

A hand is holding a wooden signpost in the foreground. In the background, there is a bronze statue of a man in a suit, and a large, ornate stone building with a tall, textured column and a circular window. The sky is clear and blue.

CONGRESS BROCHURE

INTERNATIONAL CONGRESS OF RESEARCH ON
RARE AND ORPHAN DISEASES
8TH–10TH MAY, TORONTO

RE(ACT)[®] CONGRESS AMERICA 2019

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INTERNATIONAL CONGRESS OF RESEARCH ON
RARE AND ORPHAN DISEASES
MAY 2019

TABLE OF CONTENTS

WELCOME MESSAGE _____	7
KEY FACTS _____	8
TIME TABLE _____	10
FULL PROGRAM _____	11
SPEAKER BIOGRAPHIES _____	17
SPEAKER ABSTRACTS _____	32
DELEGATE ABSTRACTS _____	66
SUPPORTERS _____	79

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WELCOME

Dear Colleagues,

Welcome to the inaugural RE(ACT) Congress America 2019 – we are excited to host you for the first time in North America in the beautiful city of Toronto, a superb setting for learning and networking.

Over the next few days, a stimulating program awaits with a dedicated, global community of scientists and experts, and many opportunities to discuss progress in rare diseases research. The overall aim of the Congress is not only to bring together scientific leaders, experts, and young researchers with patients, but also to present and promote cutting-edge research on rare and orphan diseases among the general public, industry and policy makers – all with the ultimate goal of enhancing the rapid delivery of new and promising diagnostics and therapies to patients all around the world.

The RE(ACT) Congress – the International Congress of Research on Rare and Orphan Diseases – was initiated in 2012 by the BLACKSWAN Foundation to create a forum for and promote scientific cooperation and research on rare and orphan diseases. This fifth edition of the Congress is co-organized in collaboration with the Office of Rare Diseases Research (ORDR) within the National Center for Advancing Translational Sciences (NCATS) at the National Institutes of Health (NIH), in partnership with the Canadian Organization for Rare Disorders (CORD), the Canadian Institutes of Health (CIHR), Genome Canada, and the Children’s Hospital of Eastern Ontario (CHEO).

Thank you in advance for your active participation in the discussions and events over the coming days, and, on behalf of the organizers, we hope you will enjoy your time in Toronto.

Dr. Olivier Menzel
Chairman and founder
BLACKSWAN Foundation

Pr. Alex MacKenzie
Professor of Paediatrics
CHEO

Dr. Christopher P. Austin
Director
NCATS/NIH

KEY FACTS

Scientific program committee

Jacques Beckmann, CH - PJ Brooks, USA - Alice Chen, USA - Jeanine D'Armiento, USA - Marisa Jaconi, CH - Daria Julkowska, FR - Stanislas Lyonnet, FR - Michael Morris, CH - Alexandre Reymond, CH - Hamish S. Scott, AUS - Eric Sid, USA - Jason Wan, USA- Lu Wang, USA

Organizing committee and advisory board

Suzanne Beaton, CIHR-IG, CAN - Cindy Bell, Genome Canada, CAN - Christine Cutillo, NIH/NCATS, USA - Jeanne Egar, CIHR-IG, CAN - Steve Groft, NIH/NCATS, USA - Paul Lasko, McGill University, CAN - Alex MacKenzie, CHEO, CAN - Chris McMaster, CIHR-IG, CAN - Olivier Menzel, BLACKSWAN Foundation, CH - Anne Pariser, NIH/NCATS, USA - Étienne Richer, CIHR-IG, CAN - Durhane Wong-Rieger, CORD, CAN

Venue

The RE(ACT) Congress America 2019 is held at the Sheraton Centre Toronto Hotel. In the heart of downtown's business and entertainment districts, the Sheraton Centre Toronto Hotel is connected to PATH, a 16-mile underground network of shops and services. It is steps from the Eaton Centre shopping mall and Toronto's convention centre. Experience a fresh kind of classic. A 2.5-acre waterfall garden atrium highlights our new lobby. Newly renovated ballrooms and meeting spaces total more than 120,000 square feet. Savour some of the city's best burgers and comfort food at BnB. Each of the 1,372 modern guest rooms offer the plush comfort of the Sheraton Signature Sleep Experience. Sheraton Club Rooms offer another level of service with an array of upgraded amenities and access to the stylish 43rd-floor Sheraton Club Lounge.

Congress Initiator

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

Congress Organizers

BLACKSWAN Foundation
Canadian Institutes of Health Research - CIHR-IRSC
Office of Rare Diseases Research (ORDR) - NIH/NCATS
The Children's Hospital of Eastern Ontario - CHEO

Congress Partners

The Children's Hospital of Eastern Ontario - CHEO
Canadian Institutes of Health Research - CIHR-IRSC
Canadian Organization for Rare Disorders - CORD
Genome Canada
National Institutes of Health/National Center for Advancing Translational Sciences - NIH/NCATS

Professional Congress Organizer

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Important information for speakers

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

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

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

Presentation should be created in Microsoft PowerPoint, Keynote or PDF. Furthermore, please use standard fonts of Windows. To facilitate allocation, please create a respective folder on your storage medium including your presentation (e.g. RE(ACT) 2019_Speaker's name_Session).

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

Important information for abstract presenters

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

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

- Posters may be set up on 8th May from 8am.
- Posters should be removed on 10th May from 5pm.
- Poster which have not been removed after this time will be discarded. Please note that the posters and others material will not be sent to you after the conference.

Posters

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

Disclaimer:

Biographies and abstracts are printed as received by the authors.

TIME TABLE

WEDNESDAY, MAY 8th

Parallel sessions 9 am to 12:

- Multi-national clinical trials/registries – Chair: Anne Junker (Provincial North Room)
- Generalizable therapeutic approaches for RD – Chair: Chris McMaster (City Hall Room)

A. Session, Afternoon 2pm to 5pm, City Hall Room “Gene Editing” – Chair: Jacques Beckmann

POSTER SESSION 5pm to 6pm

Public Opening Ceremony 6 pm to 8 pm

THURSDAY, MAY 9th

B. Session, Morning 9am to 12, City Hall Room “Cell & Gene Therapy” – Chair: Philip (PJ) Brooks

Lunch 12 to 1pm

POSTER SESSION B & C 1pm to 2pm

C. Session, Afternoon, 2 pm to 5 pm, City Hall Room “Indigenous Populations” – Chair: Cheryl Rockman-Greenberg

POSTER SESSION B & C 5pm to 6pm

FRIDAY, MAY 10th

D. Session, Morning 9am to 12, City Hall Room “Stem Cells/Regenerative Medicine/Genetically Modified Cell Therapies/Clinical Applications of Gene Therapies” – Chair: William L. Stanford

Lunch 12 to 1pm

POSTER SESSION D & E 1 pm to 1:30pm

E. Joint Session with CORD/RDI, Afternoon 1:30 pm to 5:30 pm, Gran West Ballroom, “Patient focused drug development” – Chair: Daria Julkowska

FULL PROGRAM

WEDNESDAY, MAY 8th

Special morning sessions 9am-12pm

Parallel session 1: Multi-national clinical trials/registries – Chair: Dr Anne Junker (Maternal Infant Child and Youth Research Network)

Panellists:

- Brendan Lee, USA

“Brittle Bone Disorders Consortium: The skeletal system as a target and model for rare disease research”

- Sabine Kläger, FR

“Challenges, considerations and support for investigator initiated, multi-national trials across Europe – ECRIN”

- Beth Potter, CAN

“Generating evidence to improve care and outcomes for pediatric inherited metabolic disease: the Canadian Inherited Metabolic Diseases Research Network”

Parallel session 2: Generalizable therapeutic approaches for RD – Chair: Pr. Chris McMaster (Dalhousie University)

Panellists:

- James Dowling, CAN

“Developing therapies for congenital myopathies: unmet needs and potential successes”

- Hanns Lochmuller, DE

“Targeted therapies for rare neuromuscular disorders – first steps towards a treatabome”

- Anne E. Carpenter, USA

“Targeting Disease via Cell Painting and Image-Based Profiling”

A. Session, Afternoon 2pm-5pm "Gene Editing"

- Special talk: Aled Edwards, CAN
"Open science drug discovery – the scientific case and an operating business model"
- Dwi Kemaladewi, CAN
"Interventional genomics in congenital muscular dystrophy"
- Jacques P. Tremblay, CAN
"Development of therapies for hereditary diseases by modifying genes with the CRISPR/Cas9 technology"
- Lauryl Nutter, CAN
"Genome editing to produce precision models for precision medicine"

POSTER SESSION A 5pm-6pm

Public Opening Ceremony 6pm-8pm

THURSDAY, MAY 9th

B. Session, Morning 9am-12pm "Cell & Gene Therapy"

- Alberto Auricchio, IT "AAV gene therapy from bench to bedside"
- William Stanford, CAN
"Preclinical stem cell models of tuberous sclerosis complex and its related lung neoplasm lymphangioleiomyomatosis for therapeutic development"
- Stephanie Cherqui, USA
"Hematopoietic Stem Cell Gene Therapy for Cystinosis: Clinical Translation and Mechanism of Action"
- Marina Cavazzana, FR
"Gene therapy for inherited diseases of the hematopoietic system"

Lunch 12pm-1pm

POSTER SESSION B & C 1pm-2pm

C. Session, Afternoon, 2pm-5pm **“Indigenous populations”**

- Laura Arbour, CAN

“Rare diseases in Indigenous populations: Where do we start?”

- Gareth Baynam, AUS

“Life Languages”

- Victoria Siu, CAN

“Genetic Disorders in the Amish and Mennonite communities:
Harnessing the results of research to benefit child health”

- Maui Hudson, NZ

“The Responsibility of Researching Rare Disorders & Rare Populations”

- Cheryl Rockman-Greenberg, CAN

“From gene discovery to newborn screening in Indigenous populations”

FRIDAY, MAY 10th

D. Session, Morning 9am-12pm **“Stem Cells/Regenerative Medicine/Genetically Modified Cell Therapies/Clinical Applications of Gene Therapies”**

- Tony Rupar, CAN

“Gene therapy in Lysosomal storage diseases

– Fabry disease and Metachromatic Leukodystrophy”

- Ian MacDonald, CAN

“Ocular gene therapy: what are we learning from clinical trials”

- Monica Justice, CAN

“Therapeutic insights for Rett syndrome from the study of MECP2 modifiers in mice”

- James J Hickman, USA

“Building human-on-a-chip phenotypic models to predict in vivo outcomes for efficacy and toxicity for rare diseases”

- Tejashri Purohit-Sheth, USA

“FDA Expedited Pathways and Regenerative Advanced Therapy Designation”

- Kathleen Reape, USA

“Clinical and Regulatory Considerations and the U.S. Approval of LUXTURNA™ (voretigene neparvovec-rzyl)”

Lunch 12pm-1pm

POSTER SESSION D & E 1pm-2pm

E. Collaborative Session (CORD, RDI, CIHR, CADTH, CHEO, NCATS, FDA, EMA, UDNI, IRDiRC) Afternoon 2pm-5pm **"Patient focused drug development"**

- [Marlene Haffner, USA](#)

"I am a Patient. Please Listen to ME"

- [Nick Sireau, UK](#)

"Developing a treatment for the ultra rare Black Bone Disease"

- [Larissa Lapteva, USA](#)

"Patient-Focused Development of Medical Products: Regulatory Perspective"

- [Calvin N. Ho, USA](#)

"How Advocates Can Bring Patient Experience Data to Regulators and Industry"

- [Soo-Kyung Lee, USA](#)

"What Does the FOX Say? FOXG1 Orchestrates Cortico-Cortical Connections"

- [Keith Massey, CAN](#)

SATURDAY and SUNDAY, MAY 11th & 12th

Rare Disease International (RDI) & Canadian Organization for Rare Disorders (CORD): "A Rare International Dialogue"

SPEAKER BIOGRAPHIES

ARBOUR, LAURA

Dr. Laura Arbour is a Professor in the Department of Medical Genetics at the University of British Columbia situated at the Island Medical Program in Victoria, BC and a Medical Geneticist at Island Health. Her clinical practice and research focuses on northern and Indigenous health issues as they pertain to genetics. Trained as both pediatrician and clinical geneticist, her research integrates maternal child health issues and the understanding of the genetic component of Indigenous health of all ages. Notable studies include addressing Long QT Syndrome (LQTS) in Northern BC, potential risk of CPT1A P479L for infant mortality in Nunavut, and the genetics of Primary Biliary Cholangitis in First Nations women of BC. Her LQTS work in Northern BC led to the development of a multidisciplinary province wide program to address inherited arrhythmias in all British Columbians (The BC Inherited Arrhythmia Program). She is also the project lead on a Genome Canada/CIHR funded grant, "Silent Genomes: Reducing health-care disparities and improving diagnostic success for Indigenous children with genetic disease" which aims to address the challenges of equitable access to genetic/genomic diagnosis and care for Canadian Indigenous populations.

AURICCHIO, ALBERTO

Alberto Auricchio, MD is Full Professor of Medical Genetics at the Department of Advanced Biomedicine, "Federico II" University in Naples, and Full Investigator at Telethon Institute of Genetics and Medicine (TIGEM) in Naples, Italy. His research is focused on gene therapy of retinal and metabolic diseases using adeno-associated viral vectors. Prof. Auricchio is co-author of more than 130 peer-reviewed publications on international scientific journals. He is a member of the editorial boards of Molecular Therapy, Embo Molecular Medicine and Translational Vision Science and Technology, and is an inventor on several international patents on the use of viral vectors for gene therapy. Prof. Auricchio has received the 2006 Outstanding New Investigator Award of the American Society of Gene Therapy and has been nominated in 2007 "Cavaliere of the Italian Republic" by the President of the Italian Republic. In 2011 and 2016 respectively, Prof. Auricchio received the prestigious Consolidator and Advanced grants from the European Research Council.

BAYNAM, GARETH

Gareth focuses on equitable and community engaged health innovation and implementation through public-private-philanthropic partnerships and under a precision public health paradigm. He is Head of the Western Australian Register of Developmental Anomalies (combined birth defects and cerebral palsy registers); a Clinical Geneticist at Genetic Services of Western Australia; an Adjunct Policy Advisor on Clinical Genomics at the WA Department of Health; and Director of the Undiagnosed Diseases Program (UDP) WA. He is a founding member of the Board of Directors of the Undiagnosed Diseases Network – International; Vice-Chair of the Diagnostics Scientific Committee of the International Rare Diseases Research Consortium; a member of the Governance Council of the International Cerebral Palsy Genomics Consortium; and a Director of the Academy for Child and Adolescent Health. He is a Clinical A/Prof at the School of Paediatrics and Child Health, University of Western Australia; the Institute for Immunology and Infectious Diseases, Murdoch University;

at Spatial Sciences, Curtin University; and at the School of Population and Global Health, University of Melbourne. He Co-Directs the Genetic and Rare Diseases Program at Telethon Kids Institute. His PhD was in genetic modifiers of vaccine response in children and he leads a 3D facial analysis team. He translated, to public health system implementation, the first Aboriginal genomic reference range in Western Australia and supervises the first genetic counsellor dedicated to Australian Aboriginal genetic health care. He led the implementation of a knowledge management platform for rare diseases in the WA Health System, Patient Archive. He is on the Scientific Advisory Board for Solve-RD. He is a Board Member of the Genetic and Rare Diseases Network, WA and a member of the Rare Voices Australia Scientific and Medical Advisory Committee.

BIFFI, ALESSANDRA

Alessandra Biffi is the current director of the Gene therapy Program at Dana-Farber/Boston Children's Cancer and Blood Disorders Center. Her previous position was in Milano, at the San Raffaele Telethon Institute for Gene Therapy where she trained and developed a Research and Clinical Unit dedicated to the treatment of lysosomal storage disorders (LSDs) by means of hematopoietic stem cell (HSC)-based approaches. She is actively involved in gene therapy trials for genetic diseases of childhood. Her specific research is dedicated at enhancing the efficacy of HSC-based therapeutic approaches for LSDs with severe nervous system involvement by i) fostering brain microglia replacement by donor cells after HSC transplantation upon detailed understanding of this phenomenon (Capotondo et al., PNAS 2012), and ii) enhancing the potential of enzyme delivery to the affected nervous system by means of the gene corrected progeny of the transplanted, lentiviral vector (LV)-transduced HSCs (Biffi et al., Science 2013; Sessa et al., Lancet 2016).

CARPENTER, ANNE E.

Dr. Carpenter is an Institute Scientist directing the Imaging Platform at the Broad Institute of Harvard and MIT. Her research group develops algorithms and data analysis methods for large-scale experiments involving images. The team's open-source CellProfiler software is used by thousands of biologists worldwide. Carpenter is a pioneer in image-based profiling, the extraction of rich, unbiased information from images for a number of important applications in drug discovery and functional genomics.

Carpenter focused on high-throughput image analysis during her postdoctoral fellowship at the Whitehead Institute for Biomedical Research and MIT's CSAIL (Computer Sciences/Artificial Intelligence Laboratory). Her PhD is in cell biology from the University of Illinois, Urbana-Champaign. Carpenter has been named an NSF CAREER awardee, an NIH MIRA awardee, a Massachusetts Academy of Sciences fellow (its youngest at the time), and a Genome Technology "Rising Young Investigator".

CAVAZZANA, MARINA

Marina Cavazzana is a paediatrician, Professor of Haematology since 2000, Director of the Department of Biotherapy at Hospital Necker, University Paris Descartes. She is the Director

of the Inserm / Assistance Publique – Hôpitaux de Paris GHU Ouest Biotherapy Clinical Investigation Center and leads a research Laboratory at Imagine Institute. She studied medicine in Padua, Italy and received the degree of Doctor of Medicine in 1983, her certification in Paediatrics in 1987 and a PhD in Life Sciences in 1993 (University Paris VII). Her main research and clinical interests are development of the immune system, genetic diseases of the haematopoietic system and cell and gene therapy. She has initiated several clinical trials based on the use of ex vivo gene modified cells to treat patients with inherited disorders, the preliminary clinical results of which are encouraging. This work was rewarded by the American Society of Hematology (Award on Clinical Research in Gene Therapy in 1999), by the French Academy of Sciences (Special Medical Award in 2000 and Jean-Pierre Lecocq Award on Gene Therapy in 2004). She was awarded the title of Officier de l'Ordre National de la Légion d'honneur in 2011, given the Irène Joliot Curie 2012 award "Scientific Women of the Year" (Science Academy and French Ministry of Education and Research). She was also awarded with the French National Academy of Medicine in 2016 and the 2017 Ernest Beutler Lecture and Prize for Clinical Science (American Society of Hematology).

CHERQUI, STEPHANIE

The main focus of her lab is to develop stem cell and gene therapy strategies for degenerative multi-systemic disorders, and to understand the mechanisms by which hematopoietic stem and progenitor cells (HSPC) can lead to tissue repair. Her work is leading to the first-in-human clinical trial for autologous hematopoietic stem cell gene therapy for cystinosis, but also her findings on the cellular mechanism of HSPC-mediated tissue preservation led to the application of this strategy to other disorders including the neuro-muscular degenerative disease, Friedreich's ataxia.

Stephanie Cherqui received her Ph.D in 2002 at Necker hospital (Paris, France); her research project focused on the molecular characterization of cystinosis and the generation of the mouse model. She then specialized in stem cells and gene therapy during her post-doctoral internship at The Scripps Research Institute where she was appointed Assistant Professor in 2009. In 2012, Dr. Cherqui joined the University of California, San Diego, Department of Pediatrics, Division of Genetics and became Associate Professor in 2016.

She is the Chair of the Cystinosis Stem Cell and Gene Therapy Consortium. Dr. Cherqui is also the chair of the Gene and Cell Therapy of Genetic and Metabolic Diseases at the American Society of Gene and Cell Therapy (ASCGT). She is a member of the Scientific Review Board of the Cystinosis Research Foundation and a Scientific Council member for the Cure Cystinosis International Registry (CCIR). Her research is funded by grants from the National Institute of Health (NIH), California Institute of Regenerative Medicine (CIRM), and the Cystinosis Research Foundation.

DOWLING, JAMES

Dr. James DOWLING is a clinician-scientist focused on gene discovery and therapy development for childhood muscle diseases. He is a staff clinician and senior scientist at the Hospital for Sick Children as well as the Mogford Campbell family chair in paediatric neurosciences, and an Associate Professor of Paediatrics and Molecular Genetics at the

University of Toronto. Dr. Dowling received his BSc and MSc from Yale University and his MD/PhD from the University of Chicago. His PhD work was performed in the laboratory of Elaine Fuchs. He did his residency in child neurology at Children's Hospital of Philadelphia and completed postdoctoral research with Jeff Golden (UPenn) and Eva Feldman (University of Michigan). Before coming to Toronto in 2013, he was an assistant professor at the University of Michigan.

Dr. Dowling's clinical expertise is in childhood neuromuscular disorders and he is considered one of the leading authorities on the diagnosis and management of congenital myopathies. His research examines questions of disease pathogenesis and therapy development for congenital myopathies and childhood muscular dystrophies, and his laboratory has helped pioneer the use of the zebrafish as a model for these disorders. He has authored or co-authored more than 80 peer reviewed manuscripts and been fortunate to enjoy funding from several sources, including CIHR, NIH, MDA, and Genome Canada.

EDWARDS, ALED

Aled Edwards is the founding and current CEO of the Structural Genomics Consortium (SGC), a public-private charitable partnership that generates research tools and knowledge to support basic science and drug discovery. Edwards is also the founder of M4K Pharma, a drug discovery company whose mission is to invent new medicines for rare and common diseases of children, and price them affordably.

Aled is a pioneer of open science and open partnerships with the private sector. Since 2003, under his leadership, the SGC has adopted a policy not to file for patents on any of its research output, while over the same period has attracted well over 0M in funding from global pharma, and a similar amount from governments and foundations. M4K is the first drug discovery company to eschew patents and prioritize rapid data sharing.

Aled is a Professor at Toronto, Oxford and McGill Universities. He studied biochemistry at McGill and Stanford Universities.

HAFFNER, MARLENE E.

MARLENE E. HAFFNER, MD, MPH is the CEO of Haffner Associates, LLC a firm dedicated to the strategy, development and policy of drug development with a special emphasis on rare diseases and the products that treatment them. For 20 years, Dr. Haffner served as Director of the Office of Orphan Products Development (OOPD) of the Food and Drug Administration (FDA). As OOPD Director she was responsible for the leadership and management of the FDA orphan products development program, the first Orphan Products program in the world. In addition to her FDA responsibilities, Dr. Haffner assisted in the development of Orphan Drug programs in the EU, Japan, Australia and beyond. She is well known as an expert in orphan drug development and is a sought after speaker and consultant in that area of regulatory science.

In addition to her consulting activities Marlene is Adjunct Professor, Department of Preventive Medicine and Biometrics, and Clinical Professor, Department of Medicine, at the F. Edward Hébert School of Medicine, Uniformed Services University of the Health Sciences (USUHS) in Bethesda, Maryland. A sought after speaker and consultant, Dr. Haffner has received many awards for her work in drug development including The Outstanding Contributions to Pharmaceutical Medicine Award from the American Academy of Pharmaceutical

Physicians, and the Woodrow Wilson Award for Outstanding Government Service from the Johns Hopkins University. She is the author of multiple articles in peer reviewed literature concerning issues of orphan product development.

HO, CALVIN N.

Calvin N. Ho, PhD, is a Patient Reported Outcomes Scientist at AstraZeneca, where he ensures that patients' experiences are captured and analyzed in clinical trials. Previously, as Science Project Coordinator at the Tuberous Sclerosis Alliance, Dr. Ho organized an Externally-Led Patient-Focused Drug Development (ELPFDD) meeting with the US Food and Drug Administration (FDA). He also conducted the patient experience research behind the international drug development survey and Voice of the Patient report that accompanied the meeting. The ELPFDD meeting, one of the first such meetings ever held, empowered patient advocates to tell FDA representatives about their experiences living with the disease. These data can inform regulators' reviews of new treatments as well as drug and device companies' development plans.

HUDSON, MAUI

Associate Professor Maui Hudson is based in the Faculty of M ori and Indigenous Studies at the University of Waikato. He is an interdisciplinary researcher who explores the interface between Indigenous Knowledge, Science and Technology. He co-authored the Te Mata Ira Guidelines for Genomic Research with M ori, and the He Tangata Kei Tua Guidelines for Biobanking with M ori. Professor Hudson is also the co-convenor for SING Aotearoa (Summer Internship for Indigenous Genomics), a co-founder of Te Mana Raraunga M ori Data Sovereignty Network, and a member of the Senior Leadership Team for Genomics Aotearoa.

HICKMAN, JAMES J.

James J. Hickman is the founder and current Chief Scientist of a biotechnology company, Hesperos, Inc., that is focusing on cell-based systems for drug discovery and toxicity. He is also the Founding Director of the NanoScience Technology Center and a Professor of Nanoscience Technology, Chemistry, Biomolecular Science, Material Science and Electrical Engineering at the University of Central Florida. Previously, he held the position of the Hunter Endowed Chair in the Bioengineering Department at Clemson University. Dr. Hickman has a Ph.D. from the Massachusetts Institute of Technology in Chemistry. For the past twenty-five years, he has been studying the interaction of biological species with modified surfaces, first in industry and in the latter years in academia. While in industry he established one of the first bioelectronics labs in the country that focused on cell-based sensors and their integration with electronic devices and MEMS devices. He is interested in creating hybrid systems for biosensor and biological computation applications and the creation of functional in vitro systems for human body-on-a-chip applications. He has worked at NSF and DARPA in the area of biological computation. He has 135 publications and 20 book chapters, in addition to 27 issued patents out of 47 total patent applications. He is a Fellow of both the American Institute of Medical and Biomedical Engineers (AIMBE) (2004)

and the American Vacuum Society (AVS) (2007). He was a Board Member for AIMBE from 2009-2013 and Co-Chaired 6 AIMBE/NIH Workshops on “Validation and Qualification of New In Vitro Tools and Models for The Pre-clinical Drug Discovery Process” held at the NIH Campus, Bethesda, MD (2012 – 2017). He was also a Charter Member, NIH Bioengineering of Neuroscience, Vision and Low Vision Technologies (BNVT) Study Section. Dr. Hickman along with Dr. Michael Shuler, won the Lush Prize, in the Science Category, which Supports Animal Free Testing in 2015.

JUSTICE, MONICA

Dr Justice’s research aims to improve human health through genetics. Genetics and genomics strategies are employed to identify the genetic basis for rare diseases and find rational pathways for therapies. Her current work focuses on a genetic suppressor screen in a mouse model for Rett syndrome, which has identified missing pathway components, new genetic interactions, and unexpected drug targets. Dr. Justice was recruited to Sick-Kids Research Institute as Senior Scientist and Head, Program in Genetics and Genome Biology from Baylor College of Medicine, Houston, Texas, where she was a Professor in the Department of Molecular and Human Genetics and Director of the Mouse Embryonic Stem Cell Core and the NIH-funded Knockout Mouse Program (KOMP2). In fall of 2018, she assumed the role of Scientific Director of The Centre for Phenogenomics in Toronto. A pioneer in mouse mutagenesis, Dr. Justice received her PhD from Kansas State University in developmental genetics, and was a postdoctoral fellow in the Mammalian Genetics Laboratory at the US National Cancer Institute. She is Editor-in-Chief of Disease Models and Mechanisms, and a Senior Editor of Current Protocols in Mouse Biology. She was elected a Fellow of the American Association for the Advancement of Science for her seminal contributions to mouse genetics.

KEMALADEWI, DWI U.

Dr. Kemaladewi has a strong interest in understanding the molecular mechanism underlying different pathophysiology associated with neuromuscular disorders (NMD), and translating these mechanisms into a variety of therapeutic strategies. She received her PhD in October 2012 from Leiden University, the Netherlands under the mentorship of Prof. Gert-Jan van Ommen and Prof. Peter ‘t Hoen. Subsequently, she joined the laboratory of Prof. Ronald Cohn at the Hospital for Sick Children, Toronto, Canada as a post-doctoral fellow. During her PhD and in the first few years of postdoctoral training, she focused on the development of genetic technologies, such as antisense oligonucleotides and CRISPR/Cas9 as therapeutic tools to counteract pro-fibrotic pathways and correct underlying mutations in Duchenne muscular dystrophy. Subsequently, she leveraged her expertise in muscle physiology and genetic therapies to investigate disease mechanisms involved in another rare pediatric NMD called LAMA2-deficient congenital muscular dystrophy (LAMA2-CMD). She identified polyamine metabolism as a protective disease modifier, developed and evaluated the therapeutic potentials of CRISPR/Cas9-based strategies to correct a causative mutation and upregulate a compensatory gene in a mouse model of LAMA2-CMD. In February 2019, she will start a new position as an Assistant Professor at University of Pittsburgh and a Principal Investigator at the Center for Rare Disease Therapy, Children’s Hospital of Pittsburgh, USA. Her independent research program will

exploit the use of cutting-edge genetic technologies and novel animal models to understand neuromuscular disorders from the perspective of peripheral nervous system.

KLÄGER, SABINE

Sabine Kläger is the Clinical Operations Manager of the European Clinical Research Network (ECRIN), one of the European Research Infrastructure Consortia (ERIC). Based at the head office in Paris, she is responsible for a portfolio of 40+ multi-national, investigator initiated clinical trials, working with Sponsors and investigators by providing coordinated operational services to their multinational clinical trials across the European participating countries. Most of these projects are being supported by public or public-private European funding schemes (i.e. H2020, IMI). Before joining ECRIN-ERIC in 2017, she was instrumental as Operations Director for the set-up and development of the NIHR UKCRC accredited Cambridge Clinical Trials Unit (Cambridge UK), a centre of excellence in delivering investigator-initiated clinical trials in any clinical speciality present on the Cambridge Biomedical Research Campus/ University of Cambridge. She has an extensive knowledge and understanding of clinical trial operations, management, Sponsor responsibilities, regulations and legislation across Europe. Dr Kläger obtained her PhD in Parasitology/Biology in 1989 at the University of Tübingen, Germany, and pursued her scientific vocation over 12 years in the UK, starting as post-doctoral fellow at The University of Cambridge, with a key focus on Onchocerciasis and Filariasis control, including clinical trials located in countries across Sub-Saharan Africa.

LAPTEVA, LARISSA

Dr. Larissa Lapteva is the Associate Director in the Division of Clinical Evaluation, Pharmacology, and Toxicology in the Office of Tissues and Advanced Therapies in the Center for Biologics Evaluation and Research at FDA. Dr. Lapteva is a physician with long-standing experience in clinical research with novel drugs and biological products. Prior to her work at FDA, Dr. Lapteva was trained as a rheumatologist at the National Institute of Arthritis, Musculoskeletal and Skin Diseases (NIAMS), National Institutes of Health (NIH), where she later conducted clinical studies in rheumatic diseases. Since joining FDA in 2006, Dr. Lapteva has held review and leadership positions in the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research and provided scientific and regulatory advice for clinical development programs with investigational products across different therapeutic areas. Dr. Lapteva is a practicing clinician and serves as faculty at NIAMS, NIH. She received her degrees of Master of Health Sciences from Duke University and Master of Business Administration from R.H. Smith School of Business.

LEE, BRENDAN

Dr. Lee is the Robert and Janice McNair Endowed Chair, Professor, and Chairman of the Department of Molecular and Human Genetics, Director of the Center for Skeletal Medicine and Biology at Baylor College of Medicine, and co-Director of the Texas Medical Center Bone Disease Program of Texas. As a pediatrician and geneticist, Dr. Lee studies structural birth defects and inborn errors of metabolism. Dr. Lee identified the first genetic causes of human skeletal dysplasias and studies their implications for cancers of the skeleton. In the area of

metabolic disease, he has studied nitric oxide dysregulation and developed new treatments for maple syrup urine disease and urea cycle disorders. Dr. Lee has been recognized by election to the National Academy of Medicine, Fellow of the American Association for the Advancement of Science (AAAS), the Association of American Physicians (AAP), the American Society for Clinical Investigation (ASCI), and the Society of Pediatric Research (SPR). He has also been awarded the American Society of Human Genetics Curt Stern Award for Outstanding Scientific Achievement, the Texas Academy of Medicine, Engineering, Science and Technology (TAMEST) Peter and Edith O'Donnell Award in Medicine, the Society for Pediatric Research E. Meade Johnson Award for Pediatrics Research, the Michael E. DeBakey Excellence in Research Award, the American Philosophical Society's (APS) Judson Darland Prize for Patient-Oriented Clinical Investigation, and Best Doctors in America. Dr. Lee was previously an Investigator of the Howard Hughes Medical Institute prior to his appointment as Chairman of the Department of Molecular and Human Genetics in 2014. The Department is the leading genetics program integrating basic, translational, clinical, and diagnostic laboratory activities. It is composed of over 140 primary faculty members encompassing research, clinical, laboratory diagnostic, and genetic counseling missions. It ranks #1 among genetics departments in total funding and number of grants from the National Institutes of Health.

LEE, SOO-KYUNG

Soo-Kyung "Soo" Lee completed her B.S. degree in Pharmacy at Chonnam National University in Gwangju, Korea, and remained at Chonnam National University to earn her M.S. and Ph.D. degrees. In 2001, she moved to the Salk Institute in San Diego for postdoctoral studies. She was appointed assistant professor at Baylor College of Medicine in 2004. Dr. Lee came to OHSU in 2010 as an associate professor in the Pediatrics department and was promoted to professor in 2014. She holds a joint appointment in the Vollum Institute. The goals of Dr. Lee's lab are to understand the gene regulatory mechanisms that govern the generation of diverse neural cell-types with specialized function and connection pattern during central nervous system development and to understand how disruption of these processes leads to various neurodevelopmental disorders in humans. The recent study in Dr. Lee's lab uncovered the molecular mechanism underlying brain structural deficits in human FOXG1 syndrome.

LOCHMÜLLER, HANNS

Hanns is a neurologist and clinical academic specializing in genetic neuromuscular disorders and rare disease. He was recently appointed as Senior Scientist at the Children's Hospital of Eastern Ontario (CHEO) Research Institute. He also holds appointments as Professor of Neurology in the University of Ottawa Faculty of Medicine and the Department of Medicine, Division of Neurology at The Ottawa Hospital. He is affiliated with the University of Ottawa Brain and Mind Research Institute and Department of Cellular and Molecular Medicine and with the Ottawa Centre for Neuromuscular Disease.

Hanns trained as a neurologist in Munich, Germany and in Montreal, Canada. From 2007 to 2017, he held the chair of experimental myology at the Institute of Genetic Medicine at Newcastle University in the UK. He continues to hold a scientific appointment at the

Department of Neuropediatrics and Muscle Disorders of the Medical Center – University of Freiburg in Germany and as visiting scientist at the Centro Nacional de Análisis Genómico (CNAG), Centre for Genomic Regulation, Barcelona in Spain.

His research interests include molecular therapies of neuromuscular disorders; molecular pathogenesis of muscle and neuromuscular junction disorders; neurogenetics and translational research; data sharing and -omics in neuromuscular and rare diseases; and genomics and systems medicine. In addition to his scientific and clinical research interests, he is internationally active in rare disease science policy and research collaborations. He chaired the Interdisciplinary Scientific Committee of the International Rare Diseases Research Consortium (IRDiRC) and the Executive Committee of the TREAT-NMD Alliance. He initiated and coordinated the highly successful “RD-Connect” international infrastructure for rare disease data and biosample sharing and analysis, is co-founder and former coordinator of the German muscular dystrophy network (MD-NET), and former scientific coordinator of EuroBioBank, a European (and Canadian) network of biobanks for rare disorders.

Hanns’s clinical activities focus on clinical research and care of patients with rare neuromuscular disorders, including myotonic dystrophy (DM1), spinal muscular atrophy (SMA), muscular dystrophy and congenital myasthenic syndromes (CMS). He has a strong commitment to working with patients and patient organizations in Canada, as he has with organizations in Europe for many years.

MACDONALD, IAN

Ian M. MacDonald MSc, MD CMtrained first as a clinical geneticist. Having been introduced to patients with genetic eye diseases, he then qualified as an ophthalmologist to better understand the complexities of inherited disorders of vision. After beginning his professional career in Ottawa as clinician scientist, he moved to Alberta in Western Canada where he served as Chair of the Department of Ophthalmology and Visual Sciences of the University of Alberta in Edmonton. In recognition of his work in Canada to foster the development of academic Ophthalmology, he was elected as a Fellow to the Canadian Academy of Health Sciences.

Dr. MacDonald’s area of clinical and research interest is inherited retinal disorders, in particular, disorders of the macula and choroideremia, an X-linked condition. With funding from the Canadian Foundation for Innovation, the Canadian Institutes for Health Research, Alberta Innovates-Health Solutions, the Foundation Fighting Blindness Canada, and the Choroideremia Research Foundation, Canada Inc., he led a team that completed, in 2017, the first trial of ocular gene therapy in Canada.

MASSEY, KEITH

Science Director and member of the The Cure RTD Foundation’s Board. A graduate of Carleton University and University of Manitoba, Keith received his BEng in Aerospace Engineering, MSc in Biomechanical Engineering and did his Ph.D. studies in Neurology with specialization in neuromuscular control. After his daughter Julia was diagnosed in 2013 with RTD Type 2 he dedicated himself to the RTD cause and was one of the co-founders of the Cure RTD Foundation. He is now one of the leading advocates and experts on living

with RTD, RTD research, and clinical aspects of the disease. He speaks regularly with researchers and clinicians to help organize meetings, symposiums and plan research related to RTD and is in regular contact with families affected by RTD around the world.

NUTTER, LAURYL M. J.

Lauryl Nutter trained as a geneticist at the University of Calgary working with *Drosophila*. After obtaining her doctorate in 1997, she moved to Toronto, first as a post-doctoral fellow and then a research associate at The Hospital for Sick Children. At SickKids, her research used mouse models of pre-B cell leukemia to look at leukemogenesis and the genetic factors enabling leukemia to invade the central nervous system. In 2007, Lauryl joined the management team at The Centre for Phenogenomics (TCP) where she directed the Molecular Biology and Cryopreservation and Recovery Cores until early 2019. In this role, Dr. Nutter established the methodology for mouse and rat model production using CRISPR/Cas9-based genome editing. Dr. Nutter also Co-Chairs the Cas9 Working Group and the Immunophenotyping Working Group for the International Mouse Phenotyping Consortium. Dr. Nutter is now the Senior Director, Science and Technology Development at TCP.

POTTER, BETH

Beth Potter has a PhD in Epidemiology from the University of Western Ontario. She is currently an Associate Professor of Epidemiology and Public Health and the University Research Chair in Health Services for Children with Rare Diseases at the University of Ottawa. She is also an Affiliate Investigator at the Children's Hospital of Eastern Ontario and a Senior Adjunct Scientist at the Institute for Clinical Evaluative Sciences. Her research focuses on developing evidence to improve health care for children with rare genetic diseases and to inform newborn screening programs. She is Principal Investigator for the Canadian Inherited Metabolic Diseases Research Network (www.cimdrn.ca), a network of 14 Canadian treatment centres and more than 50 researchers with funding from the Canadian Institutes of Health Research. She uses mixed methods to study clinical care and outcomes, health care experiences, and health system impacts for children diagnosed with rare metabolic diseases.

PUROHIT-SHETH, TEJASHRI

Dr. Tejashri Purohit-Sheth is currently the Director of the Division of Clinical Evaluation and Pharmacology/Toxicology (DCEPT) in the Office of Tissues and Advanced Therapies (OTAT) in the Center for Biologics Evaluation and Research at the Food and Drug Administration. She provides supervisory oversight for the clinical and pharmacology/toxicology review of submissions to OTAT. She previously served as the Clinical Deputy Director in DAGRID/ODE/CDRH/FDA as well as Acting Division Director and Branch Chief in Office of Scientific Investigation overseeing Bioresearch Monitoring in CDER/FDA and as a Medical Officer in the Division of Pulmonary and Allergy Products (CDER/FDA).

She completed an Internal Medicine Residency at Naval Medical Center Portsmouth followed by a fellowship in Allergy/Immunology at Walter Reed Army Medical Center. Fol-

lowing fellowship, she took over as Service Chief of the Allergy/Immunology clinic at National Naval Medical Center in Bethesda, MD. Following her end of obligated service as an active duty Naval Officer, she transferred her commission to the U.S. Public Health Service and began her FDA career.

REAPE, KATHY

Kathy Reape, MD is the Chief Medical Officer at Spark Therapeutics and is responsible for all clinical, pharmacovigilance, and medical affairs activities in the company. She has more than 18 years of pharmaceutical industry experience in clinical drug development, and has overseen numerous clinical trials and been involved in the approvals of more than two dozen products including small molecules, biologics, biosimilars, and devices spanning a wide range of therapeutic areas. She has authored a number of abstracts and manuscripts and is named on several patents. With Spark since 2015, she's been responsible for global clinical programs utilizing gene therapy in rare diseases including hemophilia, metabolic and central nervous system disorders, and inherited retinal dystrophies. She was involved in Spark's submission of the BLA and MAA for LUX-TURNA® (voretigene neparvovec-ryzl), leading to US FDA approval in 2017 and EMA marketing authorization in 2018 indicated for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy. Prior to joining Spark, Kathy was Senior Vice President, Head of Clinical Development, Global Brands R&D for Allergan, plc where she led the Clinical Development function for the entire brand R&D portfolio, including programs in ophthalmology, cardiovascular, gastrointestinal, anti-infectives, respiratory, women's health, urology, dermatology/aesthetics, and central nervous system (CNS). Kathy has also held leadership positions in Clinical R&D and Medical Affairs at Teva Pharmaceuticals, Duramed Research, Barr Labs, and Wyeth Pharmaceuticals. She received her MD from the University of Pennsylvania and completed her internship and residency at the University of Florida and the University of Medicine and Dentistry of New Jersey.

ROCKMAN-GREENBERG, CHERYL

Dr. Cheryl ROCKMAN-GREENBERG obtained her MD degree from McGill University in 1974. She became a Fellow of the Royal College of Physicians and Surgeons of Canada (Pediatrics) in 1979 and in Medical Genetics in 1996. She has been a Fellow of the Canadian College of Medical Geneticists since 1982. Dr. Greenberg served as Medical Director of the Child Health program, WRHA, and Head of the Department of Pediatrics and Child Health, University of Manitoba, from 2004-2014. Dr. Rockman-Greenberg has practiced as a clinical and metabolic geneticist in Winnipeg since 1979. She is a clinician scientist in the Children's Hospital Research Institute of Manitoba (CHRIM) and holds the academic rank of Distinguished Professor in the Department of Pediatrics and Child Health and the Department of Biochemistry and Medical Genetics, University of Manitoba. Dr. Rockman-Greenberg was named to the 2012 list of Canada's Most Powerful Women: Top 100, in the Trailblazers and Trendsetters category. Most recently, she was inducted into the Canadian Medical Hall of Fame in April 2018 and into the Order of Manitoba in July 2018.

RUPAR, TONY

Dr. Rupar, PhD, is a Fellow of the Canadian College of Medical Geneticists and Professor in the Depts. of Pathology & Laboratory Medicine, Pediatrics and Biochemistry at Western University and the London Health Sciences Centre in London Ontario, Canada. He directs the Biochemical Genetics Laboratory and is the current chairman of the advisory committee for the Province of Ontario Newborn Screening Program. Dr. Rupar's research interests include, with Dr. Victoria Siu, the provision of genetic services including gene discovery to isolated Amish and Mennonite communities. He also maintains an active collaborative research program in developing gene therapies for lysosomal storage diseases especially Fabry disease and metachromatic leukodystrophy.

SIREAU, NICK

Dr Nicolas Sireau is the CEO and Chair of Trustees at the AKU Society, a patient group that helps people with AKU (short for alkaptonuria), a rare genetic disease affecting both his children. He is also co-founder and Chair of Findacure, an organisation that helps rare disease patient groups. Previously, Nick was the CEO of SolarAid, an NGO working in Africa. He is a fellow of the Ashoka Fellowship of Social Entrepreneurs and has a PhD in the social psychology of social movements. He is the editor of 'Rare Diseases: Challenges and Opportunities for Social Entrepreneurs' (Greenleaf 2013) and of the 'Patient Group Handbook: A Practical Guide for Research and Drug Development' (Findacure 2016).

SIU, VICTORIA

Dr. Siu completed her medical degree at the University of Toronto in 1982, then received her FRCPC in pediatrics and FCCMG in medical genetics. She is currently the medical director of the Medical Genetics Program of Southwestern Ontario in London, Ontario. Since 1989, she has been involved in cataloguing the natural history and identifying several new genes associated with rare disorders in the Ontario Amish and Mennonite population. Together with Dr. Tony Rupar, she has created the Amish, Mennonite, and Hutterite genetic database, a publicly accessible resource, established a newborn screening program for treatable genetic disorders in the Ontario Amish population, and started an adult carrier screening program for Old Order Amish and Mennonite couples. Her special research interest lies in applying the results of gene discovery in the provision of optimal healthcare to this population. Dr. Siu is committed to ensuring that the rapid advances in medical genetics at a molecular level are translated clinically to benefit patient care.

STANFORD, WILLIAM (BILL) L.

Dr. William (Bill) L. STANFORD, PhD, is trained as a chemist (Duke) and as an Immunologist (UNC at Chapel Hill). Currently, Dr. Stanford is a Senior Scientist at the Ottawa Hospital, a Full Professor at the University of Ottawa, Investigator in the Ottawa Institute of Systems Biology, Scientific Director of the Ottawa Human Pluripotent Stem Cell Facility, and Canada Research Chair in Integrative Stem Cell Biology. Dr. Stanford's interdisciplinary research

uses a combination of unbiased systems and reductionist methodologies to dissect the molecular control of cell fate decisions in the context of human development, aging, and disease including cancer, with a focus on human somatic and pluripotent stem cells. Dr. Stanford uses induced pluripotent stem cells (iPSCs) and genome editing of embryonic stem cells (ESCs) to study the rare premature aging disease Hutchinson-Gilford Progeria Syndrome, Tuberous Sclerosis Complex and its related lung disease Lymphangioleiomyomatosis (LAM). Dr. Stanford has published more than 100 manuscripts, which have been cited nearly 10,000 times.

TREMBLAY, JACQUES P.

Jacques P. Tremblay received a B.Sc. in Biochemistry from McGill University in 1970, and a Ph.D. in Neuroscience from UCSD (University of California in San Diego) in 1974. From 1975 to 1976, he was a postdoctoral fellow at the Laboratory of Neurobiology of l'Hôpital de l'Enfant-Jésus. Subsequently, he spent his entire career at Laval University: Professor under grant from 1976 to 1981 in the Department of Anatomy; Assistant Professor from 1981 to 1985; full Professor from 1985; Director of the Department of Anatomy from 1987 to 1997, and Professor of the Department of Molecular Medicine from 2010 to now. He is currently a regular researcher at the Axis of Neuroscience of the CHU Research Center of Quebec-Université Laval.

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SPEAKER ABSTRACTS

BRITTLE BONE DISORDERS CONSORTIUM: THE SKELETAL SYSTEM AS A TARGET AND MODEL FOR RARE DISEASE RESEARCH

MULTI-NATIONAL CLINICAL TRIALS/REGISTRIES

Brendan Lee, MD, PhD. Department of Molecular and Human Genetics Baylor College of Medicine, TX USA

The Brittle Bone Disorders Consortium (BBDC) is multi-center clinical research program established in 2014 which focuses on understanding and providing better care for rare diseases characterized by bone fragility and fractures. The BBDC is a consortium within the NIH Rare Diseases Clinical Research Network (RDCRN). The BBDC is composed originally of 12 clinical sites in North America and Germany (Houston, Chicago, Portland, LA, Baltimore, NYC, Washington DC, Montreal, Omaha, Tampa, Wilmington, and Cologne), one advocacy partner site (Osteogenesis Imperfecta Foundation, OIF), and three cores sites (Seattle, Houston, and Tampa). The BBDC is funded by the NIH through the Office of Rare Diseases Research (U54 AR 068069), and a collaboration between NCATS and NIDCR, NICHD, and NIAMS. The OIF is an integral partner and is charged with the training mission targeting a broad spectrum of health care providers in the diagnosis and treatment of osteogenesis imperfecta (OI) and trainees in the research of rare brittle bone diseases. Together with the OIF we have established a fellowship for clinical research training, hosted clinical bone research training workshop at the American Society for Bone and Mineral Research, and an ancillary rare bone disease meeting, and developed web-based training for primary healthcare providers to extend the knowledge gained by research studies to patients. The BBDC is currently conducting two clinical studies and three pilot studies. The Longitudinal study (LS) of OI is focused on skeletal, non-skeletal, and craniofacial features of OI and has accrued over 850 participants. We are performing a Phase I trial of an anti-TGF therapy Fresolimumab in severe OI in the context of a safety and dose ranging study followed by an extension repeat dosing study. Our pilot studies include a laboratory study as well as two survey based studies. The goal of the laboratory pilot study is to develop a non-invasive test mass spectrometric assay of urinary collagen crosslinks to determine OI subtype. Our survey based studies utilize the RDCRN's contact registry: 1) to determine pregnancy outcome in OI and 2) to validate Patient Reported Outcome Measures in adults with OI. These hypothesis driven studies will ignite larger, more in-depth studies to be implemented by the consortium in the future.

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CHALLENGES, CONSIDERATIONS AND SUPPORT FOR INVESTIGATOR INITIATED, MULTI-NATIONAL TRIALS ACROSS EUROPE – ECRIN

MULTI-NATIONAL CLINICAL TRIALS/REGISTRIES

Dr Sabine Kläger, PhD, MSc, Head of Clinical Operations Unit ECRIN, Paris, France

Investigator-initiated clinical trials are being conducted mainly in a single-centre setting due to the many challenges for non-industry Sponsors to conduct multi-centre and multi-national clinical trials. However, especially in the field of Rare Diseases (RD), considering the limited numbers of patients per clinical site and country, it is of major importance to be able to recruit across many sites and countries. We will present the considerations for non-industry Sponsors in the preparation and funding of international clinical trials and medical device investigations. Focus will be on the EU regulatory framework, and the insurance, ethical review, data protection, and event reporting requirements and how the European Clinical Research Infrastructure Network (ECRIN) aims to overcome some of these challenges. ECRIN is supporting the authorisation, set-up and conduct of a portfolio of 50 multinational clinical trials through its devolved organisational structure across Europe. In addition, ECRIN is part of several H2020 funded new research infrastructure instruments and initiatives, focusing on specific areas, like Rare Diseases and Paediatrics, and aiming to facilitate access to patient population, national clinical hubs and investigator networks.

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GENERATING EVIDENCE TO IMPROVE CARE AND OUTCOMES FOR PEDIATRIC INHERITED METABOLIC DISEASE: THE CANADIAN INHERITED METABOLIC DISEASES RESEARCH NETWORK

MULTI-NATIONAL CLINICAL TRIALS/REGISTRIES

Beth K Potter, PhD; University Research Chair in Health Services for Children with Rare Diseases, Associate Professor and Interim Graduate Program Director, School of Epidemiology and Public Health, University of Ottawa; Affiliate Investigator, Children's Hospital of Eastern Ontario Research Institute; Senior Adjunct Scientist, Institute for Clinical Evaluative Sciences; Epidemiologist, Newborn Screening Ontario

Background: Advances in screening and diagnosis and the development of new therapies have improved care and health for many children with rare diseases, including inherited metabolic diseases (IMDs). Despite these important advances, evidence gaps remain related to the effectiveness of interventions embedded in health care systems and in association with a range of patient-centred outcomes from across the 'triple aim' (i.e., clinical outcomes, patient and family experiences with care, and health system impacts). Methods: The Canadian Inherited Metabolic Diseases Research Network (CIMDRN) is a pan-Canadian multi-disciplinary network of centres and collaborators created to address these gaps through a program of practice-based research that leverages observational data to understand existing variation in care and outcomes. CIMDRN has established a consent-based cohort of children born from 2006 to 2015 and receiving care for any of 31 targeted IMDs across 13 participating Canadian treatment centres. For participating children, families, and centres, we collect data from a range of sources including clinical charts, parent interviews and surveys, provider surveys, and health care administrative data. Results: We have enrolled 798 children in our cohort. Clinical and parent-reported data have been valuable for identifying areas of important variation in practice as well as child and family experiences with care. Toward the creation of a registry as a platform for embedded randomized trials and other evaluative studies and in partnership with patients and families, we have also established core outcome sets to harmonize collection of rigorous outcomes for two specific pediatric IMD. Conclusion: A collaborative multi-disciplinary network of investigators and centres has led to important insights about variation in care and outcomes for children with IMDs. As a sustainable long-term strategy to generate evidence to improve care, core outcomes-focused registries developed in partnership with patients and their families hold promise. Such registries may facilitate future efficient evaluative studies for IMDs and their methods may be generalizable to other rare pediatric diseases.

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DEVELOPING THERAPIES FOR CONGENITAL MYOPATHIES: UNMET NEEDS AND POTENTIAL SUCCESSES

GENERALIZABLE THERAPEUTIC APPROACHES FOR RARE DISEASES

James J. Dowling, MD, PhD Mogford Campbell Family Chair of Paediatric Clinical Neuroscience, Staff Clinician, Division of Neurology, Senior Scientist, Program for Genetics and Genome Biology Hospital for Sick Children. Associate Professor, Departments of Paediatrics and Molecular Genetics, University of Toronto

Congenital myopathies are a clinically and genetically heterogeneous group of neuromuscular conditions united by the observation of structural abnormalities seen on muscle biopsy. They include four major subtypes: nemaline myopathy, centronuclear/myotubular myopathy, core myopathy, and congenital fiber type disproportion. As a group, they typically present in infancy, are associated with severe disabilities and co-morbidities, and often result in early mortality. At present there are no treatments for these devastating conditions. However, work from several groups is changing the therapeutic landscape. In this presentation, I will describe progress in drug development across the spectrum of congenital myopathies. In particular, I will emphasize discovery efforts for X-linked myotubular myopathy, where recent data point to a new therapeutic era for the disease. I will also discuss the therapeutic pipelines for RYR1 related myopathies and nemaline myopathy, and highlight successes and failures related to drug development for these disorders.

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TARGETED THERAPIES FOR RARE NEUROMUSCULAR DISORDERS – FIRST STEPS TOWARDS A TREATABOLOME

GENERALIZABLE THERAPEUTIC APPROACHES FOR RARE DISEASES

Hanns Lochmüller MD, PhD, FAAN Senior Scientist, Molecular Biomedicine Program, CHEO Research Institute Professor, Department of Neurology, Faculty of Medicine, University of Ottawa Neurologist, Division of Neurology, The Ottawa Hospital

Most rare genetic diseases do not currently have curative gene-based therapies available, but in some cases a particular drug or intervention can have a significant effect on disease course and functional ability. Ideally, this information would be immediately accessible to the clinician treating the patient at the time of diagnosis, but too often this is not the case and the details can only be discovered after more extensive literature study or expert referral, meaning that for many patients there is a delay before they are put on the optimal therapy. The question is further complicated by the fact that some treatments are only effective for certain genetic causes, even when the overall phenotypic presentation is very similar. We use the example of congenital myasthenic syndromes (CMS), rare but highly treatable neuromuscular diseases, to explore this question. We performed a systematic review of the literature to extract treatment evidence for each CMS subtype linked to genetic details and conclude that even though there is very little evidence from randomised controlled trials, which would be considered the top level of evidence to validate treatment effect, all known CMS subtypes do in fact receive treatment in clinical practice and this information is worthy of presenting to the clinician in a more easily accessible fashion. We propose that just as information about the pathogenicity of specific variants is captured in online databases thanks to major curation efforts by the international diagnostic community, similar open databases curated by disease experts could capture evidence on treatment options linked to variant details in a so-called “treatabolome”, in order that this information could be flagged up to the clinician at the time of diagnosis. The decision about how to treat a patient is still a matter for expert clinical judgement and cannot be left to a computer algorithm, but what the computer algorithm can do is help ensure that the clinician has the evidence available to inform their judgement. This approach is currently being trialled by the European Solve-RD project, where disease experts from several different European Reference Networks will perform similar reviews of the evidence and bioinformaticians from the Centro Nacional de Análisis Genómico (CNAG-CRG) in Barcelona will make them accessible in database form for incorporation into genomic analysis platforms such as RD-Connect.

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TARGETING DISEASE VIA CELL PAINTING AND IMAGE-BASED PROFILING

GENERALIZABLE THERAPEUTIC APPROACHES FOR RARE DISEASES

Anne E. Carpenter, Ph.D. Senior Director, Imaging Platform, Broad Institute of Harvard and MIT, Cambridge MA

Microscopy images contain tremendous information about the state of cells, tissues, and organisms. We work with biomedical researchers around the world to extract metrics from cell images, particularly in high-throughput screening experiments testing drugs in disease model systems. As the cell systems and phenotypes of interest become more complex, so are the computational approaches needed to properly extract the information of interest; we continue to bridge the gap between biologists' needs, such as 3D organoid models, and the latest in computational science, such as deep learning algorithms. Beyond measuring features that biologists specify, we extract even more from images through profiling experiments using the Cell Painting assay, where thousands of morphological features are measured from each cell's image. We are working to harvest similarities in these "profiles" for identifying how drugs and genes affect cells, identifying the functional impact of cancer-associated alleles, discovering disease-associated phenotypes, and identifying novel therapeutics. Ultimately, we aim to make perturbations in cell morphology as computable as genomics data. All novel algorithms and approaches from our laboratory are released as open-source software, including CellProfiler, CellProfiler Analyst, and cytominer.

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OPEN SCIENCE DRUG DISCOVERY – THE SCIENTIFIC CASE AND AN OPERATING BUSINESS MODEL

GENE EDITING

Aled Edwards, Structural Genomics Consortium & M4K Pharma

M4K Pharma (Meds for Kids) is a virtual open science drug discovery company that relies on regulatory exclusivity as its primary intellectual property and commercial asset, in lieu of patents. In many cases and in key markets, using regulatory exclusivity can provide equivalent commercial protection to patents, while also being compatible with open science. M4K has attracted >\$4M in funding for its drug discovery program from government, foundation and individual funders, whose collective expectation for returns on investment will make it possible to commercialize therapeutics at affordable prices. M4K is piloting this open science business model in a rare paediatric brain tumour, and we have just launched M4ND (NeuroDegeneration) to initiate open science drug discovery programs in ALS and Parkinson's disease. Based on the interest in the model, and the scientific and commercial need in the area of rare diseases, we intend soon to launch M4RD and drive a community-driven, open science model to invent affordable treatments for rare diseases.

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INTERVENTIONAL GENOMICS IN CONGENITAL MUSCULAR DYSTROPHY

GENE EDITING

Dwi U. Kemaladewi, Div. of Medical Genetics, Dept. of Pediatrics School of Medicine, University of Pittsburgh, USA

Congenital muscular dystrophies (CMD) represent a heterogeneous group of autosomal recessive disorders, manifesting as severe muscle wasting and poor motor movements, which present at birth or shortly thereafter. About 40% of CMD cases are classified as LAMA2-deficient and caused by mutations in the LAMA2 gene encoding Laminin-2 protein, which plays a crucial role in the structural stability of skeletal muscle and Schwann cells. Individuals with LAMA2-CMD present with significant hypotonia and weakness of mainly the lower extremities and never achieve independent ambulation. There are currently no treatments available for these patients. We have previously shown that CRISPR/Cas9-mediated correction of a splice-site mutation improves the dystrophic phenotypes in Lama2-deficient mice (dy2j/dy2j). However, due to the heterogeneity of disease-causing mutations, translation of this strategy to clinic requires individualized, mutation-specific development of treatments, which may be challenging from a regulatory- and drug development point of view. In contrast, targeting disease modifier gene provides an approach that is mutation-independent and thus can be applicable to all patients. Therefore, we present an approach to robustly upregulate a previously characterized disease modifier gene, Lama1, using a CRISPR/dCas9-based transcriptional activation system, in the dy2j/dy2j mice. We demonstrate that upregulation of Lama1, when initiated at birth, successfully prevents the manifestation of dystrophic pathophysiology. An important question for future therapeutic approaches for a variety of disorders concerns the therapeutic window and phenotypic reversibility. We show that therapeutic intervention initiated at an older age with advanced disease progression can lead to significant rescue of the dystrophic phenotype, indicating that post-symptomatic treatment provides a substantial benefit in the dy2j/dy2j mouse model, even in the context of pre-existing dystrophic pathology and peripheral neuropathy. Collectively, our data demonstrate the feasibility and therapeutic benefit of CRISPR/dCas9-mediated modulation of a disease modifier gene, which opens up an entirely new and mutation-independent treatment approach for all LAMA2-CMD patients. Moreover, it serves as a proof-of-concept strategy that can be applied to a variety of disease modifier genes and a powerful therapeutic approach for rare diseases.

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GENOME EDITING TO PRODUCE PRECISION MODELS FOR PRECISION MEDICINE

GENE EDITING

Lauryl MJ Nutter, The Centre for Phenogenomics, The Hospital for Sick Children, Toronto, Canada

Genome editing using RNA-guided nucleases such as CRISPR/Cas9 has enabled rapid and efficient production of mouse and rat models of human variants for diagnostic, mechanistic, and therapeutic development studies. Complementing the bespoke models produced for individual scientists are the efforts of the International Mouse Phenotyping Consortium to produce single-gene knockouts for every protein-coding gene in the mouse. The Centre for Phenogenomics encourages nominations from scientists to feed its high-throughput knockout mouse phenotyping and production pipeline to leverage these activities for their own research. In this way, we have supported the identification of several Autism Spectrum Disorder gene candidates that affect neuroanatomical development. We have further produced customized mouse models with point mutations orthologous to human disease alleles that are being used in preclinical studies. Recently we have completed a collaborative effort for genome-wide analyses to assess off-target mutagenesis mediated by Cas9 activity during model production. Together these approaches and data provide affordable and timely access to research tools and data that support rare disease research.

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BASE EDITING STRATEGY ALLOWS HIGH FREQUENCY INSERTION OF THE PROTECTIVE A673T MUTATION IN THE APP GENE TO PREVENT THE DEVELOPMENT OF ALZHEIMER'S DISEASE

GENE EDITING

Antoine Guyon, Jacques P. Tremblay, Joël Rousseau, Tom Bertin, Frédéric Raymond

There are currently 47.5 million cases of Alzheimer's disease (AD) in the world and there will be 75.6 million cases in 2030 according to the World Health Organization. Among these cases, 5 to 10% are due to rare mutations in key-genes, which favour the accumulation of plaques. Amyloid precursor protein (APP) is usually cut by the alpha-secretase, however an abnormal cut by beta-secretase leads to the accumulation of beta-amyloid peptides, which form plaques in Alzheimer patient brain. However, it was discovered that a variant of the APP gene (A673T) in Icelanders reduces by 40 % beta-secretase cutting and prevents the development of AD in older person (more than 95 years). We hypothesized that the insertion of this mutation in the patient genome would be an effective and sustainable treatment to slow down the progression of familial Alzheimer's disease forms (FAD). The objective of our project was in a first time to show the protective effect of A673T in a FAD APP gene and determine against which mutation the treatment was the most effective. Secondly, we wanted to achieve a permanent correction by base editing to insert the A673T mutation and obtain evidence of the reduced formation of amyloid plaque. Plasmids containing one mutation responsible for a FAD were transfected in neuroblastoma SH-SY5Y and the supernatant was harvested 72 hours later. Another plasmid containing this mutation in addition of the A673T mutation was transfected in parallel. Every known FAD mutations in exon 16 and 17 of APP were tested. The concentrations of A 40 and A 42 peptides were quantified with the Meso Scale Discovery's A kit. The A 40 and A 42 peptides were decreased when the A673T mutations was added to most of the FAD mutations, this reduction reached 80% in some cases. Next, we tried to introduce the A673T mutation by base editing with the CRISPR/Cas9 system. The APP gene was modified in HEK 293T cells and in SH-SY5Y neuroblastoma using a nCas9-cytosine deaminase enzyme, which allowed to change a cytosine into a thymine. Several deaminase and Cas9 variants were tested to compare the conversion efficiency. The results were characterized and quantified by Deep Sequencing. We succeeded to insert the A673T mutation in up to 57% of the APP genes. Our approach aims to attest the protective effect of A673T on Alzheimer's familial forms and the efficiency of base editing in the development of treatment against genetic diseases.

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AAV GENE THERAPY FROM BENCH TO BEDSIDE

CELL & GENE THERAPY

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The first AAV-based drugs have received market approval in both US and EU, and a number of additional products are under development for both inherited and acquired diseases. Among them are lysosomal storage diseases, and our group has developed a therapeutic approach based on systemic administration of AAV8 that targets liver for stable systemic release of lysosomal enzymes whose safety and efficacy are currently being investigated in a phase I/II trial in patients with mucopolysaccharidosis VI. We are also interested in overcoming one of the major challenges of AAV-mediated gene transfer which is its limited cargo capacity. In this case we are testing up to humans strategies based on the combined use of two or more AAVs each carrying one part of a large expression cassette using the retina as a target tissue for gene therapy of inherited retinal degenerations.

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PRECLINICAL STEM CELL MODELS OF TUBEROUS SCLEROSIS COMPLEX AND ITS RELATED LUNG NEOPLASM LYMPHANGIOLEIOMYOMATOSIS FOR THERAPEUTIC DEVELOPMENT.

CELL & GENE THERAPY

William L Stanford, Ottawa Hospital Research Institute, Ottawa, ON Canada

Tuberous sclerosis complex (TSC) is a rare multi-system disorder arising from inherited or spontaneous heterozygous germ line mutations in the TSC1 or TSC2 genes. Somatic second hit mutations cause low-grade tumors in the brain, kidneys, heart, eyes, lungs, and skin. TSC neoplasms broadly fall into two categories: neurological tumors that arise from neural progenitor cells that can cause severe epilepsy and cognitive impairment and mesenchymal neoplasms such as angiofibroma, renal angiomyolipoma, and pulmonary lymphangioleiomyomatosis (LAM), which contain smooth muscle-like cells expressing neural crest markers, suggesting a neural crest cell of origin. LAM only occurs in women of reproductive age, arising spontaneously or in 30% of TSC women. Consistent with hyperactive mTOR signaling in TSC tumors, the mTORC1 inhibitor rapamycin is the only approved treatment for LAM and other manifestations of TSC; however, rapamycin is only tumorstatic and only slows clinical progression. The inability to grow primary TSC patient cells in culture has impaired the identification of novel drugs to complement rapamycin and kill TSC tumor cells. To overcome the inability to grow primary TSC and LAM cells, we used reprogramming and genome editing to generate human stem cell-based models of neural and mesenchymal TSC tumors, which demonstrate the physiological and molecular hallmarks of TSC neoplasms. Furthermore, working with collaborators we co-developed a novel lung mimetic 3D culture system in which to grow LAM-like neural crest cells. Small molecule drug and CRISPR-based synthetic lethal screens have identified novel drugs that demonstrate specific cytotoxicity against TSC-deficient cells.

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HEMATOPOIETIC STEM CELL GENE THERAPY FOR CYSTINOSIS: CLINICAL TRANSLATION AND MECHANISM OF ACTION

CELL & GENE THERAPY

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Cystinosis is a lysosomal storage disorder caused by mutations in the CTNS gene, encoding the lysosomal transmembrane transporter cystinosin. As a consequence, cystine builds up in all tissues and eventually causes multi-organ degeneration, especially affecting the kidney and eye. We previously showed in *Ctns*^{-/-} mice that transplantation of hematopoietic stem and progenitor cells (HSPCs) resulted in abundant integration of bone marrow-derived cells within all tissues, tissue cystine decrease and long-term kidney, eye and thyroid preservation. We observed that HSPCs differentiated into macrophages that extended intercellular bridges called tunneling nanotubes (TNTs). In vivo, we visualized TNTs crossing the tubular basement membrane in the kidney of HSPC-transplanted *Ctns*^{-/-} mice and transfer of cystinosin-bearing lysosomes from the interstitial macrophages into proximal tubular cells. Similar mechanism was observed in the eye and thyroid. Given the risks of mortality and morbidity associated with allogeneic HSPC transplantation, we developed an autologous transplantation protocol of HSPCs, ex vivo modified using a Self-Inactivated-lentiviral vector to introduce a functional version of the CTNS cDNA, pCCL-CTNS (backbone pCCL-EFS-X-WPRE). We held pre-pre-Investigational New Drug (IND) and pre-IND meetings with the Food and Drug Administration (FDA). Following the FDA recommendations, we are currently finishing the pharmacological and toxicological studies, we obtained the large-scale Good Manufacturing Practice (GMP) lentivirus vector particle preparation for the clinical trial and complete the manufacturing process development. We are now assembling the IND for a phase I/II clinical trial for autologous, lentiviral vector-modified, CD34⁺ HSPC transplantation for cystinosis. The proposed clinical trial will take place at the University of California, San Diego (UCSD) and will include six patients affected with cystinosis

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GENE THERAPY FOR INHERITED DISEASES OF THE HEMATOPOIETIC SYSTEM

CELL & GENE THERAPY

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Pioneering gene therapy trials have shown that the genetic engineering of haematopoietic stem and progenitor cells can be an alternative to allogeneic transplantation in the treatment of primary immunodeficiencies. Early trials also highlighted the risk of insertional mutagenesis and oncogene transactivation associated with the first generation of gammaretroviral vectors. These events prompted the development of safer, self-inactivating lentiviral or gammaretroviral vectors. These lentiviral vectors have been successfully used to treat over 200 patients with 10 different haematological disorders (including primary immunodeficiencies, haemoglobinopathies and metabolic disorders) and for the generation of chimeric antigen receptor-T cells for cancer therapy. However, several challenges, such as effective reconstitution during inflammation, remain if gene therapy is to be extended to more complex diseases in which haematopoietic stem and progenitor cells can be altered by the disease environment. We discuss the progress made and future challenges for gene therapy and as well as the challenges for its wider use.

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CONSIDERING RARE DISEASE DIAGNOSIS IN INDIGENOUS POPULATIONS: WHERE DO WE START?

INDIGENOUS POPULATIONS

Laura Arbour, Department of Medical Genetics at the UBC Island Medical Program in Victoria, BC.

Indigenous populations face unique health challenges, inequities, and barriers to health-care in Canada and around the world. As such, they typically have poorer health outcomes than do non-Indigenous groups. In the current mainstream milieu of advancing diagnostic and therapeutic technologies, there is great potential for further disparity between non-Indigenous and Indigenous populations in accessing equitable diagnostic opportunities including those related to rare disease. One in 12 persons world-wide is affected with a rare disease including in Indigenous populations. Based on this measure, it would be expected that more than 100,000 Indigenous persons in Canada will be affected. Furthermore, rare disease may become common in certain communities and geographic regions resulting in shifts of health care priorities to address those conditions usually considered rare. In British Columbia, long QT syndrome, a genetic condition predisposing to sudden cardiac death, and primary biliary cholangitis are two examples. In keeping with the United Nations Declaration on the Rights of Indigenous Peoples, Indigenous peoples have a 'right to self determination' and the 'right to access, without any discrimination, to all social and health services'. We argue these rights include access to rare disease diagnosis and services. Silent Genomes: Reducing health care disparities and improving diagnostic success for children with genetic diseases from Indigenous populations, is a recently funded Genome Canada/Canadian Institutes for Health Research Initiative and will address these issues in the context of genetic disease.

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LIFE LANGUAGES

INDIGENOUS POPULATIONS

Gareth Baynam, Faculty of Health and Medical Sciences, The University of Western Australia

Without language, one cannot talk to people and understand them; one cannot share their hopes and aspirations, grasp their history, appreciate their poetry or savour their songs. -Nelson Mandela From birth we communicate with each other through language. This includes written languages; oral languages; and our body language, such as our facial expressions. The precise and culturally safe use of language is critical to improving both Aboriginal Health, and the lives of individuals living with rare diseases. The Life Languages project is to retain and empower Aboriginal language, for all the benefits that brings, and partner that with our genetic language to transform health care.

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GENETIC DISORDERS IN THE AMISH AND MENNONITE COMMUNITIES: HARNESSING THE RESULTS OF RESEARCH TO BENEFIT CHILD HEALTH

INDIGENOUS POPULATIONS

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For over 25 years, we have been cataloguing the clinical features and molecular etiology of rare genetic disorders in the Old Order Amish (OOA) and Old Order Mennonite (OOM) populations of southwestern Ontario, and have created a publicly accessible and searchable database (www.biochemgenetics.ca/plainpeople). Since 2003, we have been offering newborn, childhood and adult genetic screening in the OOA and OOM population. Expanded newborn screening through targeted mutation analysis has led to the diagnosis of rare disorders before the onset of symptoms. Recognition of pathognomonic features and targeted mutation analysis enables rapid diagnosis of affected children, thus avoiding extensive and expensive investigations for families who are self-pay. Carrier testing allows for the identification of couples at risk, so that management plans can be set in place prior to delivery. In the Ontario OOA population, homozygous Y454S variants in the histidyl tRNA synthetase (HARS) gene (OMIM #614504) cause a disorder characterized by progressive sensorineural hearing loss and cone-rod dystrophy, which was originally classified as Usher syndrome type 3b. However, mild viral illnesses may lead to high fever accompanied by encephalopathy, visual hallucinations, and acute, sometimes reversible, loss of hearing and vision. In severe cases, there may be a capillary leak syndrome with life-threatening acute respiratory distress syndrome. Mortality rate has been over 25%. We have documented the natural history of children with HARS syndrome and have established an extremely high carrier frequency of 1 in 5 in the OOA Ontario population. The features of HARS syndrome overlap with other recessive aminoacyl-tRNA synthetase disorders, with growing evidence for an autoinflammatory effect triggered by abnormal tRNA function. Functional studies have shown that histidine incorporation by mutant Y454S HARS is impaired at high temperatures and rescued with histidine supplementation. These observations have led us to use nonsteroidal anti-inflammatories (NSAID's) in the management of fevers in children with HARS syndrome. As well, we are conducting a clinical trial on the use of L-histidine in the treatment of children with HARS syndrome and monitoring their vision and hearing over a 2 year period.

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THE RESPONSIBILITY OF RESEARCHING RARE DISORDERS & RARE POPULATIONS INDIGENOUS POPULATIONS

Maui Hudson | Faculty of M ori and Indigenous Studies |The University of Waikato, New Zealand

Genomic research has longstanding problems with diversity, especially for Indigenous peoples who made up only 0.05% of all genome-wide association studies in 2016. Indigenous populations worldwide face unique health challenges, inequities, and barriers to healthcare resulting in typically poorer health outcomes than non-Indigenous groups. While genomics research has greatly advanced health outcomes in mainstream populations, the dearth of relevant genomics research for Indigenous peoples may actually increase health inequities. Unequal access to genomic technologies and lack of relevant population genetic variation data all contribute to limited relevance and reduced effectiveness of genetic and genomic research for Indigenous peoples. Science will strive to improve its understanding of indigenous genomics and rather than follow a path that disempowers indigenous communities through the appropriation of their genetic heritage, we would like to see research partnerships that shift the frame from benefit-sharing to power-sharing. Enabling indigenous led partnerships through investment in capacity building and infrastructure and supporting community control over the use of indigenous samples and genomic data are key pathways to building trust and confidence. This presentation will describe efforts to develop and implement Indigenous Guidelines for Genomic Research in New Zealand.

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FROM GENE DISCOVERY TO NEWBORN SCREENING IN INDIGENOUS POPULATIONS IN MANITOBA

INDIGENOUS POPULATIONS

Dr. Cheryl Rockman-Greenberg, University of Manitoba, Winnipeg, Manitoba, Canada

Newborn screening is a system for identifying genetic and biochemical disorders in newborns that will lead to overall improvement in the public's health and improvement in the long-term health of individuals diagnosed with these conditions. Principles of newborn screening traditionally follow the principles outlined by Wilson and Jungner, 1968. Specifically, the condition should be severe, should be treatable, screening test should be sensitive and specific, with diagnostic testing and follow-up resources in place and have a positive cost: benefit to society. Newborn screening in the province of Manitoba, Canada continues to evolve since its inception in the 1960's. Manitoba has a population of ~1.24 million individuals with ~18% of the Manitoba population being Indigenous (First Nations, Metis, or Inuit) vs. 5.6% of Canada's total population (StatsCan, 2016). The proportion of Indigenous people in Manitoba ranges from 50-100% of the population in northern and remote areas of the province to < 5% in some communities in the southern urban and rural areas. Numerous autosomal recessive single gene disorders have been identified in Manitoba's Indigenous population. Our approach to the management of 2 hereditary disorders overrepresented in Indigenous communities in Manitoba and causing significant morbidity and mortality - specifically glutaric aciduria type 1 (GA1) and severe combined immunodeficiency disorder (SCID) will be presented. The background to these 2 clinical entities, the results of basic research to identify their cause, the development, implementation and results of targeted newborn screening programmes, lessons learned and recent programmes including transition to universal newborn screening will be presented. The importance of community engagement and ensuring expanded newborn screening programmes are tailored to one's population cannot be overemphasized.

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GENE THERAPY IN LYSOSOMAL STORAGE DISEASES - FABRY DISEASE AND METACHROMATIC LEUKODYSTROPHY

STEM CELLS/REGENERATIVE MEDICINE/GENETICALLY MODIFIED CELL THERAPIES/
CLINICAL APPLICATIONS OF GENE THERAPY

C. Anthony Rupa(d), Jeffrey A Medin(a),(b), Aneal Khan(c), Ju Huang(b), Dwayne Barber(b), Christiane Auray-Blais(e), Graeme Fraser(f), Daniel H Fowler(g), Armand Keating(b), Michael L West(h), Ronan Foley(f) , Stephanie Newman(d), Srinitya Gavannavarapu (d) Medical College of Wisconsin, Milwaukee, WI, United States; (b)University Health Network, Toronto, ON, Canada; (c)University of Calgary, Calgary, AB, Canada; (d)Western University, London, ON, Canada; (e)Universite de Sherbrooke, Sherbrooke, QC, Canada; (f) McMaster University, Hamilton, ON, Canada; (g)Rapa Therapeutics, Rockville, MD, United States; (h)Dalhousie University, Halifax, NS, Canada.

Disease specific treatments for lysosomal storage diseases (LSDs) include enzyme replacement therapy (ERT), small molecule chaperones and substrate inhibitors, haematopoietic stem cell therapy (HSCT), and in vivo/ex vivo gene therapy. ERT and gene therapies rely on the ability of cells to uptake exogenously provided lysosomal enzymes from ERT or over-expressing distal transduced cells. Fabry disease which typically presents with parathesias, angiokeratomas and progresses to renal failure and hypertrophic cardiomyopathy is caused by a deficiency in alpha-galactosidase A (a-gal A) activity. Fabry disease is treated with ERT treats which is expensive and intrusive. We describe a multi-center, phase I clinical trial using gene transfer to treat men with Fabry disease (clinicaltrials.gov#NCT02800070) and to determine the feasibility and safety of this procedure. The protocol involves mobilization of Fabry patient hematopoietic stem/progenitor cells (HSPCs), ex vivo recombinant lentivirus-mediated gene transfer of a-gal A cDNA into those cells and infusion of the transduced HSPCs into minimally ablated autologous recipients. The first Fabry patient received a single dose of vector-transduced cells in January 2017. Two other Fabry patients have since received the transduced cell product (with more patients in the queue). No serious adverse events have occurred to date. We report results for patient 1 at two years post-infusion of the transduced cells. We tracked a-gal A activity in leukocytes and plasma, vector copy number in peripheral blood and bone marrow cells, antibody titers in plasma, and the concentrations of substrates and catabolites in both plasma and urine. Results show durable engraftment and persistence of vector-transduced HSPCs in this Fabry patient that are functionally enabled to produce a-gal A continually. This protocol appears to be feasible and safe; application to other patients and long-term effectiveness are still to be studied. Metachromatic Leukodystrophy is a LSD that affects the central and peripheral nervous systems and typically presents in infancy. Many LSDs have neurological symptoms that are refractory to ERT as the exogenous enzymes cannot cross the blood brain barrier. HSCT with cells that have been transduced with a lentivector and overexpress ARSA appears to be effective in preventing CNBS disease in pre-symptomatic children. We describe preclinical studies using ICV delivery of vectors to rapidly express ARSA in the CNS.

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OCULAR GENE THERAPY: WHAT ARE WE LEARNING FROM CLINICAL TRIALS

STEM CELLS/REGENERATIVE MEDICINE/GENETICALLY MODIFIED CELL THERAPIES/
CLINICAL APPLICATIONS OF GENE THERAPY

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After the success of ocular gene therapy for Leber congenital amaurosis (LCA), patients with eye diseases have been keenly interested in gene therapy. To date, only Luxturna™ for the treatment of the RPE65 form of LCA has achieved approval from the US FDA. There are now many opportunities to enroll in trials of ocular gene therapy. Of the trials currently underway, some report Phase I/II results (achromatopsia, age-related macular degeneration, choroideremia, Leber hereditary optic neuropathy, X-linked juvenile retinoschisis), while others are still without results (X-linked retinitis pigmentosa, Usher syndrome). The trials are not restricted to viral mediated gene replacement, but may include gene silencing with anti-sense oligonucleotides. Partnerships with industry have been important as the costs to investigator-sponsored trials are considerable. In undertaking clinical trials, the investment of resources has been significant such that only a few centres now have the capacity and expertise to undertake trials. Patients in many cases must travel and commit significant time to participate in the trials. Clinical trials of eye disorders can rely on many modalities to test visual function and visual structure, providing measures of safety and efficacy of a product. Some outcome measures may be particularly important for a specific eye condition, whereas other measures will be more important to determine change for a different condition. The eye is a complex organ that demands a tailored approach to the design of clinical trials. Regulators are also learning to accept that alternates to conventional outcome measures may need to be considered as surrogate measures of visual function. To date, virtually all patient trials of ocular gene therapy have experienced immune responses to the existing approach of either subretinal or intravitreal delivery of viral vectors. The advantages of ocular gene therapy are threefold: 1) compartmentalization of the vector in the eye, 2) the ability to manage the consequences to the eye from inflammation, and 3) the relative immune privilege of the eye itself. Despite these advantages, inflammation still occurs and must be addressed in future designs of gene therapy trials. Finally, in our rush to offer gene therapy to patients, researchers must carefully consider the possibility of failure and the great risk of psychological harm from offering a trial to the patient who, in fact, considered the approach to be a treatment.

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THERAPEUTIC INSIGHTS FOR RETT SYNDROME FROM THE STUDY OF MECP2 MODIFIERS IN MICE

STEM CELLS/REGENERATIVE MEDICINE/GENETICALLY MODIFIED CELL THERAPIES/
CLINICAL APPLICATIONS OF GENE THERAPY

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The onset and expression of clinical features can vary widely in genetic diseases with a common molecular root, often due to second site gene modifiers. Identifying the modifiers represents a transformative discovery for the disease they alter, shifting understanding of pathogenesis and providing avenues for diagnosis, prognosis, and therapy development. We carried out a forward genetic suppressor screen in a mouse model for Rett syndrome (RTT), a neurological condition caused by mutations in X-linked methyl CpG binding protein 2 (MECP2). MECP2 regulates key activities in the brain and body, with mutations impacting both adult and childhood neuropsychiatric and immune disorders. A modifier screen is an unbiased forward-genetic approach to find mutations that suppress or enhance a phenotype of interest, allowing the organism to reveal important pathways for morbidity. In a screen of over 3000 genomes, 96 mouse lines that improve health traits and prolong life of the *Mecp2* mice were isolated. Whole exome sequencing and association analysis was employed to identify the modifying mutations in candidate genes, which fall into common biological pathways. One group of modifiers points to lipid metabolism as being perturbed in RTT, suggesting that metabolic modulation is a treatment avenue. MECP2 provides a bridge for the repressor complex NCoR1/SMRT/HDAC3 to regulate its targets on DNA, and the modifiers suggest that this complex is key to RTT pathology. Surprisingly, mutations in multiple genes involved in the DNA damage response, which repairs double-stranded breaks, can improve RTT-like symptoms in mice. Because neurons are non-dividing cells, an ongoing question is how mutations in this pathway improve symptoms. Unbiased genetic screens in model organisms can uncover unexpected pathways that contribute to disease pathophysiology and provide insight into therapies. Many of the lines carry more than one modifier locus, and combining modifiers from two different pathways greatly improves symptoms, suggesting that combination therapies will be effective in treating RTT. Our work demonstrates how model organisms can be used as platforms for understanding variation in rare disease severity and onset, thereby informing therapeutic intervention.

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BUILDING HUMAN-ON-A-CHIP PHENOTYPIC MODELS TO PREDICT IN VIVO OUTCOMES FOR EFFICACY AND TOXICITY FOR RARE DISEASES

STEM CELLS/REGENERATIVE MEDICINE/GENETICALLY MODIFIED CELL THERAPIES/
CLINICAL APPLICATIONS OF GENE THERAPY

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An in vitro system that in preclinical studies can predict efficacy for human genotypic response to drugs, especially for rare diseases, would be useful for the development of appropriate patient specific pharmaceutical interventions. Hesperos has developed human-on-a-chip technology that is composed of commercially available human cells and cells derived from iPSCs as demonstrated in our 2- and 4-organ systems published in Nature Scientific Reports, Biomaterials and Advanced Functional Materials. The interconnected systems with continuous medium recirculation allows both the parent compound and its metabolites to be evaluated in the same platform due to a low volume of fluid resulting in accumulation of metabolites at a physiologically relevant concentration. This interconnected platform is better suited for preclinical drug testing than single organ systems for the same reason that human and animal models are currently the gold standards for toxicity and efficacy determination as they allow communication between the organ systems in the body. This system is capable of predicting efficacy for specific disease phenotypes for rare diseases using patient specific iPSCs but can also examine concurrent toxicity as well as of its application to evaluation of CRISPR gene editing technologies. Hesperos has received Phase II and Phase IIB SBIR grants from NCATS to apply advanced manufacturing technologies and automation to these systems in collaboration with NIST in addition support from pharmaceutical and cosmetic companies. This talk will also give results of six workshops held at NIH to explore what is needed for validation and qualification of these new systems.

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FDA EXPEDITED PATHWAYS AND REGENERATIVE ADVANCED THERAPY DESIGNATION

STEM CELLS/REGENERATIVE MEDICINE/GENETICALLY MODIFIED CELL THERAPIES/
CLINICAL APPLICATIONS OF GENE THERAPY

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FDA has several programs that support the expedited review of medical products for the treatment of severe and life-threatening conditions: Accelerated Approval, Priority Review Designation, Fast Track Designation, Breakthrough Designation, and Regenerative Medicine Advanced Therapy Designation. Accelerated Approval allows for the approval of a drug/biologic addressing an unmet medical need earlier based on a surrogate endpoint, and Priority Review shortens the review time to 6 months for serious conditions where there is an unmet medical need. Fast Track, Breakthrough, and Regenerative Medicine Advanced Therapy Designation programs are intended to expedite product development and review. This presentation will review FDA Expedited Programs with a focus on the FDA experience with the most recently implemented program, Regenerative Medicine Advanced Therapy Designation.

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CLINICAL AND REGULATORY CONSIDERATIONS AND THE U.S. APPROVAL OF LUXTURNA™ (VORETIGENE NEPARVOVEC-RZYL)

STEM CELLS/REGENERATIVE MEDICINE/GENETICALLY MODIFIED CELL THERAPIES/
CLINICAL APPLICATIONS OF GENE THERAPY

Kathleen Reape MD, Chief Medical Officer, Spark Therapeutics

Objective: This presentation will describe some of the challenges encountered in the clinical development program underlying the U.S. approval of voretigene neparvovec-rzyl for use in patients with vision loss due to biallelic RPE-65 associated inherited retinal dystrophy. **Description:** From a translational standpoint, a large animal model (Briard dogs) existed and nonclinical proof of concept was quite robust. However, developing a clinical program to support the regulatory approval of a gene therapy for a rare inherited retinal disease for which there were no other treatments available at the time was far from straightforward. For this program, a novel primary endpoint was developed (the multi-luminance mobility test or MLMT), that was relevant to the clinical deficits specific to this condition. This test was refined over the course of the Phase 1 studies, and a number of measures were taken in order to introduce a high level of rigor into the interpretation of the MLMT. The use of a novel endpoint necessitated a separate validation study. As this was a rare genetic disease without any other treatments, genotyping in this patient population was not universal, and patient identification was difficult. Choice of controls was also a point of significant discussion. Related to the rarity of the condition, there was a dearth of natural history data, so a separate natural history study was also conducted. Gene therapy trials require long-term follow-up of clinical trial participants, and this is currently ongoing. **Conclusions:** There are unique challenges associated with the development of gene therapies for rare diseases where no approved product currently exists. It is helpful to engage with patients, families, advocacy groups, researchers, investigators and regulators early and often to ensure that the clinical development and regulatory strategies support the demonstration of efficacy and safety in individuals with rare diseases.

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I AM A PATIENT. PLEASE LISTEN TO ME

PATIENT FOCUSED DRUG DEVELOPMENT

Marlene E. Haffner, MD, MPH - Haffner Associates, LLC - Orphan Solutions

Budding physicians are taught early in their medical school experience to “listen to the patient.” Drug developers and researchers did not always listen to the patient and what needs they had. In fact, pharmaceutical companies were hesitant to include patients in any aspect of drug development unless the patients were in clinical trials or until the time of Advisory committee meetings to advise if FDA should approve the product. But, the patient knows his/her disease better than anyone. Drug developers and regulators, even though highly skilled, are not experts in the experience of living with the disease. A study was done in the Netherlands of young boys with Duchenne Muscular Dystrophy. Many were already wheelchair bound. It was expected the answer would be – “to walk again.” But no, the answer was, to be able to use their arms and hands to use computer skills, to brush their teeth, to feed themselves. These were what was important to them. In 2012, FDA developed the Patient Focused Drug Development Project. Patient groups worked together to advise FDA on what was desirable to them in a new treatment for their disease. And so, in 2019, let’s listen to the patient. Let’s involve them early in the design of clinical trials. Let’s find out what is important to those we, as developers and regulators, wish to serve.

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DEVELOPING A TREATMENT FOR THE ULTRA RARE BLACK BONE DISEASE

PATIENT FOCUSED DRUG DEVELOPMENT

Nick Sireau, PhD, Chair and CEO of the AKU Society

Alkaptonuria is an ultra rare genetic disease also called AKU or Black Bone Disease. It is caused by a defective enzyme that leads to the accumulation of a substance called homogentisic acid at 2,000 times the normal rate. This causes bones and cartilage to go black – a process called ochronosis – leading to severe osteoarthritis at an early age. The AKU Society is a patient group that is co-leading an EC-funded consortium of 13 organisations (hospitals, pharma, biotechs, patient groups and universities) called DevelopAKUre. This consortium has carried out a phase 2 and a phase 3 clinical trial of a drug called nitisinone that stops the accumulation of homogentisic acid. The three-month phase 2 trial was successful and identified a dose of the drug to use in the four-year phase 3 trial. The clinical part of the phase 3 trial ended in January this year. The team is now analyzing the data, with results expected in the autumn of this year. If successful, the pharma company that owns nitisinone (SOBI) will file for marketing authorization with the European Medicines Agency. In parallel, we have also been carrying out an off-label study of nitisinone at the National AKU Centre hosted by the Royal Liverpool University Hospital in the UK. Five-year results of this off-label study have been published and show that nitisinone arrests and can even partially reverse the damage caused by AKU. Our mouse model of AKU – hosted by the University of Liverpool – also shows that nitisinone leads to a significant reduction in homogentisic acid and blocks the progression of the ochronosis that causes the problems in AKU. The AKU Society is at the centre of a global movement of AKU patient groups that includes many countries in Europe, the Middle East, Asia, North America and South America. Despite being an ultra rare disease, patients are active in their respective countries and internationally to raise awareness about the illness and improve access to treatment.

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PATIENT-FOCUSED DEVELOPMENT OF ADVANCED THERAPIES: REGULATORY PERSPECTIVE

PATIENT FOCUSED DRUG DEVELOPMENT

Larissa Lapteva, M.D., M.H.S., M.B.A., Associate Director, Division of Clinical Evaluation, Pharmacology, and Toxicology Office of Tissues and Advanced Therapies Center for Biologicals Evaluation and Research, Food and Drug Administration

US FDA's Office of Tissues and Advanced Therapies oversees development of advanced therapies and helps facilitate their manufacturing and clinical testing. Advanced therapies include cell- and tissue-based products, gene therapy products, therapeutic vaccines and immunotherapies, among others. In the recent years, FDA has been implementing several initiatives aimed to incorporate patient perspectives and experiences in the development, review, and regulatory decision-making for drugs and biological products. Dr. Lapteva's presentation will outline the current programs and advances in promoting inclusion of patient input into development of cell and gene therapy products intended for use in rare diseases in different therapeutic areas. Key initiatives in patient-focused drug development, new methodological approaches, patient engagement, science of patient input, and incorporation of patient experience data in product development programs will be highlighted. References to the available FDA guidance documents will be provided at the end of the presentation.

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HOW ADVOCATES CAN BRING PATIENT EXPERIENCE DATA TO REGULATORS AND INDUSTRY

PATIENT FOCUSED DRUG DEVELOPMENT

Calvin N. Ho, PhD

All stakeholders in the medicines market are increasingly paying attention to patients' experiences with their disease. Drug regulatory authorities and payers consider patient experiences when deciding whether to approve a new treatment. On the manufacturers' side, clinical trials often hinge on whether patients report feeling better on the investigational drug. Both sides want to bring more treatments to rare disease patients. A key challenge, though, is that there is limited data on what it is like to live with these diseases. Which symptoms matter most to patients? How does the disease affect a patient's quality of life? This presentation discusses one rare disease group's experience with the FDA's Externally-Led Patient Focused Drug Development program. The Tuberous Sclerosis Alliance collected data that help regulators and industry understand how tuberous sclerosis complex and lymphangioleiomyomatosis affect patients and their families. This is just one example of how patient advocates can bring their expertise into drug regulation and development.

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WHAT DOES THE FOX SAY? FOXG1 ORCHESTRATES CORTICO-CORTICAL CONNECTIONS

PATIENT FOCUSED DRUG DEVELOPMENT

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The hallmarks of FOXG1 syndrome, which results from mutations in a single FOXG1 allele, include cortical atrophy and corpus callosum agenesis. However, the etiology for these structural deficits and the role of FOXG1 in cortical projection neurons remain unclear. We found that Foxg1 in pyramidal neurons plays essential roles in establishing cortical layers and the identity and axon trajectory of callosal projection neurons. The neuron-specific actions of Foxg1 are achieved by forming a transcription complex with Rp58. The Foxg1-Rp58 complex directly binds and represses Robo1, Slit3, and Reelin genes, the key regulators of callosal axon guidance and neuronal migration. We also found that inactivation of one Foxg1 allele specifically in cortical neurons was sufficient to cause cerebral cortical hypoplasia and corpus callosum agenesis. Together, our study reveals a novel gene regulatory pathway that specifies neuronal characteristics during cerebral cortex development. Furthermore, our study sheds light on the etiology of FOXG1 syndrome.

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DELEGATE ABSTRACTS

TAMOXIFEN THERAPY IN A MURINE MODEL OF MYOTUBULAR MYOPATHY

ABSTRACT N° B001_2019 / GENERALIZABLE THERAPEUTIC APPROACHES FOR RARE DISEASES

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X-linked centronuclear myopathy (XLCNM), otherwise known as myotubular myopathy (MTM), is a fatal pediatric congenital myopathy caused by loss-of-function mutations in myotubularin (MTM1). Myotubularin functions to regulate endosomal trafficking and the formation of vital muscle substructures such as skeletal muscle triad: a specialized regulator of excitation-contraction (EC) coupling. In addition to its high rate of early childhood disability and neonatal mortality, no effective therapies for MTM currently exist. Consequently, the development of effective therapies for this devastating disease remains of utmost importance. In a murine model of MTM, we identify tamoxifen as a novel therapeutic candidate for MTM. By way of *in vitro* studies and *in vivo* phenotypic rescue with 17- β -estradiol, we show the beneficial effects of tamoxifen to be mediated primarily through estrogen receptor signaling in murine muscle. Moreover, through RNA sequencing and protein expression analyses, we are the first to discover that tamoxifen can improve disease pathophysiology through a novel mechanism of action: the post-transcriptional regulation of dynamin-2 (DNM2), a known genetic modifier of MTM1. Our results uncover the first small molecule therapeutic with pre-clinical efficacy and clinical translatability for myotubular myopathy. Given the widespread use of tamoxifen in pediatrics for indications including breast cancer, rhabdoid tumors, and precocious puberty, our findings provide the necessary groundwork for considering testing via clinical trial of tamoxifen in MTM patients, and thus have immediate clinical implications for this devastating, and presently incurable disease.

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THERAPEUTIC APPROACHES FOR EPIDERMOLYSIS BULLOSA SIMPLEX

ABSTRACT N° B002_2019 / GENERALIZABLE THERAPEUTIC APPROACHES FOR RARE DISEASES

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Epidermolysis bullosa simplex (EBS) is a rare autosomal dominant skin disease characterized by non-scarring blisters and erosions caused by minor mechanical trauma. EBS is caused by different mutations within the KRT5 or the KRT14 gene and results in misfolded keratins that impair normal assembly of the keratin intermediate filaments. Current therapies are palliative, aimed at treating infections and maintaining an acceptable quality of life. In a first attempt to reduce the quantity of keratin aggregates in the cytoplasm of patients' keratinocytes, therapeutic assays at the cellular level using small chaperone molecules were performed. Given their reproducible but temporary and patient-dependent impact on the molecular defect and as several works proposed gene knockout of allele causing disease as a potent therapeutic option for autosomal dominant diseases, we decided to use the Clustered Regularly Interspaced Short Palindromic Repeat (CRISPR)-Cas9 genome editing tool to inactivate the mutant allele for two severe mutations in KRT5 gene. Preliminary deep sequencing results showed specific silencing of this allele. Our next step is to engineer autologous gene edited skin tissue grafts for EBS patients. The production of autografts from patient's edited cells should open the way to precision medicine for epidermolysis bullosa.

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UNDERSTANDING THE DISEASE PATHOGENESIS OF X-LINKED MYOTUBULAR MYOPATHY

ABSTRACT N° B003_2019 / GENERALIZABLE THERAPEUTIC APPROACHES FOR RARE DISEASES

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Centronuclear myopathies (CNM) are a subtype of congenital myopathy characterized by severe muscle weakness and wasting¹. The most common and severe form of CNM is X-linked myotubular myopathy (MTM), a fatal condition affecting 1/50,000 newborn males every year. MTM is caused by mutations in myotubularin1 (Mtm1), which encodes a lipid phosphatase². MTM1 regulates endocytic processes in skeletal muscle including endosome maturation and autophagy³. The main hallmark of the disease is presence of central nuclei, and other characteristics include small muscle fiber size, abnormal T-tubules and calcium homeostasis, and mitochondria aggregation. It has also been shown that depletion of MTM1 results in transcriptional changes. Although we understand the structural and functional consequences of MTM, it is still unknown how the disease pathogenesis progresses. Mtm1 KO mice are great disease model, representative of the disease phenotypes observed in patients. These mice have a lower body weight, hindlimb paralysis and muscle weakness in comparison to their WT littermates at day 35, which is their endpoint as they have shorter lifespan. Mtm1 KO mice are visually different in size than their WT littermates at around day 21. Histological analyses at day 21 show early signs of central nuclei, mitochondria and dysferlin mislocalization. Also, calcium homeostasis genes expression levels are dysregulated at this timepoint. This is suggesting that the transcriptional changes are present during the initiation of histological changes. We are currently performing RNAseq and CHIPseq to further examine the role of transcriptome and epigenetics at this timepoint. In future, other timepoints are going to be investigated to be able to identify the main disease drivers. In the second half of this project, we are currently working to understand the role of MTM1 in muscle by mass spectrometry. Previously, MTM1 and KMT2A, a histone lysine methyltransferase, has been showed to interact⁵. KMT2A is known to modulate the chromatin state to regulate transcription. This could be the potential explanation of the epigenetic changes seen in MTM. Therefore, investigating what MTM1 interacts will give insight into its function as well as the disease pathogenesis.

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INVESTIGATING THE ROLES OF VMA21 IN RELATION TO AUTOPHAGY AND MYOPATHY WITH EXCESSIVE AUTOPHAGY (MEA)

ABSTRACT N° B004_2019 / GENERALIZABLE THERAPEUTIC APPROACHES FOR RARE DISEASES

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It has been established that autophagy is a highly conserved process and is essential in degrading proteins. Dysregulation of this pathway can lead to many different groups of diseases, such as autophagic vacuolar myopathies, specifically myopathy with excessive autophagy (MEA). MEA is a genetically heterogeneous progressive skeletal muscle disease characterized by vacuolated myofibers. In MEA patients, cells have aberrant autophagy, vacuolization or abnormal lysosomal proteolysis. Presently, mutations in the X-linked gene VMA21 are the only known cause of MEA, but these mutations account for only a subset of MEA cases. It is hypothesized that VMA21 may play a role in autophagy regulation. By further understanding the role of this gene, the pathomechanism of MEA can be more defined and potential therapeutics or treatment strategies can be developed. In order to do so, I will establish different MEA disease models using cell lines, zebrafish and mice models. With these different models and patient cells the specific functions of these genes can be elucidated.

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ELUCIDATING THE ROLE OF SPEG IN STRIATED MUSCLE DEVELOPMENT AND FUNCTION

ABSTRACT N° B005_2019 / GENERALIZABLE THERAPEUTIC APPROACHES FOR RARE DISEASES

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Congenital Myopathies (CMs) are neuromuscular disorders that typically present in childhood. The overall prevalence of all CM variants is 1 in 26,000. One of the common subtypes is centronuclear myopathy (CNM) which is characterized by muscle weakness, increased number of myofibers with central nuclei and it may include breathing problems, delayed motor milestones, and cardiomyopathy. Only 60-80% have a known genetic basis and many of the mutated genes have a role in excitation-contraction coupling (ECC). One novel gene recently identified in CNM patients is the Striated Muscle Preferentially Expressed Protein Kinase (SPEG). Patients with SPEG mutations and SPEG knock-out (KO) mice have muscle weakness, increased centralized nuclei in myofibers and dilated cardiomyopathy (DCM). Additionally, SPEG KO mice have neonatal mortality. From the four SPEG isoforms produced in mammals, only SPEG¹ and SPEG² are expressed in developing cardiomyocytes, and the predominant isoform during skeletal-muscle differentiation is SPEG¹. Previous research suggests that SPEG interacts with ECC proteins. SPEG KO mice have decreased phosphorylation levels of junctophilin-2 and hyperactivated ryanodine receptor (RYR2) without changes in RYR2 phosphorylation levels. It interacts with myotubularin, and colocalizes with the calcium channel DHPR and with the calcium transporter SERCA, suggesting it localizes near the Sarcoplasmic Reticulum. Furthermore, disruption of Ca²⁺ transients is due to a process affected prior to Ca²⁺ activation of the cross-bridges. Moreover, SPEG phosphorylates SERCA2a facilitating Ca²⁺ reuptake into the Sarcoplasmic Reticulum. However, the exact mechanism through which absence of SPEG leads to CNM and DCM, as well as its relationship with the ECC pathway remain to be elucidated. Therefore, I aim to establish and characterize a zebrafish SPEG KO model to better understand the role of SPEG during embryonic development. I will also identify more targets that are being phosphorylated by this kinase using AP-MS.

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MULTI EXON SKIPPING AS A POTENTIAL THERAPY FOR NEMALINE MYOPATHY IN ZEBRAFISH

SENTHURI VITHY

ABSTRACT N° C002_2019 / GENE EDITING

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Nemaline Myopathy (NM) is a childhood congenital myopathy which currently has no therapy. The gene nebulin (NEB) accounts for 50% of all cases of NM, with most patients being compound heterozygous for two different mutations in NEB. Patients with NM have significantly reduced levels of nebulin. Nebulin is a giant protein that is mainly expressed in the skeletal muscle, specifically in the sarcomere. Most of the protein consists of repetitive repeats that help nebulin bind to the thin filament. A potential therapy is to delete the repeats that harbor the pathogenic mutations to express a truncated but functional nebulin. This is based on the idea that mutations in NEB lead to reduced protein expression due to the repeats in the proteins being out of frame. For this project, I will be using a zebrafish model of NEB-related NM, which has significantly reduced expression of NEB, motor deficiency and short survival due to a splice donor site mutation in exon 46 in NEB. I will use CRISPR-CAS9 as a tool to delete a whole repeat in the genome of this zebrafish model. My project will be to test the concept of exon skipping as a therapeutic strategy to produce a truncated, but functional nebulin in zebrafish.

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GENE EDITING USING CRISPR/CAS9 IN NEMALINE MYOPATHY

ABSTRACT N° C003_2019 / GENE EDITING

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Gene editing in cells has revolutionize the paradigm of modern cell biology. The ease of use of the CRISPR/Cas9 system for gene manipulation has led to rapid and wide adoption across many fields, including biological research, biotechnology and medicine. This technology allows gen modification by producing a specific double strand cut in the DNA and the repair by homology-independent targeted insertion (HITI) of DNA. We used CRISPR/CAS9 to modify specific mutations in-vitro in muscular disorder to show its potential as a therapeutic tool. We used cells from patients diagnosed with Nemaline myopathy with homozygous loss of exon 55 in the NEB gene due to a founder mutation. Taking advantage of DNA repair mechanism, we use the HITI to reintroduce exon 55 and reestablish its expression at the RNA and protein level. This study provides another piece of evidence that CRISPR/CAS9 based genome editing is a viable therapeutic avenue that can be pursued for treatment of neuromuscular disorders.

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BLACKSWAN FOUNDATION

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

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

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

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

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

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