Us on Social Media

#IRDIRC #IRDIRC2017

@irdirc



Contact Persons during the Event

Denise Maiocchi and Thomas Amiconi, from Amiconi Consulting (www.amiconiconsulting.ch), who are at the reception desk.

Denise Maiocchi

conference@irdirc-conference.org



Thomas Amiconi

conference@irdirc-conference.org





IRDiRC

INTERNATIONAL
RARE DISEASES RESEARCH
CONSORTIUM