The 4th International CDKL5 Congress 2nd- 3rd June 2017 – Rome

The 4th International CDKL5 Congress was held at the A. Roma Lifestyle Hotel in Rome on the 2nd and 3rd of June 2017. As in the past, the meeting was attended by families and carers along with researchers and some clinicians and other healthcare professionals.

The meeting was hosted by Antonino Caridi and Omar Fumagalli of CDKL5 Insieme Verso La Cura Italia. During the introduction we heard from Majid Jafar who spoke about the work of the Lou Lou Foundation, Domenica Taruscio who spoke about the Istituto Superiore Sanita and Anna Maria Cazzato who spoke about Telethon Italia. The first day of the meeting then focussed on recent research activity from a number of groups in Europe and the US. On the second day we heard talks on treatment strategies and also presentations on the development of an International CDKL5 Registry and from a number of CDKL5 family associations.

Day 1

On the first day there were presentations on basic discoveries, disease models and new therapeutic developments. There were also talks on the CDKL5 Disorder and a panel discussion from industry.

Basic Discovery

Professor John Rouse, from the University of Dundee, presented his work on identifying the substrates of CDKL5. His unit focusses on the study of kinases – which are specialised proteins called enzymes – that activate other proteins through a process called phosphorylation (that's the kinase bit). The proteins that a kinase activate are called its substrates and Professor Rouse has been identifying the substrates of CDKL5 using a technique called mass spectrometry. By starting with CDKL5 and working through the biological pathways, it is hoped that the function of CDKL5 – what it actually does in the nerve cell – will become clearer. So far, 15 substrates have been identified of which two, MAP1s and CEP131, may be relatively important. These proteins are associated with the formation and regulation of tubular structures such as cilia. The significance of this is yet to be understood but in common with a previous study it raises the possibility the CDKL5 could be a ciliopathy.

Maurizio Giustetto from the University of Turin presented his research on the role of CDKL5 in a process involving what are called the shank family of proteins which are involved in maintaining synapse function between nerve cells.

Charlotte Kilstrup-Nielson of the University of Insurbia presented her work looking at the potential role of a substance called pregnenolone in CDKL5. Pregnenolone is a neurosteroid and has been found to have a role in the development and maintenance of microtubules in nerve cells. It may therefore have a part to play in supporting brain development.

Disease Models

This section focussed on the various CDKL5 disease models that are being used to study CDKL5. Professor David Wylie from the University of Edinburgh described his work using a rat model and discussed some of the early neurophysiological research that had been done.

Professor Tomasso Pizzorusso from the University of Florence discussed his recent work in the mouse model looking at the visual cortex and in particular, visual responses which might ultimately prove to be a useful biomarker for use in future studies. However, in both cases, the big issue is that neither of these CDKL5 animal models display the seizure activity we see in affected children. The reason for this remains unclear. Is it because they are just resistant to seizures or does a CDKL5 mutation in isolation not cause seizures implying other molecular factors yet to be identified are involved???

Professor Alysson Muotri presented some of the work his lab is undertaking at the University of California with iPS cells. It is possible to take a skin biopsy and through biochemical manipulation, convert the skin cells from the biopsy through what are called Induced Pluripotent Stem Cells (iPS cells) into nerve cells. The nerve cells that are produced contain the same genetic information as the original skin cells that were biopsied. Therefore if the biopsy comes from a child with CDKL5 then the subsequent neurons that are produced will contain the same CDKL5 mutation. Through this technique Professor Muotri has acquired many iPS-neurons with a variety of different CDKL5 mutations.. Furthermore, he is able to grow these cell lines into 3-D structures which are like mini-brains. He is therefore able to study whether different mutations produce different effects on neural development and he can also use these to study the effects of various therapeutic agents.

New Therapeutic Developments

Michael Green from the University of Massachusetts discussed his work on reactivating the CDKL5 gene on the inactive X-chromosome. You remember the story – females have two X-chromosomes – one from mum and one from dad - one of which is randomly inactivated in each cell. Statistically, 50% of our neurons function with mum's X inactivated and 50% with dad's X inactivated. If the inactivated X contains the mutated CDKL5 gene then all is good. However, if the inactivated X contains the good gene then that cell (neuron) has to function with the mutated gene – and that's bad. Professor Green presented some of his research on the identification of molecules involved in the X-inactivation process. These can then be blocked with the idea of allowing the CDKL5 gene on the inactive X to be be re-activated. This reactivation occurs regardless of whether that gene is the normal or mutated CDKL5 gene and each cell will then have the CDKL5 gene from each X-chromosome active. The hope would be that this would lead to more normalised neuronal and brain development. However, there was a discussion about what it might mean for the function of neurons having both the normal and mutated CDKL5 genes active together and also what the effects might be if other genes in the vicinity of the CDKL5 gene were also re-activated (nature inactivates one X-chromosome for a reason).

Kyle Fink from the University of California has an interest in the genetic engineering techniques of transcription activator-like effector (TALE) and clustered regularly interspaced short palindrome repeats (CRISPR). These can be used to modify gene expression in genetically-linked conditions. He discussed the potential application of this to CDKL5 through the modification of the mutated gene.

Finally, Stefania Trazzi from the University of Bologna discussed pharmacological approaches to rescue brain development. Through identifying molecular pathways it is possible to identify stages where there is a deficiency in a molecular process caused by a CDKL5 mutation. It might then be possible to either replace or reverse this deficit again in the hope that this will improve neuronal and brain development. Stefania discussed 2 such areas – TrkB agonists and Gsk3β inhibitors for which further research will be required. To a certain extent, this work links back to the work on identifying the substrates of CDKL5 that Professor Rouse discussed in the first presentation..

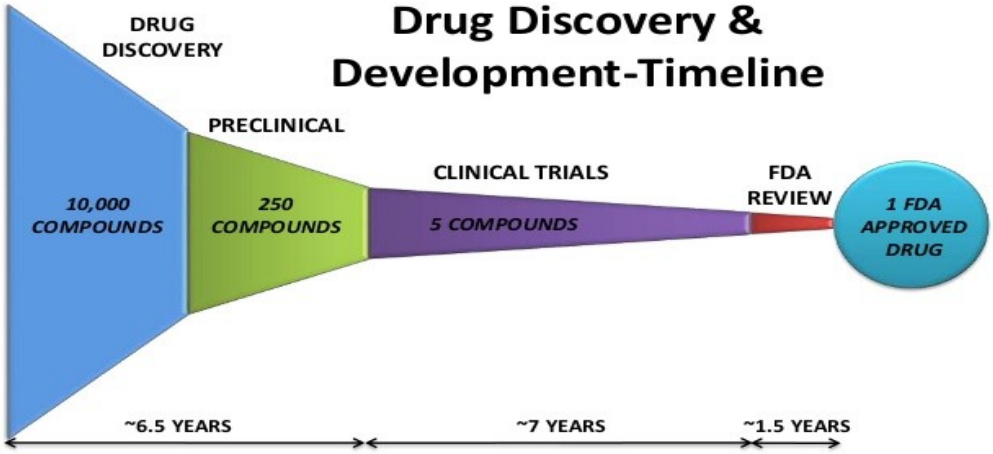
CDKL5 Disorder

Maria Trivisano from the Bambin Gesu Hospital, Rome presented a pilot study on the use of a drug called Ganaxolone in children with epileptic encephalopathy. The trial involves 4 patients with a relatively short follow-up. So far, 3 of the 4 have shown an improvement in seizures with better sleep and more seizure free days reported. Seizures in the 4th worsened and so their treatment was discontinued. The group running the trial are hoping to recruit more patients into the trial and information about this will become available in due course.

Dr Tim Benke from the University of Colorado has led in the establishment of a CDKL5 Centre of Excellence in the US. He presented a review of their service whilst Stefania Bigoni discussed the clinical presentation of 12 patients described as having the Hanefeld RTT variant.

Domenica Battaglia from the Policlinico Gemelli Hospital presented the electro-clinical findings in 4 children with CDKL5. This was followed by a brief discussion regarding the so-called “3 stages of epilepsy” in CDKL5 and whether this was still a valid way of thinking about CDKL5-related seizures.

Finally, the day concluded with a panel discussion from industry. There was an interesting presentation about new drug development with some startling facts in terms of both the time, usually as long as 15 years (as shown below) at a cost of $2.5 billion.



Day 2

Day 2 began with a review of the research presented on day 1 by Elisabetta Ciani. This is a theme that was started last year at the 3rd European Meeting in Birmingham where the research presentations are summarised for parents and carers.

We then heard talks from Care Givers on various therapeutic approaches to the day to day symptoms of CDKL5 that we all have to deal with. There was a talk on the ketogenic diet, although no specific cases in relation to CDKL5 were presented. There was also a talk on the psychology, particularly in relation to grief and the 5 stages of the grief reaction, namely – denial and isolation, anger, bargaining, depression and acceptance. Finally, there was a talk on alternative communication techniques.

In the afternoon there were presentations on a CDKL5 Register for Italian families and also an International Registry that is being developed and supported by the Lou Lou Foundation. Families are being encouraged to join the International Registry and can do so via their Facebook page - CDKL5 Patient Database Alliance Finally, we heard presentations from members of the CDKL5 Associations from the UK, Germany, Holland, Slovakia, the US and Spain.

Overall, the meeting was a great success and a great experience for those who attended. New research and new ideas for potential therapeutic options were discussed. The meeting allowed parents, carers and affected children to meet with each other and to discuss various issues and ideas with researchers and clinicians. This particular format does seem to work well and we now look forward to the next European meeting which will be held in the UK in 2 years time. Further details will follow.

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