JOHN VAN GEEST BUILDING FOR BRAIN REPAIR & ADDENBROOKE'S HOSPITAL

2018 HUNTINGTON'S DISEASE

Roger Barker – Introduction

Welcome to our newsletter. Over the last 12 months we have been involved in many new ventures with you all. We have been part of the exciting new trial targeting the abnormal protein in HD. We published the results from our own study looking at a drug called rilmenidine that was used on the ground that it may help cells get rid of the abnormal huntingtin problem. We found the drug was well tolerated and may help. We have also been very busy looking at all sorts of thinking problems in HD and Sarah Mason has brought together a brilliant new group of researchers to address this as you can read below. Finally, I would like to thank the team who help run all our work, especially Sue Hill who works tirelessly for the HDA to help families / patients in the community. Of course none of what we do from a research point of view would be possible without you and the families and for that we are so grateful. Thank you so much.

Katie Andresen – The trials of HD

I am fairly new to the group having joined last June as a Research Assistant working mainly on clinical trials. My role is to manage the drug trials so if you have any questions about any of these then please do contact me on 01223 331141.

IONIS HTTRx CS1

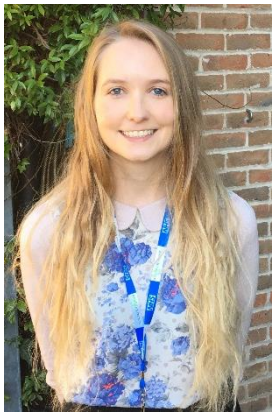
One of the trials we are involved in concentrates on silencing the abnormal HD gene product. The agent is called an antisense oligonucleotide, or ASO and had been designed to lower the level of mutant Huntingtin by telling cells to delete the 'message molecule' from the Huntingtin gene. The long-term hope with this agent is to slow down or stop the disease. We have been working with the American Pharmaceutical company IONIS who have developed the drug called IONIS-HTTR. We have just finished working on the first phase of the study which has appeared to show good safety results that supports its continued development as was announced widely just before Christmas. We are one of multiple sites worldwide that is now hoping to undertake the next phase of the study in 2018.

HD Clarity

We are also working in collaboration with University College London on a new study they are co-ordinating across the UK looking at cerebrospinal fluid (CSF) in HD patients. CSF is an ideal fluid compartment for assessing HD biomarkers due to its proximity to the brain it is collated via a lumbar puncture and will be used to

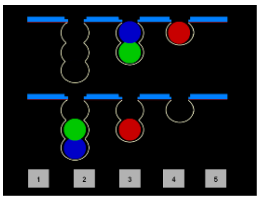
look for new biomarkers which in turn may help in the evaluation of future potential novel therapeutics in HD. We aim to start in the first quarter of 2018 and are currently recruiting participants from our HD clinic. If you are interested in hearing more about HD Clarity, then please contact Katie Andresen on 01223 331141 or kera2@cam.ac.uk.

Laura Sherlock – Enroll-HD



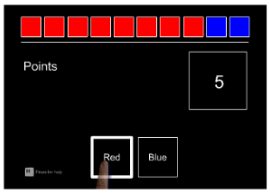
I recently joined the group in September as a Research Assistant, where I am now largely focusing on the Enroll-HD study. Enroll-HD is a large, worldwide cohort study. It is an observational study, which means that it aims to track changes over time, rather than testing a new drug or therapy. The study aims to gather as much information as possible in order to understand how HD affects the mind and body. There are currently around 15,000 people taking part in Enroll-HD across 149 sites in 16 different countries. At our clinic, we have over 150 participants taking part and we were one of the top 20 recruiting centres in December. Those recruited to the study are invited to complete one visit per year usually at the same time as their appointment at the HD clinic. A study visit involves completing some questionnaires and cognitive assessments and giving a blood sample. This information is anonymised and added to the Enroll database which we and other researchers can use to try to answer a wide range of questions about HD. The Enroll database is also a great platform for those recruiting to clinical trials as it provides a large cohort of potential participants, all of whom already have up to date health information that has been tracked over time. This makes it easier for researchers to create their own sub studies which are linked to Enroll, such as the HD- Clarity trial (above). If you would like more information, please feel free to contact me Laura on ls787@cam.ac.uk

Sarah Mason – Social Economics



Joking Flustered

Desire Convinced



We know that some people with HD can have difficulty managing their money and often need a little help and support from their friends and family. This doesn't just mean helping them to buy items and pay bills, but is now equally as much about protecting them from financial manipulations and swindles that are becoming all too common. Fake emails, pressure selling and telephone scams are increasingly becoming a feature of everyday life that we are all having to learn to navigate around, but for some people with HD, this is an almost impossible task. Understanding why HD patients find it so difficult to identify and avoid these type of schemes will hopefully allow us to find ways to better protect them and their families from falling victim to financial abuse. Over the last year we have started to investigate this area though a new study that invited patients at all different stages of the disease, to come to our institute and play a series of games designed to test different aspects of thinking such as memory and risk-taking behaviour that may be related to how we make good financial decisions. From this we have some data to suggest that the way that people with HD make decisions about their money is strongly associated with their ability to accurately judge the thoughts, feelings and intentions in other people. This may mean that patients are less able to tell whether the person they are talking

to is trustworthy or not which may explain why they find it harder to know if someone is trying to trick them but we will need further research to know for certain.

We are now planning to continue this work and will be starting a new programme of research, funded by the Huntington's Disease Association, that aims to better understand the factors which make HD patients vulnerable to financial abuse. If you would like to know more about this please contact Sarah (slm64@cam.ac.uk or 01223 331160).

Alice White – Thinking Symptoms

Doctors, scientists and patients alike have noted that people with Huntington's disease (HD) do not all have the same problems in memory and thinking. Some patients have problems with their memory, while some have problems with understanding instructions and others don't have any such problems at all.

We are starting a new project to investigate how these changes in thinking or cognition affect patients' abilities to make decisions. We will use concepts developed by behavioural economists and apply them to HD patients. Behavioural economics blends a psychological understanding of human behaviour with mathematical explanations about how we make choices. It is helpful to share knowledge with another field because decision-making can be a complex process. For example, sometimes we go to the shop and know immediately what we want to buy and other times we walk up and down the aisles aimlessly unable to decide. Why is this? Behavioural economics will help us to understand the components of decision-making and to try and figure out where in the decision-making process HD patients are having problems. We hope that understanding this will help us to predict potentially bad decision-making and manage it as HD progresses.

Kate Harris – Dopamine's role in Huntington's Disease

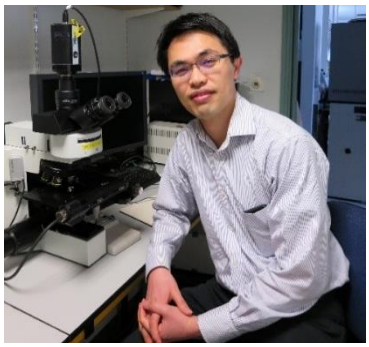
I am investigating the role that the brain chemical dopamine plays in Huntington's disease (HD)and this chemical is known to control movement and thinking as well as motivation.

In HD its known that there are early changes in the levels of dopamine. We recently conducted a study to see whether dopamine reducing medication (e.g. Olanzapine and Tetrabenazine), which are commonly used in HD to treat motor symptoms, influenced cognitive performance. We found surprisingly that a one-off dose of a dopamine blocking drug improved short-term memory which implies that reducing dopamine could also be beneficial in treating cognitive problems in HD. I am now using the Enroll HD sample (that Laura talked about earlier) to assess how long-term use of such medications may influence cognitive abilities.

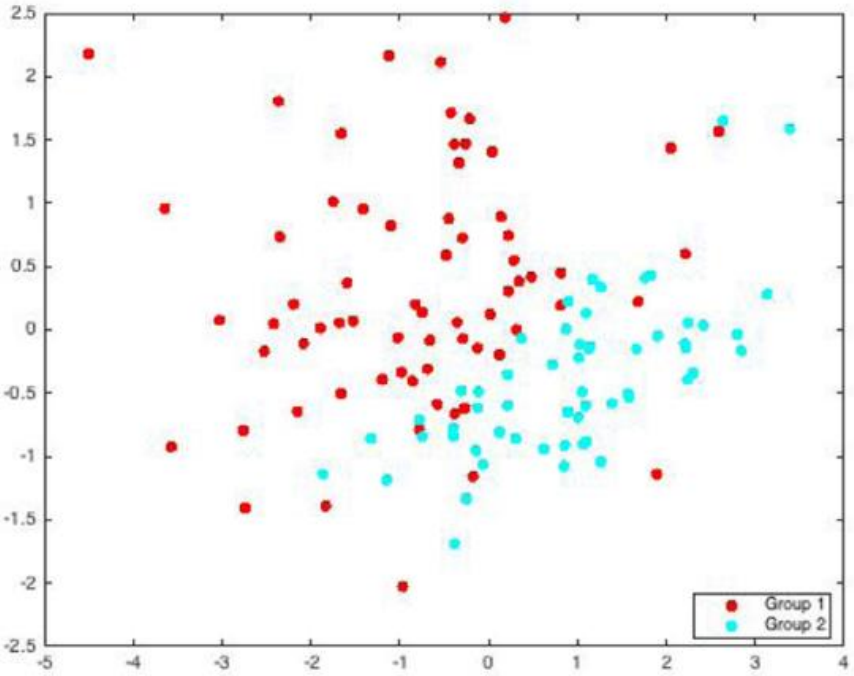
To complement this, I am conducting laboratory studies to assess how altering levels of dopamine effects the health of cells in brain areas which are important for cognition (for example, the hippocampus). I am looking to see whether decreasing dopamine protects these cells and restores their function.

This research will help us to understand how we can best use medications that act on the dopamine system.

William Kuan – From banking to the Brain Repair Centre



About two years ago we had a talented MPhil student with a degree in mathematics working with us. He was bored of working in the banking industry and wanted to try something "different" and "meaningful" to life. So, we gave him a full set of a clinical dataset released from Enroll-HD, (a massive spreadsheet containing 1459 columns and 223 rows) and we asked him to "play" with it. By the end of his MPhil, he came up with an equation clearly separating the "premanifest" HD into two subgroups (As shown in image). He also demonstrated that one group was cognitively less impaired than the other at a premanifest stage. We then tested his equation in our independent, in-house dataset that has longitudinally tracked individual patients for many years and showed that the cognitively less impaired group also experienced slower disease progression after developing manifest disease. Since then we have managed to obtain the relevant patient DNA samples from Enroll-HD; with the aim of identifying the underlying genetic modifier(s) separating the two groups. We are now in the process of doing this as it will help us understand the disease mechanisms further and why patients with HD behave differently over time with respect to their clinical problems. This work may also open up new avenues of therapeutic intervention.



Shaline Fazal – Mutant Huntingtin in the Brain

I am new to the group, having only started in November. My research will be focused on looking at how mutant huntingtin may cause disease and in particular the role of the immune system in this. In particular, I want to determine what the role of immune cells is in spreading the mutant protein from one cell to another. To investigate this question, I will use cells grown in the lab with the intention of performing similar studies in a commonly used Huntington's disease animal. These research questions will hopefully provide further insight into the mechanisms of how mutant huntingtin could spread around different brain regions and therefore provide more insight into how the disease could be better treated.

Lindsey Wilkin – HD Clinic Administrator

I am the clinical administrator for the Huntington's Disease clinic. I am your main contact regarding appointments for the clinic. My contact details are: Lw518@cam.ac.uk or 01223 761863. I only work part time (Monday, Thursday and Friday) but please feel free to email me or leave a message and I will get back to you on my return to the office.

Webpages of interest

Facebook page: The Barker Lab

Twitter page: @Thebarkerlablab

Our Webpage: http://thebarkerlab.co.uk/

HD Buzz: https://en.hdbuzz.net/

Huntington's Disease Association Webpage: https://www.hda.org.uk/

Huntington's Disease Youth Organization Webpage: https://en.hdyo.org/

Stats

- Throughout 2017 we had 504 appointments for our Huntington's Disease clinic.

Donations

If you would like to donate to any of our research projects, then please do contact us on 01223 331160 or send any donations (payable to the University of Cambridge to):

Prof Roger A Barker, Cambridge Centre for Brain Repair,

E.D. Adrian Building, Forvie Site, Robinson Way,

Cambridge, CB2 0PY.

Papers from 2017 regarding Huntington's Disease

- Formation of hippocampal mHTT aggregates leads to impaired spatial memory, hippocampal activation and adult neurogenesis

- REST suppression mediates neural conversion of adult human fibroblasts via microRNA-dependent and independent pathways

- Defective Sphingosine-1-phosphate metabolism is a druggable target in Huntington's disease

- Direct Neuronal Reprogramming for Disease Modelling Studies Using Patient- Derived Neurons: What Have We Learned?

- An open-label study to assess the feasibility and tolerability of rilmenidine for the treatment of Huntington's disease.

- Identification of genetic variants associated with Huntington's disease progression: a genome-wide association study

Thank you from the Roger Barker Group