

## KCNT1 Epilepsy Foundation Tours Labs in London

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KCNT1 Epilepsy Foundation, Executive Director Sarah Drislane, met London-based researchers Amy McTague MD, PhD and Jenny Lange, PhD at the Zayed Centre for Research in Rare Disease in Children (ZCR), and Gabriele Lignani, PhD at UCL Queen Square Institute of Neurology, to learn more about the KCNT1 neuronal models they are developing.

Dr McTague explained that while most people are familiar with mouse models, stem cell-derived neurons are a newer model and can be used to gain a better understanding of the KCNT1 disease mechanisms — and to test new treatments such as ASOs. “Because cortical development is different between humans and animals, human models such as patient-derived cell lines are helpful in seeing how early treatments can affect brain development,” says Dr McTague.

Dr McTague and her team used donated skin cells from patients as a starting point, then used a combination of techniques to coax the cells back to their original pluripotent state (before they get differentiated into specific types of cells). Next, they use special cellular culture technology to direct the cells to form into neurons. From there they can create both 3D and 2D cell models. Under the microscope you can see dendrites extending and making connections with other neurons. Lange explained how with the help of computer analysis, they can look into other genes and pathways that may contribute to KCNT1-related epilepsy.

After putting on gowns and gloves Dr Lange removed some neurons from the incubator. It takes approximately 60 days to grow them, test them, and ensure they express KCNT1 protein. Under careful watch over another 180-200 days, they will begin to observe neuronal activity. This important work is highly labor intensive and must be carefully controlled. “Quality control is extremely important. When you’re testing a new drug for example, we need to know that the drug is actually working on the target you intended,” said Lange.

It is important to note that these are not mini brains, despite the flashy headlines on the cover of the latest magazine. Dr Lange points out that neither 2D or 3D neurons cannot replicate all the functions or systems of the complex human brain. For example, they lack the vasculature system that keeps things flowing. And while brains have both inhibitory and excitatory neurons to keep the neural networks in balance, these cells consist mainly of excitatory neurons —but future lines will incorporate both. Literature on KCNT1 finds that problems created by variants in the KCNT1 gene cause an imbalance of inhibitory and excitatory neurons, so being able to include inhibitory neurons will be an important step to understanding these networks.

Once the neurons are matured, their activity can be verified by measuring with Electrophysiology probes and special microscopes.

How did these young researchers come to study KCNT1? Amy McTague's interest began when she met families affected with EIMFS during her neurology training. She came to GOSH/UCL to pursue a PhD in the genetics of epilepsies like EIMFS and thus became interested in *KCNT1*, sequencing a UK cohort of patients with EIMFS and finding new *KCNT1* mutations to study. Following her PhD she became a consultant neurologist at Great Ormond Street Hospital and, frustrated by the lack of treatments, started her own lab at the Zayed Centre to understand disease mechanisms and test new treatments. Dr Lange is the senior post-doctoral fellow in the McTague lab.

Jenny Lange studied psychology as an undergraduate and realized how much she enjoyed doing research and continued her studies to get a MSc and then a PhD in Neuroscience. She now focuses on rare diseases looking at the common mechanisms between them.

Gabriele Lignani is an Associate Professor, and his team works on studying the pathophysiology of epilepsy and also on developing innovative genetic therapies for genetic and acquired epilepsies. He is an electrophysiologist, but the techniques used in his lab range from molecular biology to in vitro and in vivo electrophysiology and behavior. He is collaborating with Dr McTague for the characterization of brain organoids derived from patients with neurodevelopmental encephalopathies.

Both McTague and Lange are interested in exploring shared pathways between genetic epilepsies and autism, including the gut-brain axis and the role of different cell types and pathways. Lignani works with 50 others and among other areas, is exploring how various signaling mechanisms in the brain might be utilized to inform novel treatment approaches for seizures.

One of the labs, fondly referred to as “the fish bowl” is below ground level but surrounded by upper windows so passers-by can be inspired. The researchers may feel curious eyes watching, but wave when boys and girls visiting the nearby Children’s hospital tap excitedly on the windows to the researchers below.

We know that KCNT1 variants can cause neurodevelopmental issues and epilepsy in most people with KCNT variants, but we still have more to learn. The work being done by McTague, Lange, Lignani and their whole team with these cellular models will help us have a better understanding of KCNT1 and will lead us to more treatment targets.

The Zayed Center for Research into Rare Disease in Children is adjacent to Great Ormond Street Hospital and University College London Great Ormond Street Institute of Child Health. ZCR was developed from a generous gift from Her Highness Sheikha Fatima bint Mubarak in honour of her late husband, Sheikh Zayed bin Sultan Al Nahyan. To learn more, click here <https://www.gosh.org/what-we-do/research/zayed-centre-research/legacy-of-sheikh-zayed/>