Cure CLCN4

2022

Inaugural Scientific Meeting

27th & 28th May 2022
London (UK)

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WELCOME

THE BASICS

Welcome to the **Inaugural Cure CLCN4 Scientific Meeting**. Below is some key information for the meeting:

- **Conference description**

This conference will bring together leading academic, clinical and industry speakers from the ion channel, rare disease, and therapeutic discovery fields. Through a series of short talks and panel discussions, we will review the current knowledge on the biology and clinical aspects of *CLCN4*-related condition and establish the necessary steps towards the development of therapeutic options for *CLCN4*-related condition, all the way from the early stages of basic research on animal and cellular models to clinical research, drug discovery, and precision medicine.

- **When & where?**

The meeting will take place on the **27th & 28th May 2022** in London. Please note that the conference has a different venue on each day: the 27th May is at the **Sainsbury Wellcome Centre** and the 28th May is at the **Francis Crick Institute**.

For those who cannot attend in person, there will also be an **option for online attendance** (on Zoom). Zoom access details will be sent via email to all participants.

WELCOME

THE BASICS

- **What equipment will I need if I am joining online?**

All you need to join is a desktop computer or laptop with a good internet connection and working audio. Also, make sure to have downloaded Zoom in advance of the meeting and to have the access link handy (the link will be sent via email ahead of the meeting).

- **How do I register and is it free?**

Registration is free and can be done on our website at: www.cureclcn4.org .

- **How do I get in touch with CureCLCN4?**

You can email us at info@cureclcn4.org

For further information, including travel and accommodation information please visit:

https://cureclcn4.org/clcn4_scientific_meeting/

CLCN4-RELATED CONDITION

SOME BACKGROUND

CLCN4-related condition is a rare X-linked genetic condition that can lead to developmental delay/intellectual disability, autism spectrum, epilepsy, movement disorders and mental health conditions.

CLCN4-related condition is caused by pathogenic variants (mutations) in the *CLCN4* gene, which encodes the ClC-4 protein, a 2Cl-/H+ ion channel expressed in intracellular compartments in a wide variety of tissues, but prominently in the brain and skeletal muscle.

The extent and severity of *CLCN4*-related condition, which has so far been reported in just over 100 individuals worldwide, is very variable, depending on the type of gene change, the gender of the affected individual, the pathophysiological impact of the genetic change and, as yet, incompletely understood factors.

Overall, there is currently little understanding of the basic biology of CIC-4 and no appropriate therapeutic options.

For more information visit the CLCN4 GeneReviews page or the CureCLCN4 website, indicated at the bottom of this page.

CURE CLCN4

ABOUT THE ORGANISERS

Cure CLCN4 is a UK registered charity aimed at providing support, raising awareness and, funding medical research for effective treatments for CLCN4-related condition. It was founded by Peter Trill and Gina Tan, the parents of Daphne, a little girl with *CLCN4*-related condition.

"Cure CLCN4 was set up with the goal of advancing the much-needed basic science and translational research in this condition. It is built on the foundation of hope and commitment, that one day there would be a cure for Daphne and children like her"

CURE CLCN4

OUR GOALS

To **advance scientific and clinical research in *CLCN4*-related condition**, with the aim of developing effective therapies.

To **support families with a diagnosis of *CLCN4*-related condition** and help improve diagnosis rates.

To **raise awareness of CLCN4-related condition** as a condition, both among the scientific and wider community.

To **raise funds** to support CureCLCN4's mission, with a focus on scientific research.

CURE CLCN4

WHAT WE HAVE ACHIEVED SO FAR

Funded the generation of **two *Clcn4* rat models** (in progress)

We have partnered with Simons Searchlight to establish a **CLCN4 patient registry** as well as **CLCN4 patient-derived iPSCs**

We have **raised over £60,000** towards funding research on CLCN4

With the invaluable help of our scientific advisors and colleagues, we have put together a series of **resources for affected families** (website, social media, Facebook support group and other online resources (e.g. GeneReviews)

CURE CLCN4

WHAT WE HAVE ACHIEVED SO FAR

We also held our first **Family Conference** last August, attended by over 30 families

We are also proud to have partnered with

SIMONS SEARCHLIGHT

MEMBER OF EURORDIS RARE DISEASES EUROPE

RARE REVOLUTION MAGAZINE

CHARITY PARTNER

PROGRAM DAY 1

27.05.2022. SAINSBURY WELLCOME CENTRE

Session 1 - Welcome & Introduction to Cure CLCN4 (Chair - Dr. Vera Kalscheuer)

13:00 - 13:05 pm **Opening remarks**
Dr. Vera Kalscheuer (Max Planck Institute for Molecular Genetics)

13:05 - 13:20 pm **CureCLCN4. A Welcome from Us**
Peter and Gina Trill (Founders of Cure CLCN4)

13:20 - 13:30 pm **The molecular genetic spectrum of CLCN4-related neurodevelopmental condition**
Dr. Vera Kalscheuer (Max Planck Institute for Molecular Genetics)

13:30 - 13:50 pm **Functional properties of ClC-4, the protein encoded by the CLCN4 gene**
Dr. Michael Pusch (Istituto di Biofisica)

13:50 - 14:00 pm **Expanding our knowledge of the clinical features of CLCN4-related neurodevelopmental condition and priorities for translational research**
Dr. Elizabeth Emma Palmer (Sydney Children's Hospital /UNSW)

14:00 - 14:15 pm **Panel discussion and Q&A**

Session 2 - Animal models (Chair - Dr. Vera Kalscheuer)

14:20 - 14:35 pm **Modelling neurodevelopmental diseases: lessons learnt from Down syndrome, progress and challenges ahead**
Dr. Yann Herault (Institut de Genetique et de Biologie Moleculaire et Cellulaire)

14:35 - 14:50 pm **Strategies to strengthen the value of the laboratory rodent for preclinical studies of X-linked NDDs**
Dr. Rodney Samaco (Baylor College of Medicine)

14:50 - 15:05 pm **Modelling neurodevelopment disorders in zebrafish**
Dr. Jason Rihel (University College London)

15:05 - 15:20 pm **Panel discussion and Q&A**

15:20 - 15:50 pm **Break & Networking (30 minutes)**
Tea, coffee, water and biscuits will be served

Session 3 - Cellular models (Chair - Prof. Nael Nadif Kasri)

15:50 - 16:05 pm **The promise of iPSCs: patient driven research for rare neurodevelopmental disorders**
Dr. Elizabeth Buttermore (Boston Children's Hospital)

16:05 - 16:20 pm **Combining transcriptomic and electrophysiological profiling (MEA-Seq) of stem cell-derived human neurons identifies CLCN4 as a downstream target of KANSL1, contributing to Koolen-de Vries Syndrome.**
Prof Nael Nadif Kasri (Radboud University)

16:20 - 16:35 pm **Effects of single amino acid alteration on CLCN4 in human neurogenesis**
Dr. Jinju Han (KAIST)

16:35 - 16:50pm **Targeting Xist with compounds that disrupt RNA structure and X-inactivation**
Prof. Jeannie Lee (Massachusetts General Hospital; Harvard Medical School)

16:50 - 17:05 pm **Panel discussion and Q&A**

Session 4 - Cell and Structural Biology (Chair - Dr. Michael Pusch)

17:10 - 17:25 pm **Cell physiological roles of ClC-4 – insights from its late endosomal homologues ClC-6 and ClC-7**
Prof. Tobias Stauber (Freie Universität Berlin/Hamburg Medical School)

17:25 - 17:40 pm **Intracellular Cl-/H+ exchangers regulate the firing pattern of pyramidal neurons at the CA2 region of the Hippocampus**
Dr. Raul Guzman (FZ Julich)

17:40 - 17:55pm **Cryo-EM structural investigations in CLC-7**
Dr. Richard Hite (Memorial Sloan Kettering Cancer Center)

17:55 - 18:10 pm **Panel discussion and Q&A**

18:45 - 21:00 pm **Speakers' Dinner (by invitation only - Bloomsbury Street Hotel)**

PROGRAM DAY 2

28.05.2022. FRANCIS CRICK INSTITUTE

Session 5 - Clinical perspectives (Chair - Dr. Emma Palmer)

13:00 - 13:15 pm **Opening remarks - Learnings from Day 1**
Dr. Elizabeth Emma Palmer (Sydney Children's Hospital /UNSW)

13:15 - 13:35 pm **What is Simons Searchlight?/ SFARI Resources**
Dr. Jennifer Bain (Columbia University)/ Dr. Paul Wang (Simons Searchlight))

13:35 - 13:50 pm **Understanding cognition and mental health in rare neurodevelopmental disorders: opportunities, challenges, priorities, strategies**
Dr. Kate Baker (University of Cambridge)

13:50 - 14:05 pm **Protons to patients and back again: new insights in the role of the ClC-7 Cl- transporter in lysosomal biology**
Dr. Joseph Mindell (NIH)

14:05 - 14:20 pm **GENE TARGETS: Part I**
Dr. Maya Chopra (Boston Children's Hospital)

14:20 - 14:35 pm **GENE TARGETS: Part II**
Dr. Meera Modi (Takeda)

14:35 - 14:50 pm **Panel discussion and Q&A**

14:55 - 15:10 pm **Break & Networking (15 minutes)**
Tea, coffee, water and biscuits will be served

Session 6 - Industry (Chair - Dr. Alan Wise)

15:15 - 15:30 pm **The challenges and opportunities of gene therapy in neurodevelopmental disorders**
Dr. Stuart Cobb (Neurogene/University of Edinburgh)

15:30 - 15:45 pm **Utilising automated patch clamp to research novel ion channel targets**
Dr. Sarah Williams (Charles River)

15:45 - 16:00 pm **Fixing broken chloride channels – learnings from the development of treatments for cystic fibrosis**
Prof. Martin Gosling (Enterprise Therapeutics)

16:00 - 16:15 pm **Panel discussion and Q&A**

16:15 - 16:45 pm **Break & Networking (30 minutes)**

Session 7 - Therapeutic discovery, path to precision medicine (Chair - Dr. David Fischer)

16:50 - 17:05 pm	**How genomics, new drug modalities & technologies and social media enable ultra-rare drug discovery** *Dr. David Fischer (Charles River)*
17:05 - 17:20 pm	**Using in vitro and in vivo models to develop therapies for neurodevelopmental disorders: lessons from TSC** *Prof. Mustafa Sahin (Boston Children's Hospital)*
17:20- 17:35 pm	**Adeno-associated virus gene therapy for rare diseases - Translation from preclinical proof-of-concept studies to human application** *Prof. Guangping Gao (Umass Medical School)*
17:35 - 17:50 pm	**Panel discussion and Q&A**
17:50 - 18:00 pm	**Conclusions and next steps**

SPEAKER BIOS & ABSTRACTS

Peter Trill and Gina Tan (CureCLCN4 Co-founders)

Peter Trill (Cure CLCN4 Co-founder)

Peter is co-founder of Cure CLCN4. He is a father of three awesome children, the youngest of whom is affected by CLCN4. He is a company founder and board member working in the biotechnology sector. He is also a seed investor and mentor to founders of early stage healthcare and technology companies.

Gina Tan (Cure CLCN4 Co-founder)

Gina is co-founder of Cure CLCN4, a medical clinician and mother to two girls, the younger being affected by CLCN4. She studied medicine at King's College London and trained in hospitals in London and Bath, subspecialising in Rheumatology. She undertook clinical research training at Queen Mary University London.

CureCLCN4. A Welcome From Us

In their talk, Gina Tan and Peter Trill, co-founders of the CureCLCN4 research charity, and parents of a child with CLCN4-related condition will give a brief account of their journey of a CLCN4-related condition diagnosis and how this drove them to set up the charity, which has the main goal of advancing scientific research and providing affected families with effective treatments and a better quality of life.

Dr. Vera Kalscheuer (Max Planck Institute for Molecular Genetics)

Dr. Vera Kalscheuer (PhD) is a scientist at the Max Planck Institute for Molecular Genetics in Berlin, Germany. She obtained her degree and PhD in Biochemistry from the Free University (Berlin). Vera's work focuses on the identification of novel genes linked to neurodevelopmental disabilities, and the molecular/functional characterization of selected genes and proteins to better understand underlying molecular and pathomechanisms. She has discovered and contributed to the identification of numerous genes linked to various forms of neurodevelopmental disabilities, including CLCN4, thereby establishing a molecular diagnosis for patients and their families. To better understand CLCN4-related disorders, together with Dr. Emma Palmer and other collaborators, she conducted a large study on the genetic, clinical and functional impact of newly identified CLCN4 variants. Vera, Dr. Emma Palmer and Dr. Michael Pusch are currently studying an even larger group of patients with CLCN4-related gene defects.

The molecular genetic spectrum of CLCN4-related neurodevelopmental condition

Vera M. Kalscheuer, Michael Pusch, Elizabeth E. Palmer

The CLCN4 gene is located on the human X chromosome at Xp22.2 and encodes the chloride/proton ion-exchanger ClC-4, which is important for normal neuronal development. So far, 20 missense and four protein truncating variants have been described in 24 unrelated families with CLCN4-related neurodevelopmental disorder. Shortly after the identification of the first CLCN4 variant in a male infant with developmental and epileptic encephalopathy, which suggested CLCN4 as a novel candidate disease gene, our X chromosomal exome sequencing study discovered five unrelated families with a pathogenic CLCN4 variant, including one protein truncation variant and four missense variants. Thereafter, we reported genetic and clinical findings in 11 additional families with pathogenic CLCN4 variants, including heterozygous females with de novo variants for the first time. Since then, a further six males and one female from seven families with CLCN4-related disorder have been described in the literature. All missense variants tested in Xenopus oocytes demonstrated reduced function of mutant ClC-4. In recent years, we have collaborated internationally and have investigated >60 new CLCN4 families with novel and recurrent missense and protein truncating variants, further characterised the genotypic spectrum of both males and females, including in silico predictions, and collated segregation data and clinical information where available. To gain insight into the causality of novel missense variants of unknown clinical significance and the pathophysiological mechanisms of newly identified and previously reported missense variants, the effect of mutant ClC-4 protein, as present in affected families, on electrophysiological properties in Xenopus oocytes were tested.

Dr. Michael Pusch (Institute of Biophysics)

I received my PhD in 1990 at the Max Planck Institute in Gottingen, Germany. Currently, I am holding a position of research director ("Dirigente di Ricerca") at the Institute of Biophysics in Genoa, Italy. My scientific interests focus on the biophysics and the role of ion channels and ion transporters in human genetic diseases and more recently also in cancer. In particular, I have contributed to the discovery of mechanisms of function of CLC chloride transporters and channels, and the molecular mechanisms underlying activation of volume regulated anion channels.

Functional properties of ClC-4, the protein encoded by the CLCN4 gene

Michael Pusch, Alessandra Picollo, Emma Palmer, Vera Kalscheuer

The CLCN4 gene is one of 9 different CLC genes that encode chloride transporting proteins. ClC-4 is rather ubiquitously expressed but is most important in neurons. It is a membrane protein that physiologically localizes predominantly to intracellular organelles, i.e. endosomes. In the membrane of these acidic organelles it functions as a coupled 2 Cl- / 1 H+ antiporter. In an unknown manner ClC-4 is important for the ionic homeostasis of endosomes.

As all CLC proteins, ClC-4 works as a dimer with physically separate transport pathways in each subunit. Physiologically, ClC-4 seems to dimerize preferentially with ClC-3. Thus, potential dominant effects of ClC-4 mutations in heteromeric ClC-3/ClC-4 complexes could contribute to the disease phenotype.

In heterologous systems ClC-4 is sufficiently expressed in the plasma membrane allowing analysis using electrophysiological methods (voltage clamp). Such measurements revealed a peculiar property, which ClC-4 shares with the ClC-3 and ClC-5: Ionic currents, that reflect electrogenic Cl- / H+ antiport, can be elicited only at large positive voltages and activation of currents is extremely fast. The significance of the strong "outward rectification" is unknown. It is physiologically relevant because mutations in CLCN3 that disrupt rectification cause neurological disease.

Studying many CLCN4 variants in Xenopus oocytes we found various phenotypes: 1. Several variants exhibited largely reduced functional expression. 2. Others required even more positive voltages than WT ("shifted voltage dependence"), a loss of function effect. 3. Some variants had a disrupted gating, showing currents at negative voltages at acidic pH, a gain-of function effect.

Dr. Elizabeth Emma Palmer (Sydney Children's Hospital; UNSW)

Dr. Palmer is a clinician-scientist at Sydney Children's Hospital Network & University of New South Wales (Australia) and scientific advisor to CureCLCN4. She has extensive experience at the interface of clinical and research genetics leading multidisciplinary teams and establishing international collaborations to discover new genetic conditions and translate these discoveries to improved education and management for patients and families. She was the first author on a publication describing the impact of CLCN4 gene changes in 52 individuals, and is leading the clinical aspects of an international study to better understand the genetic and clinical spectrum of CLCN4 related conditions.

Expanding our knowledge of the clinical features of CLCN4-related neurodevelopmental condition and priorities for translational research

Elizabeth E. Palmer, Michael Pusch, Vera M. Kalscheuer

We recently expanded the number of reported individuals with CLCN4-related neurodevelopmental condition to 122 individuals. All 58 hemizygous males had a developmental delay or intellectual disability, which ranged in severity from borderline to profound. Epilepsy was present in 2/3 and treatment resistant in 42%. No particular antiepileptics yet showed evidence of being more efficacious. Neuropsychiatric and behavioural conditions were common, including anxiety, autism spectrum or autistic features and hyperactivity. 68% of those who have had neuroimaging had reportable findings: the most common being abnormalities of the corpus callosum. Gastrointestinal dysfunction was common, as were sleep disorders, lax joints and hypotonia. The phenotypic features in the 64 heterozygous females known to date ranged from normal to as severe as in males. There was no evidence of X inactivation status being predictive of clinical severity. Twenty females had confirmed de novo variants: including females with an affected son, but who are unaffected themselves. With regards to genotype-phenotype correlation those with variants associated with gain of function in our Xenopus oocyte model frequently had significant growth restriction, feeding difficulties and gastrointestinal dysfunction. There is no clearly recognisable facial gestalt and no association with extra-cerebral congenital anomalies in males or females. We anticipate that the number of diagnosed individuals will further rapidly expand as neurodevelopmental gene panels, exome and whole genome sequencing become more widely available globally. Studies are now critically needed to better understand the natural history and underlying pathophysiology of this condition. This is so we can better target surveillance and therapies to improve healthcare outcomes and support for all individuals with this diagnosis and their families.

Dr. Yann Herault (Institut de Genetique et de Biologie Moleculaire et Cellulaire)

Yann Herault is a mouse geneticist as well as a cellular and molecular biologist by training. Over the last two decades he has focused his interest on neurodevelopmental disorders (NDDs), that are paradigmatic conditions of rare diseases with brain development alterations and impairments to function. They have a prevalence of about 3% worldwide and are highly heterogeneous, with symptoms like intellectual disability (ID), autism spectrum disorders (ASD), and attention-deficit/hyperactivity disorder. He has started his work on Down syndrome (DS) in order to elucidate the genotype-phenotype relationship due to the increase in gene dosage, understand the pathophysiology of the disease, find new targets and test therapies to mitigate the cognitive deficits. Over the years, Yann Herault has extended his interests to others NDDs due to copy number variation of a specific genetic interval, such as the 16p11.2 and 17q21.31 syndromes, or to single genes like PTCHD1 or DYRK1A; all leading to neurodevelopmental delay, ID, ASD, as well as other comorbidities. Common cellular and molecular mechanisms were found in those NDDs, modifying the neuronal development, the functioning of the synapse, the excitatory and inhibitory balance in the brain, or more specific molecular pathways, like Rho-GTPase or the KCTD13-CUL3 ubiquitin ligase complex pathways. Several therapies are under investigations and a few are now supported by proof-of-concept mitigating the brain dysfunction in animal models.

Modelling neurodevelopmental diseases: lessons learnt from Down syndrome, progress and challenges ahead

Marion Pellen, Damien Maréchal, Helin Atas-Ozcan, Arnaud Duchon, Claire Chevalier, Valérie Hérault, Maria del Mar Muniz Moreno, Marie-Christine Birling, Véronique Brault and Yann Hérault

Modelling neurodevelopmental disorders (NDDs) is key to understand the cause of the disease and identify the cellular and molecular mechanisms that are perturbed, and to define therapeutic paths to mitigate the conditions. We have done such approach to monitor several NDDs due either to single genes or to more complex changes such as in Down syndrome (DS) a consequence of human chromosome 21 trisomy. Here, we will report and discuss how the knowledge gained by modelling DS how we have gained on the genotype-phenotype relationship, identify main driver genes, and develop strategies to mitigate cognitive dysfunction in people with DS. We have learnt a lot from DS models only mimicking partial trisomy of human chromosome 21 but we also understood that we lacked more complete animal models for therapeutic intervention. To answer this question, we have generated DS rat models and we were able to highlight the importance of investigating a complete DS models with all the regions triplicated. Finally, we have now a novel vision of the altered gene-gene crosstalk and molecular mechanisms in DS models that should become central to better understanding of DS as a whole. Nevertheless, some major challenges are still ahead to decipher the complexity of brain dysfunction, the origins of comorbities associated with the NDDs and the best translation of therapies to human.

Dr. Rodney Cavero Samaco (Baylor College of Medicine/Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital)

Dr. Samaco is Assistant Professor and Investigator at Baylor College of Medicine, and the Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital. Dr. Samaco's research program focuses on optimizing the framework for preclinical readiness of rare disease models. His team evaluates the natural history of disease in genetically modified rodents to identify measures that may serve as surrogate endpoints. By fostering collaborations across the landscape of patient advocacy, academic, and industry groups, he strives to advance community-based participatory approaches in the research and development of actionable therapies for rare and ultra-rare genetic conditions.

Strategies to strengthen the value of the laboratory rodent for preclinical studies of X-linked NDDs

Rodney Samaco

Studies of genetic rodent models remain instrumental in the effort to uncover the nature and extent to which phenotypic endpoints may serve as either biomarkers or outcome measures in preclinical investigations. However, the relative data gap of well-defined, reproducible and reliable phenotypic endpoints is striking, and continues to be a recurring theme that significantly resonates across basic science and clinical arenas. To address the pressing need to identify actionable therapies for CLCN4-related condition yet avoid the potential missteps experienced in other fields of neurodevelopmental disorders (NDDs), the focus of the current presentation will be to provide a balanced perspective of lessons learned in other X-linked NDD fields, highlighting exemplars spanning more than two decades. While the generalizability of sound experimental design will indeed safeguard against potential confounds and strengthen the importance of foundational work, the primary objective of this presentation seeks to convey strategies to (right)-align experimental design with the end-goal motivation. By underscoring key factors concerning conceptual, technical, and logistical-operational considerations, the content conveyed from this presentation may help manage realistic expectations and expedite the development of meaningful CLCN4-related condition therapeutic modalities.

Dr. Jason Rihel (University College London)

Dr. Rihel uses molecular and behavioral genetics to probe the mysteries of sleep and arousal in zebrafish. His research focus flows naturally from a lifelong interest in the molecular and neuronal underpinnings of innate behaviors. He started his career in behavioural genetics as an undergraduate (1994-1998) in Dr. Jeff Price's lab at West Virginia University by investigating the fruit fly circadian clock mutant, double-time. After obtaining his PhD at Harvard University with Professor Catherine Dulac (1998-2004), Dr. Rihel then went on to develop methods to study sleep in zebrafish in Prof. Alexander Schier's lab at Harvard, publishing some of the first papers to demonstrate that fish have sleep-like states governed by similar genes and neurons that regulate sleep in humans. Since 2013, Dr Rihel has run his own research lab at University College London, where he continues to study the intersection of sleep and disease. His research has been funded by the European Research Council, Alzheimer's Research UK, the BBSRC, and the Wellcome Trust.

Modelling neurodevelopment disorders in zebrafish

Jason Rihel

Genome-wide association and whole-exome sequencing studies have rapidly identified hundreds of risk alleles for neurodevelopmental disorders and other human diseases. The challenge now is to build animal models of these many genetic disruptions so that we can understand how these individual genetic lesions perturb neuronal circuitry and behavior. In particular, mapping both the common and gene-specific alterations in brain development and function will be crucial for the creation of therapies that may need to be tailored to specific patients. We have been taking advantage of recent gene editing, whole-brain imaging, behavioral phenotyping, and small molecule screening methods in zebrafish to rapidly generate and test zebrafish larvae that harbor mutations in human disease genes. Our pipeline takes advantage of highly efficacious Crispr/Cas9 gene-editing technology to allow mutant generation and phenotyping in as little as one week. We can also in most cases precisely mimic human genetic lesions, as zebrafish share more than 70% of human genes and more than 85% of disease-associated genes. These genetically altered larval fish are then tracked over multiple days for changes in complex behaviors such as sleep/wake patterns. We also observe global changes in neuronal activity or synapse formation using minimally invasive imaging techniques, since the larvae are optically translucent. We then use machine learning techniques to uncover similarities between the behavioral fingerprints of mutant animals and those induced by pharmacological agents. This "predictive pharmacology" is able to identify drugs that can exacerbate or ameliorate mutant behavior, which can not only give further insights into the molecular changes that have occurred in the mutant brain but also can serve as an early-stage drug-discovery platform.

Dr. Elizabeth Buttermore (Boston Children's Hospital)

Liz's background is in neuronal cellular phenotyping and developmental neurobiology. She completed her postdoc in 2016 in Clifford Woolf's lab in the Kirby Neurobiology Center at Boston Children's Hospital. During her postdoc, she worked to develop protocols for differentiating sensory neurons from iPSCs and fibroblasts. She then used these neurons to develop assays for chemotherapy induced neuropathy and chronic pain. Prior to her postdoc, she completed her PhD in 2012 in the lab of Manzoor Bhat at the University of North Carolina, focusing on studying the organization and maintenance of molecular domains in myelinated axons. Her BS degree comes from the University of Richmond where she graduated in 2006, having majored in Biochemistry and Molecular Biology. Liz is currently leading the Human Neuron Core (HNC) at Boston Children's Hospital. The HNC offers services in neuron differentiation, neuron phenotyping, and assay development and screening. The mission of the core is to bridge the gap between the clinic and basic researchers and help establish human iPSC-derived model systems for neurological disorders as well as provide support for preclinical research developing screens to identify novel therapeutics.

The promise of iPSCs: patient-driven research for rare neurodevelopmental disorders

Elizabeth Buttermore

Drug discovery in neuroscience faces many unique challenges, including access to the central nervous system through the blood-brain barrier and a complex biology and circuitry that is still being defined. In order to overcome these challenges to identify treatments for neurodevelopmental disorders, scientists need better preclinical data. One requirement for improved preclinical data is a robust model system. Recent advances in stem cell technology have allowed for the creation of stem cells from patient skin or blood cells, called induced pluripotent stem cells (iPSCs). These patient-derived iPSCs can then be differentiated into neurons to model how a patient mutation causes changes in neuronal function compared with a healthy control neuron, followed by testing of therapeutics for reversal of these in vitro phenotypes. This strategy has already successfully transitioned from the bench to the clinic for amyotrophic lateral sclerosis (ALS). We have recently used this technology to better understand the cellular and molecular consequences of variants associated with neurodevelopmental disorders in iPSC-derived neurons. Together, these model systems and technologies can be used to screen for and identify novel therapeutic targets for neurodevelopmental disorders.

Prof. Nael Nadif Kasri (Radboud University)

Professor Nadif studied biochemistry at the KU Leuven (Belgium), followed by a PhD (2000-2004) in molecular biology at the KU Leuven with Prof. Dr. Humbert de Smedt. During his PhD thesis, Dr. Nadif studied the role of Ca2+ and calmodulin in the regulation of IP3Rs. After his PhD he worked as a postdoctoral researcher (2005-2010) in the lab of Prof. Dr. Linda van Aelst at Cold Spring Harbor Laboratory, where he studied the role of RhoGTPase signaling in excitatory synapses in the hippocampus. In 2010 he moved to the Netherlands and started his independent research group at the Radboud Medical Centre, where he is part of the Donders Institute for Brain, Cognition and Behaviour. In 2011 he received the Hypatia Fellowship and Marie Curie reintegration grant. The focus of his research is to understand the synaptic basis of neurodevelopmental disorders using in vitro human models and in vivo mouse models.

Combining transcriptomic and electrophysiological profiling (MEA-Seq) of stem cell-derived human neurons identifies CLCN4 as a downstream target of KANSL1, contributing to Koolen-de Vries Syndrome.

Nael Nadif Kasri

Despite considerable progress in elucidating the genetic architecture of neurodevelopmental disorders (NDD), including intellectual disability (ID) and autism spectrum disorders (ASD), a major gap exists between the genetic findings and deciphering the cellular or molecular pathobiology of NDDs. In particular, understanding which gene expression changes in specific cell types have the most relevant functional consequences, and whether or not those consequences overlap in different patients. Here we used a microelectrode array (MEA)-seq approach, which combines neuronal network measurements with gene expression profiling of hiPSC-derived neurons to understand the mechanism underlying Koolen-de Vries Syndrome (KdVS). Koolen-de Vries Syndrome (KdVS) is an intellectual disability syndrome caused by haploinsufficiency of KANSL1. We investigated how loss of function of KANSL1 affects neuronal development in human induced pluripotent stem cell (hiPSC)-derived neurons from KdVS individuals and healthy controls. RNA sequencing (RNA-seq) of KdVS hiPSCs and hiPSCs-derived neurons revealed cell type-specific and common gene expression changes linked to KANSL1 haploinsufficiency, pointing towards (neuro)developmental impairments. Using a MEA-seq approach, we identified CLCN4 expression to be negatively correlated with the network burst activity. Knockdown of CLCN4 in KdVS neurons reversed the network burst activity towards control level, identifying CLCN4 as a downstream target of KANSL1 contributing to KdVS pathology. Secondly, we identified mitochondrial gene expression to be positively correlated with the network burst activity, and confirmed mitochondrial function is impaired in KdVS hiPSC-derived neurons. Overall, we show that the MEA-seq approach is well-suited for studying mechanisms underlying neuronal network dysfunction in human neurons in the context of neurodevelopmental disorders, using KdVS as a proof-of-principle.

Dr. Jinju Han (Korea Advanced Institute of Science and Technology)

Jinju Han is an assistant professor at the Graduate School of Medical Science and Engineering at the Korea Advanced Institute of Science and Technology in Daejeon, Korea. Jinju studied RNA biology during her Ph.D. while her postdoc focused on neuro stem cell biology. As an independent researcher, her aim is to unravel novel molecular mechanisms regulating the development of the human brain, with a focus on neurodevelopmental diseases and using human pluripotent stem cells (hPSCs) as a model system. Jinju is interested in understanding the biological roles of CLCN4 in neuronal development. To this end, her group has generated CLCN4 mutant hPSCs which she has used to generate CLCN4 mutation carrying neurons which are now being characterised.

The effects of single amino acid alteration on CLCN4 in human neurogenesis

Dayeon Kim, Hyunsu Do, Yongjun Koh, Jaehyung Kim, Chanhee Kang, Geurim Son, Insook Ahn, Ji-Hoon Son, Mingyu Ju, Donghyuk Kim, Jong-Eun Park, and Jinju Han

Diverse mutations on different positions along the CLCN4 have been identified in patients with intellectual disability, autistic traits, and epileptic seizures. CLCN4 is a gene encoding voltage-gated chloride channel 4, CLC-4. While the expression profile of the CLCN4 shows the highest expression level in the brain among the other tissues, the biological roles of CLCN4 in brain development and diseases remain largely unknown. In this study, to investigate the effects of CLCN4 mutations in neuronal development, we generated human embryonic stem cells (hESCs) carrying mutant CLCN4 by applying the genome-editing technique. At first, we differentiated the hESCs carrying the CLCN4 mutation to neural progenitor cells (NPCs) and obtained adequate NPCs similar to the control. Next, NPCs were differentiated into neurons. The neurons with mutant CLCN4 displayed abnormal morphology at the early stage of neurogenesis compared to the control neurons and eventually died before maturation. We also observed a reduced number of neurons in the forebrain organoids carrying CLCN4 mutations. Our data show the requirement of CLCN4 for the survival of developing neurons. Currently, we are working on investigating molecular mechanisms of how CLCN4 variants cause neuronal cell death.

Prof. Jeannie Lee (Massachusetts General Hospital; Harvard Medical School)

Jeannie Lee is Professor of Genetics (and Pathology) at Harvard Medical School, the Blavatnik Institute, and is Vice Chair of the Department of Molecular Biology at the Massachusetts General Hospital. Dr. Lee specializes in the study of epigenetic regulation by long noncoding RNAs and uses X-chromosome inactivation as a model system. From 2013-2018, she co-launched the Epigenetics Initiative at Harvard Medical School and served as its Co-Director. Serving on the Board of Directors of the Genetics Society of America (GSA), Dr. Lee spearheaded the TAGC (The All-Genetics) Conference in 2016. As GSA's President, Dr. Lee established a Strategic Plan and a Development strategy for the society in 2018. She received her A.B. in Biochemistry and Molecular Biology from Harvard University and obtained M.D.-Ph.D degrees from the University of Pennsylvania School of Medicine. Dr. Lee then carried out postdoctoral work at the Whitehead Institute & MIT and became Chief Resident of Clinical Pathology at the Massachusetts General Hospital prior to joining the Faculty at Harvard Medical School. As a new investigator, she received the Basil O'Connor Scholar Award from the March of Dimes and the Pew Scholars Award. Growing knowledge of X-inactivation mechanisms and RNA biology is currently being translated to treat various human diseases (e.g., Rett, Fragile X, and CDKL5 Syndromes).

Targeting Xist with compounds that disrupt RNA structure and X-inactivation

Rodrigo Aguilar, Kerrie B. Spencer, Barry Kesner, Noreen F. Rizvi, Maulik D. Badmalia, Tyler Mrozowich, Jonathan D. Mortison, Carlos Rivera, Graham F. Smith, Julja Burchard, Peter Dandliker, Trushar R. Patel, Elliott B. Nickbarg, Jeannie T. Lee

Although >98% of our genome is noncoding, nearly all drugs on the market target one of ~700 disease-related proteins. The historical reluctance to invest in noncoding RNA stems partly from requirements for drug targets to adopt a single stable conformation. Most RNAs can adopt several conformations of similar stabilities. RNA structures also remain challenging to determine. Nonetheless, an increasing number of diseases is now being attributed to noncoding RNA and the ability to target them would vastly expand the chemical space for drug development. Here we devise a screening strategy and identify small molecules that hit the non-coding RNA prototype, Xist. The X1 compound has drug-like properties and binds specifically to Xist's RepA motif in vitro and in vivo. SAXS analysis reveals that RepA can adopt multiple conformations but favors one structure in solution. X1 binding reduces RepA's conformational space, displaces cognate interacting protein factors (PRC2, SPEN), suppresses H3K27 trimethylation, and blocks initiation of X-inactivation. X1 inhibits cell differentiation and growth in a female-specific manner. Thus, RNA can be systematically targeted by drug-like compounds that disrupt RNA structure and epigenetic function.

Prof. Tobias Stauber (Free University/ MSH Medical School Hamburg)

Professor Tobias Stauber studied biochemistry at the Ruhr University Bochum and the University of Witten/Herdecke with research stays at the Max Planck Institute for Biophysical Chemistry, Göttingen, and the Yale University School of Medicine, CT, USA. He then completed his doctorate at the European Molecular Biology Laboratory (EMBL) in Heidelberg. Subsequently, he conducted research at the Max Delbrück Center for Molecular Medicine (MDC) and the Leibniz Research Institute for Molecular Pharmacology (FMP) in Berlin and habilitated at the Charité - Universitätsmedizin Berlin. Since 2014 he has lead the working group Cellular Biochemistry at the Free University of Berlin, where he also worked as a Privatdozent. In October 2019, he joined the MSH Medical School Hamburg as Professor for Biochemistry.

Cell physiological roles of ClC-4 – insights from its late endosomal homologues ClC-6 and ClC-7

Tobias Stauber

The intracellular members of the CLC family, ClC-3 through ClC-7, function as chloride/proton exchangers in the endosomal-lysosomal pathway. ClC-3 and ClC-4, which heterodimerise, as well as the renal ClC-5 reside on early endosomes, while ClC-6 and ClC-7 localise to late endosomes/lysosomes. As mutations in CLCN4 do, dysfunction of ClC-6 or ClC-7 leads to neuronal disorders. Loss of ClC-6 leads to only mild phenotypes in murine models. However, gain-of-function variants were recently identified in patients with an early-onset neurodegeneration. In addition, a mutation that uncouples chloride from proton transport by ClC-6 was found in a patient with West syndrome, an epileptic disorder. This mutation impairs the clearance of autophagosomes by blocking autophagosome-lysosome fusion. ClC-7 is ubiquitously expressed on lysosomes and additionally on the ruffled border of bone-resorbing osteoclasts. Its dysfunction leads to osteopetrosis in mice and humans, often accompanied by a neurodegenerative lysosomal storage disease. Mutations in ClC-7 affect its ion transport in various ways, including loss-of-function, larger current amplitudes, faster activation or chloride/proton uncoupling. They underly disorders with differential alterations in lysosomal morphology and function. Elucidating the physiological roles and the pathophysiology of the late endosomal/lysosomal ClC-6 and ClC-7 will contribute to our understanding of the function of ClC-4.

Dr. Raul Guzman (Institute of Biological Information Processing, Forschungszentrum Jülich)

Dr. Raul Guzman is a group leader at the Cellular Neurophysiology Research Group, Institute of Biological Information Processing (IBI-1), Forschungszentrum Jülich, Germany. He obtained his Ph.D. in Neurophysiology, Department of Physiology (CIPMM), University of Saarland, Germany. He conducted his postdoctoral research at the Institute of Neurophysiology, Medizinischen Hochschule Hannover, Germany. He also holds a Master's in Neurochemistry at the Venezuelan Institute of Scientific Research, Venezuela. Since 2010 his research aims to understand how synaptic transmission in neurons and neuroendocrine cells is modulated by anion channels and transporters. The ultimate goal of his work is to unravel how chloride/proton exchangers regulate the excitability of nerve cells, exocytosis, and the vesicle neurotransmitter accumulation process.

Intracellular Cl-/H+ exchangers regulate the firing pattern of pyramidal neurons at the CA2 region of the Hippocampus

Qi Guanxiao, Juan Sierra-Marquez, Dirk Feldmeyer, Christoph Fahlke and Raul E. Guzman

ClC-3 and ClC-4 are 2Cl-/H+ exchangers with strong expression in the central nervous system. Genetic dysfunctions can result in neurodegeneration, intellectual disability, or epilepsy with a cellular mechanism that has not been understood. We found that disruption of ClC-3 or ClC-4 dramatically changes the bursting activity and the amplitude of the afterhyperpolarization (AHP) phase of the action potential in CA2 pyramidal cells. Whereas ~60% of the neurons in the WT CA2 region exhibited a bursting firing pattern, such behavior was only observed in 20% of the cells in the Clcn4-/- and none of the neurons in the Clcn3-/- exhibited a rhythmic bursting phenotype. In neurons of both KO animals, afterhyperpolarisation (AHP) amplitudes were significantly enlarged. Pharmacological block of KCNQ restored the bursting firing pattern in the Clcn3-/- cells, and application of retigabine, a KCNQ agonist, was more effective in enhancing the holding current and the KCNQ-mediated current in the Clcn3-/- than in the control, suggesting higher densities of KCNQ/Kv7 in the knockout conditions. Overall, our findings provide novel cellular functions of ClC-3 and ClC-4 that may contribute to understanding neuronal dysfunction in CLCN4 and CLCN3-related disorders.

Dr. Richard Hite (Memorial Sloan Kettering Cancer Center)

Richard Hite is an Assistant Member in the Structural Biology Program at Memorial Sloan Kettering Cancer Center where his lab studies intracellular ion transport and how its dysregulation can lead to disease. His lab is particularly interested ion channels and transporters in the endolysosomal system, which play critical roles in cellular homeostasis. By combining high-resolution structural approaches with electrophysiological and cell-based approaches, his lab works to understand the molecular basis mechanisms underlying the function of these proteins as well as gain insights into how mutations can lead to disease. Critically, these structures also serve as tools to help develop novel therapeutics that may be helpful in treating diseases associated with endolysosomal dysfunction.

Cryo-EM structural investigations in CLC-7

Richard Hite

The chloride-proton exchanger CLC-7 plays critical roles in lysosomal homeostasis and bone regeneration and its mutation can lead to osteopetrosis, lysosomal storage disease and neurological disorders. In lysosomes and the ruffled border of osteoclasts, CLC-7 requires a β-subunit, OSTM1, for stability and activity. Comparison of electron cryomicroscopy structures of CLC-7 in occluded states by itself and in complex with OSTM1 reveal how the heavily glycosylated and disulfide-bonded OSTM1 protects the luminal surface of CLC-7 from the degradative environment of the lysosomal lumen. OSTM1 binding does not induce large-scale rearrangements of CLC-7 but does have minor effects on the conformation of the ion-conduction pathway, potentially contributing to its regulatory role. These studies provide insights into the role of OSTM1 and serve as a foundation for understanding the mechanisms of CLC-7 regulation.

Dr. Jennifer Bain (Columbia University/Simons Searchlight)

Jennifer Bain, MD, PhD, is an assistant professor of neurology and pediatrics at Columbia University Medical Center. Dr. Bain completed both M.D. and PhD. as well as general pediatrics residency at Rutgers – New Jersey Medical School in Newark, New Jersey. She then trained in Child Neurology at New York Presbyterian – Columbia University Medical Center in New York City and is a board-certified neurologist with special certification in Child Neurology. Her early research career focused on spinal cord and brain development after injuries such as spinal cord injury and perinatal hypoxic ischemic encephalopathy. She currently works as a physician scientist at Columbia University specializing in general pediatric neurology with expertise in development, behavioral neurology and autism. Her clinical research has focused on studying the genetics of neurodevelopmental disorders including autism and cerebral palsy. The genes she has worked closely on include HNRNPH2 and related disorders, GRIN disorders, KIF1A and she is eager to collaborate on other genetic disorders such as CLCN4. She is interested in understanding clinically meaningful measures in families affected by neurodevelopmental disorders and measuring longitudinal trajectories in such disorders. She has been working closely with several patient advocacy groups, researchers, and Simons Searchlight to continuously move forward in the understanding of the developing brain.

Dr. Paul Wang (Simons Foundation)

Paul is a developmental-behavioral pediatrician who has worked in many different sectors, always with a focus on neurodevelopmental disorders. While working in academia at Children's Hospital of Philadelphia, he helped to care for hundreds of children and families affected by genetic diagnoses, autism, and intellectual disabilities. His research there focused on language and memory development. Paul subsequently worked in industry, at Pfizer and then at Seaside Therapeutics, where he led drug development efforts for autism and Fragile X Syndrome. He served later as Vice President for Clinical Affairs at Autism Speaks, and now is Deputy Director for Clinical Research at the Simons Foundation (SFARI).

What is Simons Searchlight & SFARI Resources

Jennifer Bain & Paul Wang

Dr. Bain will introduce the Simons Searchlight international research program, outline how families can join the study, and explain how sharing your valuable information and experiences with their CLCN4 registry can lead to discoveries in improving the lives of people with rare genetic neurodevelopmental disorders. Dr. Wang will present an overview of the Simons Foundation, and the types of resources and funding that it provides to support research on autism and related genetic conditions. He will cover the Simons Searchlight project, stem cell (iPSC) resources, and SFARI (Simons Foundation Autism Research Initiative) generally.

Dr. Kate Baker (University of Cambridge)

Dr Kate Baker is an Honorary Consultant in Clinical Genetics at Cambridge University Hospitals NHS Foundation Trust. She leads a programme of research at MRC Cognition and Brain Sciences Unit, University of Cambridge, focused on genomic disorders and cognitive development. Her research and clinical work addresses the post-diagnostic needs of people with neurodevelopmental disorders of known genetic origin, and their families.

Understanding cognition and mental health in rare neurodevelopmental disorders: opportunities, challenges, priorities, strategies

Kate Baker

It is now possible to diagnose a specific genetic cause of neurodevelopmental disorder in up to 60% of severely affected individuals, and more than 1500 rare genetic causes have been discovered. Genetic diagnosis engenders hope for personalised, targeted treatments and support. However, the relationships between genetic diagnoses, developmental cognitive impairments and individuals' real-world outcomes are complex, limiting the current utility of genetic diagnosis for this large group of patients. To tackle this major post-diagnostic challenge, our research focuses on groups of monogenic neurodevelopmental disorders which converge on similar molecular and cellular mechanisms – gene functional networks. Our objectives are to characterise network-associated phenotypes, and apply cognitive neuroscience approaches to study underlying mechanisms. This presentation will illustrate our approach by presenting behavioural and cognitive phenotyping studies of broadly-defined gene functional networks. Our data show that the behavioural characteristics associated with these networks are highly variable and influenced by numerous individual factors. However, it is possible to identify network-specific vulnerabilities, pointing toward shared multi-level mechanisms. These results may have short-term clinical relevance for post-diagnostic educational and psychological support, and longer-term value for targeting and monitoring novel therapies.

Dr. Joseph Mindell (NIH)

Dr. Joseph Mindell received his BS in Molecular Biophysics and Biochemistry from Yale, and his M.D./Ph.D. from Albert Einstein College of Medicine, where he did his thesis work with Alan Finkelstein on the determinants of ion selectivity in Diphtheria Toxin channels. After residency training in internal medicine, Dr. Mindell did a postdoctoral fellowship with Chris Miller at Brandeis University, where he was introduced to the CLC family of chloride channels and transporters. Since 2002 Dr. Mindell has run his own lab at the NIH, in the National Institute of Neurological Disorders and Stroke Intramural Program. Joe's scientific interests focus on the biophysics and biology of secondary active transporters. One major avenue pursued by the lab is understanding the role of a lysosomal CLC, which is a Cl-/H+ antiporter, in the critical process of lysosomal acidification using a variety of tools, from electrophysiology, to microscopy, to knockout mice. Joe is also interested in the structure- function relationships in secondary active transporters, using biochemical methods to probe activity and conformational changes related to transport in model bacterial and archaeal transporters whose structures are available.

Protons to patients and back again: new insights in the role of the ClC-7 Cl- transporter in lysosomal biology

Joseph Mindell

Lysosomes are essential focal points of cellular metabolism, digesting a wide range of macromolecules provided by endocytosis or autophagy. To this end, lysosomes rely on their highly acidic luminal pH to promote the function of their many enzymes, a pH generated by the action of a v-Type proton pumping ATPase. Since this transporter is electrogenic, parallel ion movements must occur to dissipate the generated membrane potential and promote bulk proton flux. The Cl-/H+ antiporter, ClC-7, has been proposed to play this role, moving Cl- in parallel to protons. However, the function of ClC-7 has been controversial, with conflicting reports on its contribution to lysosomal acidification. I will discuss recent work aimed at understanding the role of ClC-7 and other proteins in the acidification process. My lab uses a multipronged approach, utilizing a variety of methods to probe these processes, from flux studies in isolated organelles to knockout mice and quantitative imaging methods. In addition I will report on two patients with a novel disease manifested as widespread lysosomal dysfunction but no bone abnormalities, who both have the same missense mutation in ClC-7. Acidification defects in cells from these patients, along with electrical currents from the mutant transporter provide novel insight into ClC-7 function. These findings provide strong support for an important role of ClC-7 in the lysosomal acidification process and suggest opportunities for therapies for these patients.

Dr. Maya Chopra (Boston Children's Hospital)

Dr. Maya Chopra is a Clinical Geneticist with expertise in the and discovery and delineation of rare genetic neurodevelopmental syndromes. She is currently Director of Translational Genomic Medicine at the Rosamund Stone Zander Translational Neuroscience Center at Boston Children's Hospital. In this role, she partners closely with the other RSZ TNC cores to evaluate genetic disorders for suitability for gene-based therapies, clinical-trial readiness, and multidisciplinary clinics. She collaborates closely with local and external investigators in research efforts to understand the mechanisms underpinning neurodevelopmental syndromes, and how they can translate into treatment options.

Dr. Meera Modi (Takeda)

Meera obtained her PhD in Neuroscience at Emory University in Atlanta, GA. She completed a postdoc at Pfizer in the Neuroscience Research Unit centered on autism and other related neuropsychiatric disorders. To complement her preclinical training, she transitioned to Boston Children's Hospital where she identified electrophysiology based biomarkers for genetic neurodevelopmental disorders in both mouse models and in the parallel patient populations as the Preclinical Director of the RSZ Translational Neuroscience Center. In this role, she worked with clinicians, patient organizations, industry partners and academic collaborators to develop research programs for rare neurological diseases, utilizing iPSC and rodent models and clinical biomarker and natural history approaches. She is currently a Translational Science Lead at Takeda in the Rare Disease Unit focused on rare genetic disorders with neurological features.

G.E.N.E. T.A.R.G.E.T.S.: The Preclinical Path to Gene Therapy

Maya Chopra & Meera Modi

The G.E.N.E.T.A.R.G.E.T.S. framework is a rubric developed for evaluating the maturity of the preclinical development efforts for a Mendelian disorder related to the application of gene therapeutic strategies. The features evaluated in this rubric fit under four broad categories: genetic mechanism, preclinical validation, clinical consideration, and ethics. Within the preclinical category, genes are evaluated relative to the understanding of endogenous tissue expression and the availability of tools to target those tissues and the evidence in model systems of the reversibility of pathological phenotypes with genetic interventions. The clinical category weights the availability of natural history data, validated endpoints and biomarkers and patient access in the evaluation of gene-disease pairs. In addition to proposing a systematic method to evaluate the readiness of a program, our framework helps identify gaps in the translational pipeline for a given disorder, which can inform prioritization of future research efforts. CLCN4 was evaluated with the rubric and areas for further research will be highlighted.

Dr. Stuart Cobb (University of Edinburgh/ Neurogene)

Stuart Cobb heads a translational research laboratory at the University of Edinburgh that is focused on developing genetic therapies for severe neurodevelopmental disorders. His research aims to address the tractability of severe brain disease to genetic rescue and to develop innovative therapeutic solutions for clinical translation. A particular focus of his work has been on Rett syndrome and closely related disorders. In addition to his academic research, Stuart Cobb is Chief Scientific Officer at Neurogene Inc, a clinical stage gene therapy company advancing a pipeline of gene therapies for severe neurological indications.

The challenges and opportunities of gene therapy in neurodevelopmental disorders

TBA

Dr. Sarah Williams (Charles River)

Sarah Williams is a senior scientist at Charles River Laboratories working at Chesterford Research Park, Cambridge. Sarah is passionate about electrophysiology and in vitro assay development, with 12 years ion channel experience. She has worked in industry since 2016. Sarah's interest in ion channels and transporters started in 2009 where she worked on SERCA during a summer placement. Following this she completed her PhD at the University of Southampton where she studied the role of K2P potassium channels in cancer cells, learning how to perform manual clamp patch experiments on various cell lines. After her PhD, Sarah did postdoctoral research at Brandeis University under the supervision of Professor Steve Goldstein and Dr Leigh Plant examining the regulation of K2P potassium channels. Sarah moved back to the UK in 2016 to work for a Cambridge based CRO, where she established iPSC-derived cardiomyocyte and neuron assays, as well as working on several manual patch assays. In 2018 she moved to Charles River, where she has worked with both manual and automated patch clamp platforms. Sarah has worked on a range of voltage and ligand gated ion channel targets at Charles River, successfully delivering profiling projects and leading an HTS project from assay development into potency phases.

Utilising automated patch clamp to research novel ion channel targets

Sarah Williams

This presentation will give an overview on how automated patch clamp (APC) can be used to research different classes of ion channel and how it is capable of supporting drug discovery for historically challenging targets. The development of APC platforms over the last 20 years has improved the ability to research ion channels by enabling high throughput screens (HTS) without sacrificing data quality. Additionally, the quality of data has enabled mechanism of action data to be gathered during an HTS, which can reduce the drug discovery timeline as compounds with a desired mechanism can be selected earlier in a project. At Charles River we have utilised the Sophion Qube 384 system to design assays for a wide range of voltage- and ligand-gated ion channel targets. The quality of data and flexibility in assay design has enabled research into previously challenging ion channel classes such as chloride channels, ligand gated ion channels and lysosomal targets.

Prof. Martin Gosling (CSO, Enterprise Therapeutics UK)

Martin has spent his research career progressing the therapeutic potential of ion channels in both industrial and academic settings. Prior to co-founding Enterprise Therapeutics, Martin was Executive Director in the Respiratory Disease Area of the Novartis Institutes for BioMedical Research, UK. Whilst with Novartis he established an internal ion channel platform, was a successful Project Team Leader for multiple drug discovery programs, and played a lead role in defining the Novartis cystic fibrosis (CF) portfolio. Martin holds a BSc and Ph.D. in Pharmacology from the Universities of Leeds and Aston respectively. In addition to his position as Chief Scientific Officer of Enterprise Therapeutics, he also holds the position of Professor of Molecular Pharmacology at the University of Sussex.

Fixing broken chloride channels – learnings from the development of treatments for cystic fibrosis

Martin Gosling

Cystic fibrosis (CF), in common with CLCN4, is the result of mutations in a chloride channel. CF is the most common lethal genetic disease of Caucasians of Northern European descent with a carrier frequency of ~1 in 20 and a birth prevalence of 1 in 2500. Although the disease was first described in 1938, the underlying genetic defect in the cystic fibrosis transmembrane conductance regulator (CFTR) gene was not identified until 1989. Although a number of therapies to address the symptomatic consequences of the absence of functioning CFTR have been introduced over the last 50 years, the first therapy aimed at correcting the dysfunctional CFTR channel (Kalydeco) was not approved until 2012. The path to the discovery of Kalydeco, and subsequent CFTR modulators, has a number of potential learnings for other chloride ion channelopathies – these will be discussed in this presentation and will include genotype to phenotype correlation, use of cellular and animal models and drug discovery approaches.

Dr. David Fischer (Charles River)

David Fischer is an Executive Science Director at Charles River Discovery. David joined Charles River through the acquisition of the Galapagos' services division (BioFocus and Argenta) from Galapagos in 2014, and has taken a leadership role on a number of early-stage drug discovery programs in rare and orphan disease indications, including cystic fibrosis, Huntington's Disease, ALS, Usher III Syndrome, DMD and KCNT1 epilepsy. He brings expertise in complex and primary cell-based assays, including iPSC and hESC stem cells models. David holds a degree in chemistry and a PhD in molecular genetics from Leiden University. During six years of postdoctoral fellowships, he focused on neurodegenerative diseases, particularly Alzheimer's and Huntington's disease. Dr. Fischer has published over 60 patent applications and peer-reviewed papers.

How genomics, new drug modalities & technologies and social media enable ultra-rare drug discovery

David Fischer

In the past decades, rare disease drug discovery has delivered a number of drugs that transformative to the lives of patients and their families. These include small molecule drugs such as the Cystic Fibrosis' CFTR correctors and potentiators, oligonucleotide drugs such as nusinersen for SMA, and gene therapy such as Luxturna for RPE65 deficiency.

Out of the estimated 7,000 rare diseases, the majority is however currently not addressed by industry, often because the patient population is too small for a commercially viable product. At the same time, more and more patients get diagnosed earlier and more accurately, especially with full exome sequencing and other genomic technologies. A growing number of smaller foundations and families are now using this information to explore innovative technologies and advanced drug modalities to discover and develop potential new treatments for in some cases extremely rare diseases or even n=1 therapies. By sharing information across organizations, a collaborative approach to ultra-rare drug discovery and development is rapidly advancing science and has found a sympathetic ear at the regulators.

Prof. Mustafa Sahin (Boston Children's Hospital)

Dr. Mustafa Sahin is a developmental neurobiologist and a pediatric neurologist at Boston Children's Hospital and Harvard Medical School. He received his Sc.B. degree from Brown University, his M.D. and Ph.D. from Yale School of Medicine. He completed a pediatrics residency at Children's Hospital of Philadelphia and a child neurology residency at Boston Children's Hospital. Dr. Sahin is a Professor at Harvard Medical school and the Rosamund Stone Zander Chair at Boston Children's Hospital. At Boston Children's, Dr. Sahin is the Director of the Translational Research Program and the Rosamund Stone Zander Translational Neuroscience Center. Dr. Sahin has established and directs the Multidisciplinary Tuberous Sclerosis Program. He directs a national consortia to study biomarkers and comparative pathobiology of TSC and related neurodevelopmental disorders.

Using in vitro and in vivo models to develop therapies for neurodevelopmental disorders: lessons from TSC

Mustafa Sahin

Our lab predominantly focuses on Tuberous Sclerosis Complex, a genetic disease that presents often with epilepsy and autism. We have generated several lines of evidence showing that TSC/mTOR pathway plays crucial roles in axon specification, guidance, myelination, and regeneration. We have shown that TSC/mTOR pathway components are expressed in hippocampal neurons in a polarized manner. We found that overexpression of TSC proteins suppresses axon formation while loss of Tsc1 or Tsc2 function in cultured neurons leads to increased axon number. We also found that retinal neurons from Tsc2+/- mice project aberrantly to their CNS targets in vivo and display abnormal growth cone collapse in response to the axon guidance cue ephrins in vitro. We have subsequently found that Eph kinases, which are the receptors for the ephrins, regulate mTOR activation via the TSC1/2 complex. Working closely with Dr. David Kwiatkowski on another mouse model of TSC (Syn-Cre;Tsc1lox/lox mice), we found that one of the most striking abnormalities was a marked reduction in CNS myelination. More recently, we have been investigating the role of TSC/mTOR signaling cascade in specific circuits in the CNS. We have generated a cerebellar Purkinje neuron-specific knockout of Tsc1 that displays autistic features, such as impairments in social interaction, repetitive behaviors, and ultrasonic vocalizations. Importantly, treating these mice with an mTOR inhibitor prevents the development of these aberrant behaviors. These experiments support the notion that neurological defect in Tsc-deficient mice can be blocked by postnatal mTORC1 inhibition and have led to the design of clinical trials in patients with TSC, including one on neurocognition. More recently, my lab has turned its attention to performing phenotypic screens in TSC, and we have published one such screen (Di Nardo et al., 2020) using a high content analysis platform. At the same time, we are working towards translating these findings from basic research into clinical trials. I will discuss learning from translational research in TSC and its implications for other neurodevelopmental disorders.

Prof. Guangping Gao (UMass Chan Medical School)

Dr. Gao is an internationally well recognized gene therapy researcher who has played a key role in the discovery and characterization of new family of adeno-associated virus (AAV) serotypes, which was instrumental in reviving the gene therapy field, hugely impacting many currently untreatable human diseases. For 30+ years of his scientific research career, Dr. Gao has primarily focused on molecular genetics and viral vector gene therapy of rare genetic diseases, Dr. Gao has published 328 research papers, 6 book chapters, and 5 edited books. Dr. Gao holds 212 patents with 429 more patent applications pending. Dr. Gao has been ranked as the World Top 20 Translational Researchers for several years in a row by Nature Biotechnology.

Adeno-associated virus gene therapy for rare diseases - Translation from preclinical proof-of-concept studies to human application

Guangping Gao

This presentation will provide an overview of the key principles, state of the art and challenges of AAV gene therapy and showcase the development of gene therapy for two different rare diseases from cells to preclinical proof-of-concept in murine disease models to large animal model and to the first-in-human application. The presentation will also briefly discuss AAV-NoStop for readthrough therapy of rare diseases caused by premature termination codon mutations.

Dr. Alan Wise (CEO, Duke Street Bio)

Alan is a Trustee at Cure CLCN4. He is an experienced and successful biotech entrepreneur with in-depth knowledge of drug discovery. He is currently CEO of Duke Street Bio. Previous roles include CEO of the successful biotech, IOmet Pharma which was acquired by MSD in 2016 and senior drug discovery roles in large Pharma (GlaxoSmithKline). Alan obtained his degree and PhD in Biochemistry at the University of Leeds and conducted post-doctoral research at Glasgow University. He then spent 12 years at GSK and was involved in various areas of pre-clinical drug discovery prior to moving into the Biotech sector

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