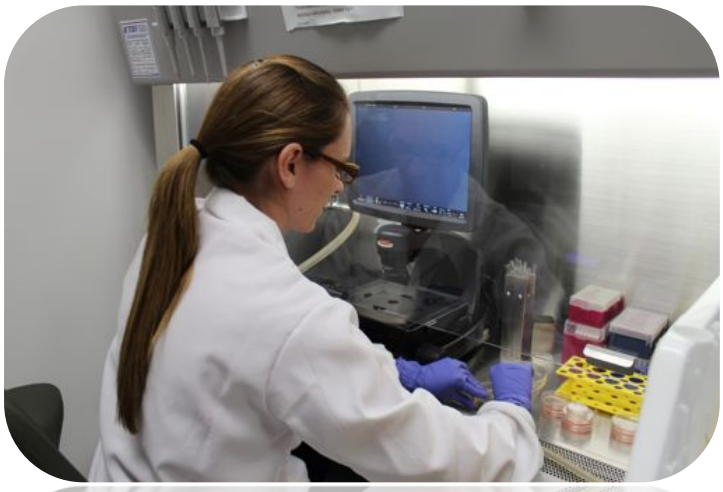
CDKL5 *RESEARCH* TIMES

Road to a Cure

IFCR and your research dollars at work!



2014 Research in Review

Dear Families, Friends and Supporters,

2014 is coming to a close, and we would like to thank each of you for your continued support of the foundation. We work diligently to fund needed scientific research for treatments and clinical centers for improved care, and to give each of us the hope of a cure for our loved ones affected by CDKL5 disorder. **In 2014, we are proud to announce that we have funded projects in excess of $710,000.00!** This year marks the largest investment in CDKL5 research to date! We could not have done this without your dedication and support, and so we wanted to take a moment to celebrate this accomplishment with each of you and highlight the important work clinicians and researchers are doing to help our children.

These exciting research opportunities are made possible by the support of families like yours. As an organization, we would like to wish you a very happy New Year, and we would like to ask you to continue to work hard alongside us. We have an aggressive research agenda planned for 2015 which will require even more funding and we are confident that, together, we can continue to push science and technology in the direction of a cure while spreading awareness across the globe!

IN THIS ISSUE

2014 Research Grants

Alysson Muotri, PhD
University of California, San Diego, USA
"Modeling CDKL5 Syndrome Using iPSC-Derived Human Neurons"

Dr. Priscilla Negraes and Dr. Alysson Muotri, with Katheryn Elibri Frame, David Frame and daughter Kiera. San Diego, CA

Utilizing advanced technology this lab has successfully been able to grow neurons directly from several children with CDKL5 from s simple skin biopsy. These CDKL5 neurons allows for many areas of investigation such as looking at pathways involved in CDKL5 disorder, including some of the pathways that may cause seizures. Using single cell gene expression profiling it has been discovered that CDKL5 neurons express a unique set of neurotransmitters. It has also been discovered that there is a unique change that happens after cells are stimulated. This information allows this technology to be used to identify how different drugs affect the function and growth of the neurons, and this will lead to the discovery of various medications that can help change the outcome of CDKL5. Also the cells will be specially screened to evaluate a specific molecular profile of CDKL5 cells, which in turn will help to determine other pathways involved with CDKL5 and could lead to more therapeutic targets.

Zhaolan Zhou, PhD
University of Pennsylvania, USA
"Modeling CDKL5 Related Disorders in Mice"

Dr. Judy Wang, a researcher in Dr. Zhou's lab, with Kiera F. at the 2nd annual CDKL5 science symposium. Washington, DC

The development of mice with CDKL5 is essential to clinically study the effects that various drugs would have in order to move research into clinical trials. This lab has created several different types of mice with CDKL5 mutations which allow us to not only study the molecular mechanisms that are important in the disorder but to evaluate how different types of mutations cause different types of effects. These models have started to identify specific molecular pathways involved in CDKL5. Utilizing these models, Dr. Zhou has started several trials with different types of compounds that may help alleviate some of symptoms of CDKL5. Dr. Zhou's lab is on the cutting edge of technology and research, one of the projects that we hope to fund in the near future is a brand new technology, a type of gene therapy that could directly repair specific mutations of the CDKL5 gene.

Dr. Claudia Fuchs, center, with Cynthia and Rick Upp, IFCR family representatives, Seattle, WA

Claudia Fuchs, PhD
University of Bologna, Italy
"Drug Therapy Targeted to Core Molecules in Neural Plasticity Cascades: A Promising Tool for the CDKL5 Variant of Rett Syndrome".
(Co-Funded with Rettsyndrome.org)

CDKL5 plays a role in a neurologic function called "plasticity" which is important for the multiple aspects of learning and memory. There are many different mechanisms that play a role in plasticity and this lab has identified some of the key pathways that involve CDKL5. Current studies include exploring existing drugs which may allow restoration of plasticity in CDKL5. If these studies show promise this would allow for a fairly rapid transition to a clinical trial.

Wenlin Liao, PhD
Institute of Neuroscience, National Cheng-Chi University, Taiwan
"Neurochemical and Therapeutic Studies in Mouse Models of CDKL5 Disorder"
Mice with CDKL5 show impaired social communication and enhanced stereotypy which are key features of autism. These mice also develop increased impulsivity and locomotor activity, simulating features of Attention Deficit Hyperactivity Disorder (ADHD). This lab is examining how CDKL5 is causing these disorders and have some very interesting results showing new pathways in which CDKL5 is involved. Utilizing these discoveries they will be studying therapies that may help to alleviate these problems.

Dr. Charlotte Kilstrup-Neilsen, PhD
University of Insubria, Italy
"Investigation of the importance of a hitherto uncharacterized MeCP2 phospho-isoform for neuronal morphogenesis and chromatin related functions"(Co-Funded with Rettsyndrome.org)
CDKL5 interacts with many different proteins, some of which cross over with Rett Syndrome. This lab is digging deeper into this relationship and is identifying how CDKL5 causes changes in appropriate neuron formation. They are examining several different pathways involved and are utilizing epigenetic pathways to discover compounds/drugs which may be able to change the dysfunctional neuronal growth caused by CDKL5 mutations.

Dr. Helen Leonard
Telethon Kids Institute, Perth, Australia
CDKL5 Database Registry
An extremely important aspect of CDKL5 research is to gain an understanding of the effects and changes that happen over time- often referred to as the "Natural History" of the disorder. This group has been studying the epidemiology of neurological disorders for many years, including Rett Syndrome. Utilizing a questionnaire developed specifically for CDKL5 we are learning so much about the spectrum of the disorder and identifying patterns of treatments and interventions that may lead to an improved quality of life for our children. Dr. Leonard and Dr. Jenny Downs work in collaboration with the CDKL5 centers of Excellence and many families and clinicians around the world. We ask everyone to please participate in this database so we can improve our understanding of CDKL5 and create a brighter future for our children. This database will also be a key source in identifying possible candidates for clinical trials. Please visit http://www.cdkl5.com/Research/Database.aspx to participate.

Dr. Charlotte Kilstrup-Neilsen, above, with Samantha U. at the CDKL5 science symposium, and seen below giving a lecture, Washington, DC, June 2014

Drs. Tim Benke and Helen Leonard, at the CDKL5 science symposium, Washington, DC, June 2014

CDKL5 Centers of Excellence

The CDKL5 Centers of Excellence funded by IFCR have had a busy year, seeing ***over 50 new CDKL5 patients*** *in a multidisciplinary setting! These clinics, which are held throughout the year at each institution, offers patients and their families the chance to see a large variety of specialists in a consolidated visit over one to two days. The centers of excellence are an invaluable source of medical care and information for families living with CDKL5. These clinics are also the sites for the combined Rett Syndrome/MECP2 duplication/CDKL5/FOXG1 natural history study funded by the NIH, and they also work closely with Dr. Helen Leonard on the separate CDKL5 database and registry. These clinicians are committed to unity and collaboration so that the clinical spectrum of CDKL5 will be better understood, and treatment guidelines and recommendations can be established as soon as possible for the benefit of all those affected by CDKL5.*

IFCR's goal is to expand the Centers of excellence in 2015 so that more geographic areas in the U.S are represented and families will not have to travel as far to access them. In addition, IFCR's commitment to families living outside the United States is unwavering, and over the next few years we are committed to expanding the centers of excellence to several other countries and to working closely with the CDKL5 communities and organizations in those places, to help meet the needs of CDKL5 families worldwide.

Children's Hospital Colorado - Tim Benke, MD, PhD

To schedule an appointment, please contact Tristen Dinkel at: rettclinic@childrenscolorado.org

Boston Children's Hospital- Walter Kauffman, MD and Heather Olson, MD

To schedule an appoint or for more information, please contact the clinic coordinator, Morgan MacCuaig at 617-919-2536 or Morgan.MacCuaig@childrens.harvard.edu.

The Cleveland Clinic – Sumit Parikh, MD

To schedule your appointment for the CDKL5 Clinic, please call 216-444-1994 or contact Lisa Sanders at sanderl@ccf.org or Dr. Parikh at parikhs@ccf.org.

SPOTLIGHT ON RESEARCHERS

Tim Benke, Md, PhD

Tim Benke, MD, PhD is the Ponzio Family Endowed Chair in Neurology Research at University of Colorado/Children's Hospital Colorado. Dr. Benke received his MS in electrical engineering at Rice University and his MD, PhD at Baylor college of Medicine. He completed his clinical training in pediatrics and pediatric neurology at Texas Children's Hospital, and did a post-doctoral fellowship at the MRC Centre for Synaptic Plasticity/University of Bristol in the UK.

After he joined the faculty at the University of Colorado School of Medicine, his lab has focused on the molecular mechanisms that are impacted by early-life seizures that go on to cause intellectual disabilities and autism.

Dr. Benke has translated his molecular and genetic research of epilepsy and developmental disabilities back to the bedside by initiating multidisciplinary clinics, in particular the Rett Syndrome clinic and the CDKL5 Center of Excellence.

IFCR is proud to support Dr. Benke's efforts to study CDKL5, both clinically and in the laboratory.. Since 2012, IFCR has helped to fund Dr. Benke's CDKL5 Center of Excellence and we are excited with what the future holds!

EYE ON IT

CDKL5 in the scientific literature

In 2014

- CAGE-defined promoter regions of the genes implicated in Rett Syndrome. Vitezic et al. BMC Genomics 2014 Dec 24;15(1):1177.
- **Early-onset epileptic encephalopathy caused by CDKL5 mutation. Hjalmgrim et al; Ugeskr Laeger**2014 Dec 15;176(25A)
- **Molecular characterization of a cohort of 73 patients with infantile spasms syndrome; Boutry-Kryza et al; Eur J med genet;** 2014 Dec 11. pii: S1769-7212(14)00218-3
- **Immune Dysfunction in Rett Syndrome Patients Revealed by High Levels of Serum Anti-N(Glc) IgM Antibody Fraction; Papini et al;** J Immunol Res. 2014; 2014: 260973.
- **Neurodevelopmental and neurobehavioral characteristics in males and females with CDKL5 duplications. Szafranski et al; Eur J Hum Genet** 2014 Oct 15.
- **Optimizing the molecular diagnosis of CDKL5 gene-related epileptic encephalopathy in boys. Mei et al; Epilepsia** 2014 Nov;55(11):1748-53
- **CDKL5 variant in a boy with Infantile Epileptic Encephalopathy: Case report. Wong et al; Brain Dev** 2014 Jul 29. pii: S0387-7604(14)00179-X
- **Loss of CDKL5 impairs survival and dendritic growth of newborn neurons by altering AKT/GSK-3β signaling. Fuchs et al; Neurobiol Dis** 2014 Oct;70:53-68
- **GluD1 is a common altered player in neuronal differentiation from both MECP2-mutated and CDKL5-mutated iPS cells. Livide et al; Eur J Hum Genet** 2014 Jun 11.
- **Mapping pathological phenotypes in a mouse model of CDKL5 disorder. Amendola et al; PLoS One** 2014 May 16;9(5):e91613.
- **Complex mosaic CDKL5 deletion with two distinct mutant alleles in a 4-year-old girl. Boutry-Kryza et al; Amer J Med Genet** 2014 Aug;164A(8):2025-8.
- **Capping of the N-terminus of PSD-95 by calmodulin triggers its postsynaptic release. Zhang et al; EMBO J** 2014 Jun 17;33(12):1341-53
- **Clinical features and gene mutational spectrum of CDKL5-related diseases in a cohort of Chinese patients. Zhao et al; BMC Med Genet** 2014 Feb 25;15:24
- **Mutations in the C-terminus of CDKL5: proceed with caution; Diebold et al; Eur J Hum genet** 2014 Feb;22(2):270-2.

How to participate in Research

Living with CDKL5 is hard, but families can start to make a difference by helping researchers with various projects.

- **CDKL5 International Database and Registry** (see page 3)

- **Rare Epilepsy Network (REN)** We are excited to announce that the **Rare Epilepsy Network (REN) Registry** is open for enrollment at http://REN.rti.org. This is a collaboration between the Epilepsy Foundation, the IFCR, RTI international, Columbia University, and many different organizations that represent patients with a rare syndrome or disorder that is associated with epilepsy or seizures. The REN will establish a registry of these patients which includes patient or caregiver-reported data in order to conduct patient-centered research. This research will be in the form of natural history studies and completion of surveys.

- **University of Minnesota.** This study is looking at cortisol levels, a hormone involved in the stress response, in children with Rett Syndrome and CDKL5. This is a study involving two parts. The first is a simple saliva collection, which is sent to you so that you can do the collection at home. The second part involves a questionnaire to fill out. There is no travel involved, and everyone can participate! Please contact Breanne Byiers to learn more and request the saliva kit. 612-626-7110, or email byier001@umn.edu.

- **NIH funded Natural History Study** is a collaboration between Rett Syndrome, MeCP2 Duplication, CDKL5 and FOXG1, and is a multi-year clinical study that will investigate longitudinal natural history and neurobehavioral assessments, biomarkers, outcome measures and neurophysiologic and imaging correlates of disease severity. More details about enrollment will be available in early 2015.

We want to hear from you!

- Please send any research related questions to dframe@cdkl5.com
- Select questions may be used in future newsletters
- We welcome your feedback and would like to hear any suggestions or answer any questions you may have.

Upcoming Events:

- Rare Disease Day
  February 28, 2015
  Worldwide
- Reminder: June 17 is CDKL5 Day and the month of June is CDKL5 Awareness Month!
- IFCR's 3rd International CDKL5 Scientific Symposium
  Spring/Summer 2015
- American Epilepsy Society Annual Meeting
  December 4 - 8, 2015
  Philadelphia, PA USA
- IFCR's 3rd Family Conference
  2016

International Foundation For CDKL5 RESEARCH℠
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Leading the way in finding a cure and treatments for CDKL5 disorder

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