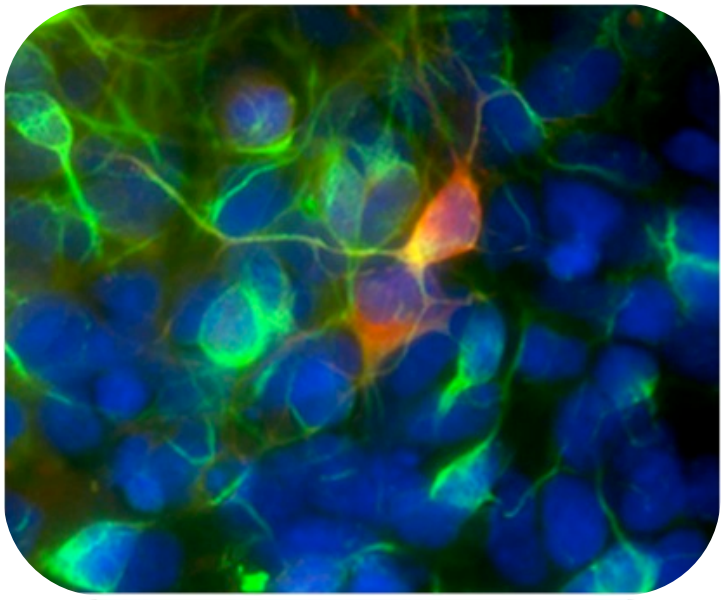
CDKL5 *RESEARCH* TIMES

Hope Love Cure CDKL5

IFCR and your research dollars at work!



Welcome to our first quarterly Research newsletter! CDKL5 Research Times was created by IFCR to keep you informed about all the latest advancements and ongoing research involving CDKL5.

IN THIS ISSUE

First Steps to a Cure: Where do we begin?

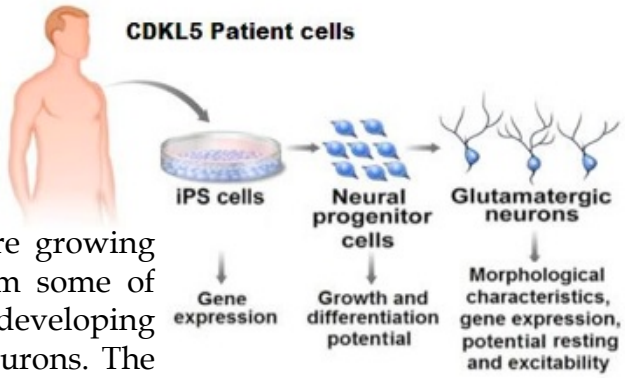
This issue focuses on two extremely important research projects that are currently underway - a mouse model and iPS cells. These are important building blocks that will help us understand how CDKL5 actually works and will form the basis for all subsequent research as we actively seek treatments and a cure.

Future issues will feature new research projects, updates on existing projects, and highlight all new publications of CDKL5 in the scientific literature.

We will also bring you highlights from scientific meetings as they occur, and introduce you to our team of researchers who are working very hard to help our children.

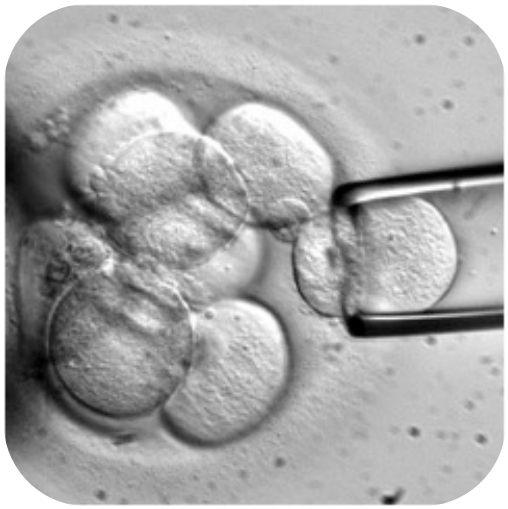
Using iPS Cells to Grow Neurons

Induced Pluripotent Stem Cells (iPS) cells are one of the newest molecular biology techniques developed to study a variety of different cells. Using highly specialized protocols it is possible to take a very small piece of skin (about the size of an eraser on the end of a pencil) and separate out cells called fibroblasts. These cells under the right conditions will actually revert back to a pluripotent stem cell. This cell is exactly what it sounds like– it is pluripotent which means that it can virtually grow into any cell in the body, including neurons. We currently have a few different laboratories that are growing these iPS cells from some of our children and developing CDKL5 affected neurons. The first lab reporting success is the laboratory of Dr. Alessandra Renieri at the University of Siena in Italy. The International Foundation for CDKL5 Research is proud to be working with Dr. Alysson Muotri at the University of California at San Diego to create several different cell lines with different mutations of



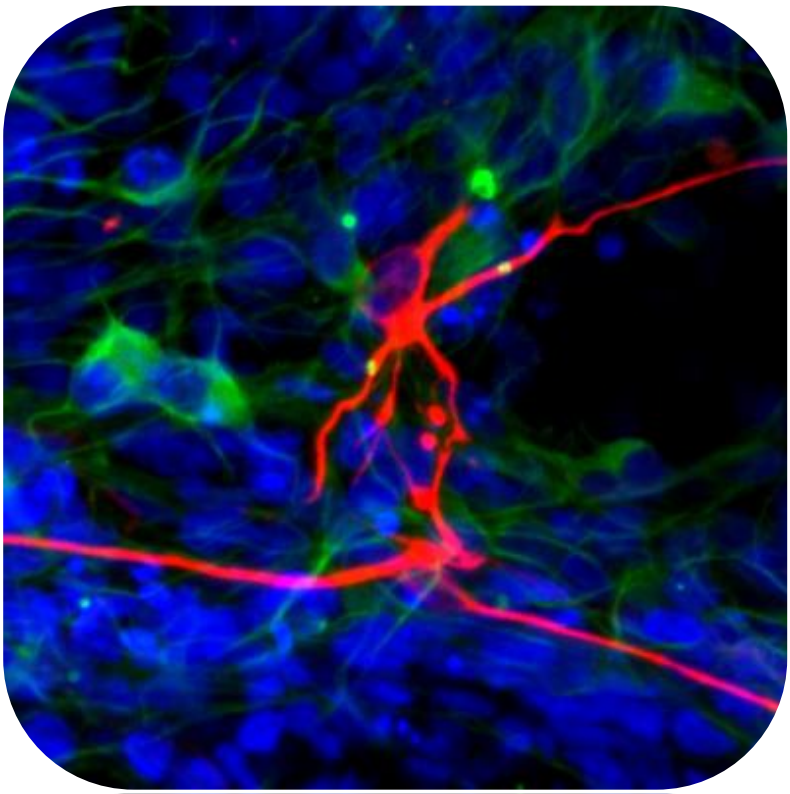
iPS cells are derived from skin samples of individuals affected by CDKL5. This is a fast and readily available option and avoids the controversy surrounding embryonic stem cells!

"iPS cell technology is rapidly advancing the pace of medical research!"



iPS cells growing in the lab will eventually differentiate into neurons

The advantages of using iPS technology is that it is a relatively rapid way to study the function of the neurons that are affected with CDKL5 and then compare these to normal neurons as well as those of other disorders such as MeCP2 mutations of Rett Syndrome. This allows for determination of gene function and measurements of different genes expressions. It will allow creation of many cells in which we can determine exactly what the role of CDKL5 is and how it changes the neuronal structure and function. This also creates a platform that will be used for drug screening which can test for hundreds or thousands of drugs in the search for a cure for those living with CDKL5.



Mouse Model of CDKL5

The second project that is critical in studying disorders such as CDKL5 is to create an animal model. The International Foundation for CDKL5 Research has co-funded this endeavor with the International Rett Syndrome Foundation and has funded the laboratory of Dr. Cornelius Gross and his post-doctorate fellow Dr. Elena Amendola to create the first model. (see Spotlight on Research, pg. 4)

While I am sure many of us do not favor using animals, it is absolutely vital that a mouse model be created in order to help with the development of drugs which can then be studied in human trials. Currently, the FDA essentially mandates that new drugs be tested on animals and a positive outcome demonstrated before the agency will allow these drugs to be tested in humans. We understand how difficult it may seem to do mouse experiments, but we have to maintain our focus and recognize that there are necessities on the road to a CURE for CDKL5.

We hope to have this first mouse model created by the fall of 2011. Researchers from other labs that have attempted to create a complete knockout (or removal) mouse of CDKL5 report that the mice are "embryonic lethal", i.e. the mice die in utero. Therefore, Dr. Cornelius Gross' lab is using a special technique called the Cre/lox method, and although it takes several extra steps it will have a higher chance of successfully creating a tissue specific knockout mouse.

Continued…

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We are currently waiting for the final step of this process and are anticipating that we will have this completed by early August 2011. Full characterization will then be done to ensure that the CDKL5 gene/protein is not present in these mice. Once this is done there will be a series of studies to identify the "phenotype" of the mice - their appearance, their capabilities on different performance tests, and different aspects of their function. Further explanation of this will be discussed in future issues.

A Second Mouse Model !

While waiting for this project to complete, the IFCR has just funded a second mouse model with Dr. Zhaolan (Joe) Zhou at the University of Pennsylvania. Dr. Zhou is developing a "knock-in" mouse which will have a nonsense mutation at R59X.

It is imperative that different types of mutations are represented in the mouse models so that we can further develop studies to tell what CDKL5 really does and to see how new drugs affect different types of mutations.

This mutation, R59X, was selected for a few reasons. It seems to be a more common mutation for CDKL5 with five reported cases in the medical literature, it is at a strategic site in the gene and we have correlative samples from both a boy and girl affected with CDKL5 in which iPS cells are also being developed concurrently(see previous story on iPS cells).

SPOTLIGHT ON RESEARCHERS

Dr. Elena Amendola, PhD

Dr. Amendola is a post-doctorate fellow in the laboratory of Dr. Cornelius Gross at the European Molecular Biology Laboratory, Mouse Biology Unit in Rome, Italy.

She received her doctorate degree in Life and Biomedical Sciences at the Open University in London, England. She has been the recipient of the Biogem Fellowship, the Genomics for Applied Research Fellowship and the Stazione Zoologica pre-doctoral Fellowship awards. Dr. Amendola has several publications including articles in the journals *Endocrinology* and *Oncogene.*

Dr. Amendola was awarded a post-doctoral fellowship grant last year which was co-funded by the International Foundation for CDKL5 Research and the International Rett Syndrome Foundation to develop a mouse model for CDKL5 (see article) as well as to begin to characterize targets of CDKL5.

The Cost of Doing Research

My mother made a coffee cake that I have tried over and over again to replicate but it just never turns out the same. Do you have a favorite recipe that your mother or grandmother made that you say "I have never had another like it"?. Similarly, most scientists put the emphasis on RE– search because so many times you need to repeat and repeat and tweak and change in order to get it right. Then it needs to be reproducible as well. This takes a lot of time, talent, personnel and very expensive reagents and equipment to do, and to RE-do. For example it typically costs over $100,000 to make a single mouse model and then more to characterize and study the phenotype. To make the iPS cells can cost over $250,000!

Once we have these building blocks the financial commitment continues because we will need research dollars to further study and collaborate with other researches to evaluate biochemical changes, neuronal changes, and functions of CDKL5. This takes many different researchers from around the world with many different specialized techniques. The cost can be several million dollars to fully characterize the role and function of CDKL5. In order to streamline costs, the IFCR is concentrating on using top researchers and is focusing on doing appropriate studies to translate this work as quickly as possible into potential therapeutic options. Outlined on page 6 are some estimated costs. *To find a cure we need everyone's help!*

EYE ON IT
Cost of Research

Estimated costs of the research correlating with the diagram pg7:

Mouse Model: $100,000/model

iPS cells: $300,000 (several lines)

Protein characterization: $1,500,000

Drug Screening: $900,000

Drug Development: $1,400,000

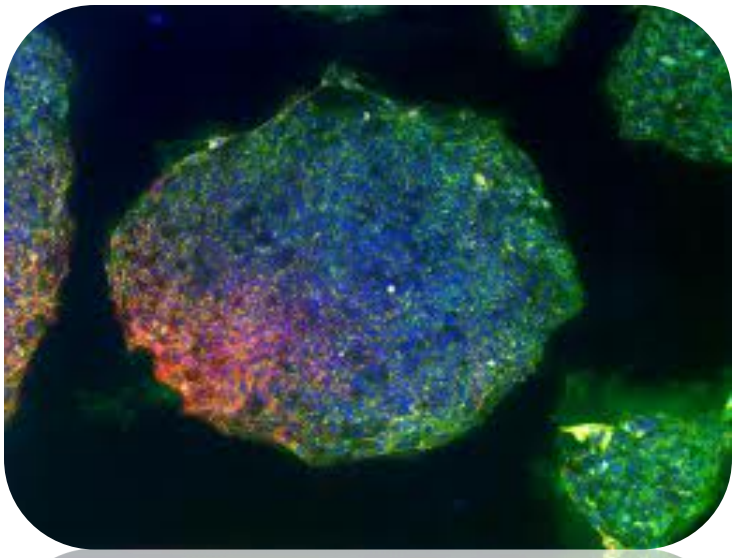
Pilot trials in humans: $1,800,000

Phase II and III trials: $8,000,000

Database, ongoing: $75,000

While these seem like daunting numbers, we must stay focused on one piece at a time. IFCR is working with scientists already specializing in specific aspects of this work and may be able to use other grants to supplement research costs. Also the IFCR is supplying smaller "seed" grants to enable researchers to obtain preliminary data to apply to other funding agencies for larger grants. We hope to discover that some drugs currently used for other purposes may show benefit for CDKL5. This would reduce development costs and allow for partnering with the pharmaceutical industry.

CDKL5 is too new and too rare for funding to be readily available through traditional grant agencies such as the NIH. This means that we bear the responsibility of supplying the grants to get all of this work started. The more grants we can give early on to develop the research tools needed, the faster this process will be.



How do we make a difference now?
What does all this research mean for children with CDKL5?

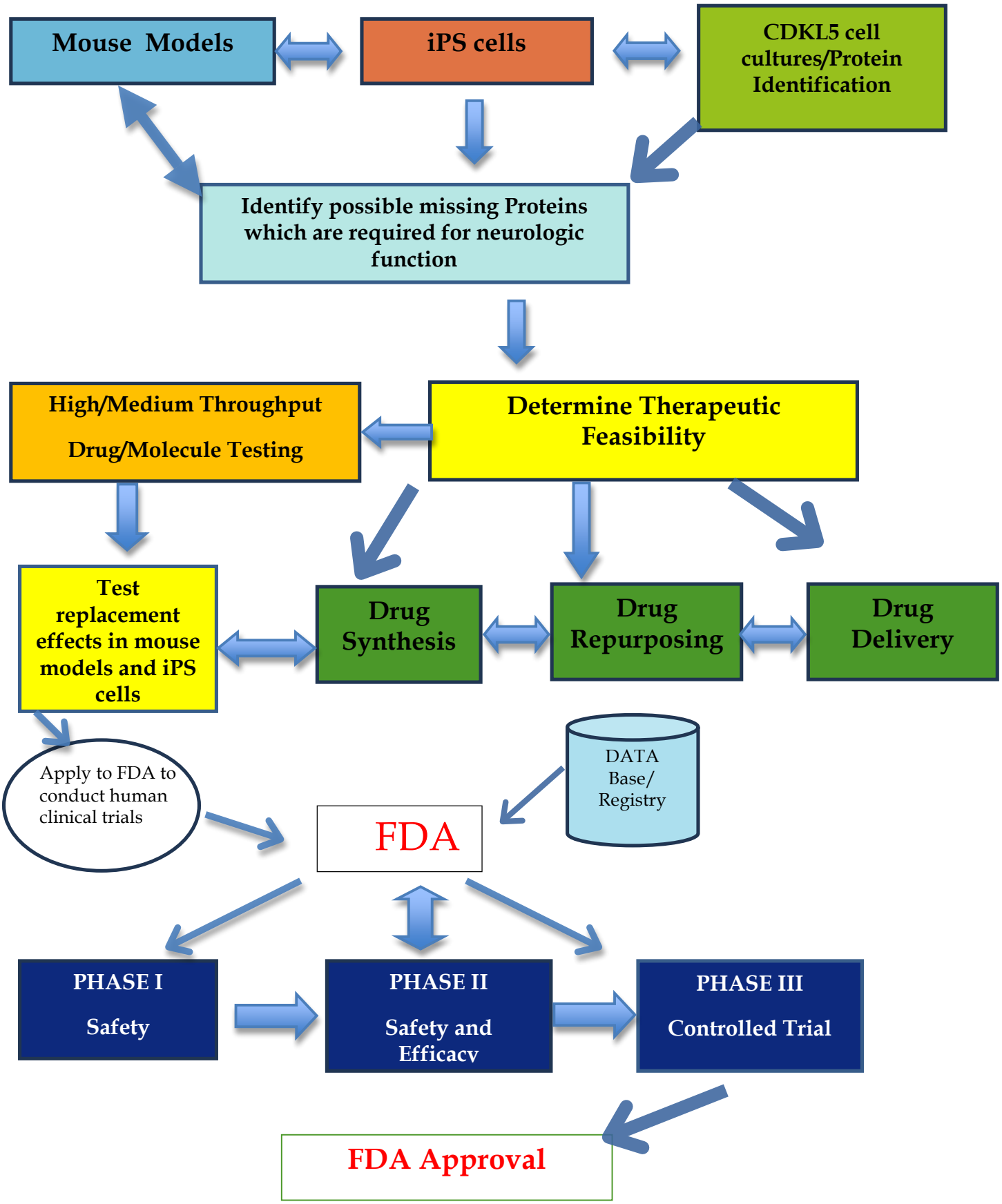
Admittedly, research is a waiting game, and sometimes a long one. IFCR is doing everything we can to accelerate the pace of research, but unfortunately we cannot speed up nature in regards to a mouse model.

In the meantime, with enough funding, there is plenty we can do! There are other areas of focus besides laboratory research, and that is the clinical aspect.

- Seizure control
- Gastrointestinal and bone health
- Various therapies that focus on improving strength, coordination, vision and language
- Diet and environmental influences.
- A Natural History Study
- A comprehensive database that all researchers can access

While some of these clinical areas may require a mouse or cell model, many do not. Basic science research is critical, but equally important is finding ways to improve the quality of life *now* for those living with CDKL5!

In the coming months, research dollars permitting, we will be investigating possible clinical research projects that are relevant to CDKL5. We are working with researchers worldwide on the creation of a database and hope to have this up and running in the next 6 to 9 months.


Mouse Models
iPS cells
CDKL5 cell cultures/Protein Identification
Identify possible missing Proteins which are required for neurologic function
High/Medium Throughput Drug/Molecule Testing
Determine Therapeutic Feasibility
Test replacement effects in mouse models and iPS cells
Drug Synthesis
Drug Repurposing
Drug Delivery
Apply to FDA to conduct human clinical trials
DATA Base/ Registry
FDA
PHASE I Safety
PHASE II Safety and Efficacy
PHASE III Controlled Trial
FDA Approval

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:

- Neuroscience 2011
  Annual meeting of the Society for Neuroscience
  November 12-16, 2011
  Washington, DC
- 7th Rett Syndrome World Congress
  June 22-26, 2012
  New Orleans, LA USA

International Foundation For CDKL5 RESEARCH℠ FROM CAUSE TO CURE

Leading the way in finding a cure and treatments for CDKL5 disorders

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