tuition, when necessary, in a way that benefits the whole group. One of the ways to do this is to find a few people within the group who are more advanced and assign them to provide one-to-one support when needed. I think sustaining good leadership in any context relies on the ability to switch focus between micro and macro landscapes. If you get caught up in the micro, then the group will not work well and if you concentrate only on the macro, then you could fail to spot stragglers within the group, thereby making the team inefficient. Working with Chris has taught our leaders to be efficient at switching from micro to macro and back again.

Finally, our work with Chris has made us better at nurturing talent. Supporting someone with Down's syndrome has given us the confidence and the willingness to support more individuals who have different abilities. We are acutely aware of the importance of inclusion. Chris has helped us to build an inclusive and supportive organisational culture. In the long run, this ensures we have a resilient and happy workforce.

One-dimensional organisations are often less flexible when dealing with social change, thus reducing their organisational resilience.

Working with people with a learning disability requires extra time and resources, and achieving success with them has led Stopgap to discover how beneficial diversity can be in a professional environment and why it is so important. Working with Chris has allowed us to get a much sharper understanding of leadership, management and collaboration and create a healthy organisational culture. Chris has helped to make Stopgap approachable and open to a wider cross section of our society.

Photo by Chris Parkes

---

The Battle to Defeat Dementia in Down's Syndrome

Liam Wilson PhD Student, Cambridge Intellectual and Developmental Disabilities Research Group, Department of Psychiatry, University of Cambridge.

It is important to note that not everyone with Down's syndrome will develop Alzheimer's disease, but those that do are at risk of developing it earlier in life than typically developing people.

The ultimate goal of the Dementia in Down's syndrome research group is to inform a clinical trial that aims to prevent people with Down's syndrome from developing Alzheimer's disease. None of this important work would be possible without the help of our enthusiastic volunteers with Down's syndrome and all the people who support them. To find out more about how we are achieving our goals in collaboration with our volunteers, you can watch our film ‘Together’ on YouTube at https://www.youtube.com/watch?v=pB7iqWUXQIM.

Over the last 20 years, the Cambridge Intellectual and Developmental Disabilities Research Group (CIDDGRG), led by Professor Tony Holland, has been working to gain a detailed understanding of the factors that affect the lives of people with intellectual disabilities. For much of this time, the group has held a special interest in investigating why and how people with Down's syndrome develop dementia, which has now developed into an extensive program of research called the Dementia in Down's Syndrome Project.

Dementia comes in many forms, and typically affects older people over the age of 65. Alzheimer's disease is the most common type of dementia and the first symptoms to appear are often subtle memory problems, such as forgetting words, names, and recently made appointments. At its worst stage, Alzheimer's disease can cause people to forget even those who are closest to them.

We know that the people with Down's syndrome that do develop Alzheimer's disease, are at risk of doing so earlier in life than typically developing people. Scientists believe that this is because of a gene on chromosome 21 called APP, which makes the Amyloid Precursor Protein. In the brains of people with Alzheimer's disease, the Amyloid Precursor Protein is cut up into small pieces called beta-Amyloid (or A-beta, for short), which sticks together to form amyloid plaques between the brain's cells (or neurons). Although there is still a lot of uncertainty around the exact role that A-beta plays in Alzheimer's disease, it has come to rest at the centre of a very prevalent theory of how the disease develops, known as the amyloid cascade hypothesis. This theory proposes that the build-up of A-beta is one of the first events in Alzheimer's disease, and triggers a chain of events that eventually leads to the brain's neurons dying.
In 2009, the research at CIDDRG took a hi-tech turn to investigate how the build-up of amyloid is related to changes in brain structure and function in people with Down’s syndrome. This shift in focus was made possible thanks to the development of the PiB-PET brain scan – a method for imaging the brain which, when combined with images from a Magnetic Resonance Imaging (MRI) scan, gives detailed information about the location of A-beta plaques in the brain.

The first data that the Dementia in Down’s syndrome group collected using this technology were from a “pilot” study, involving 10 volunteers, which aimed to assess whether it was safe and feasible for people with Down’s syndrome to participate in this kind of research. The pilot study was a success, and resulted in the publication of an interesting research paper and a new, ambitious brain imaging project that aimed to scan the brains of many more volunteers with Down’s syndrome.

As part of this study, which was funded by the Medical Research Council (MRC), Tiina Annus (my fellow PhD student) and I visited more than 60 people with Down’s syndrome in their homes across the UK, and collected PiB-PET and MRI scans, in addition to detailed psychological test data and blood samples for biochemical analysis, from 47 volunteers. Combining the new data with that from the pilot study, we published a research paper in 2016 detailing how amyloid builds up in the brains of people with Down’s syndrome who are older than 40 years-of-age. We have also investigated how the brain’s structural and functional connections are affected by both Down’s syndrome and amyloid and we hope to publish papers on these exciting findings very soon.

Finally, at the very end of our project, PhD student Maddie Walpert helped Tiina and I to rescan the brains of 15 of the volunteers after three years, to see if we could detect changes occurring in the brain over time. This is an essential step in the scientific research process, enabling us to confirm (or perhaps refute) what we have found in our initial studies and learn more about the progression of Alzheimer’s disease in Down’s syndrome. A new project now underway at CIDDRG will invite more of the original participants back for rescans and we hope that this ‘longitudinal’ data will be highly informative.

As time goes on, the Dementia in Down’s syndrome group’s research continues to diversify, pursuing further lines of enquiry in the hope of finding an early sign that could help us predict whether someone with Down’s syndrome is going to develop Alzheimer’s disease in the future. Following on from Dr Alex Phillips’ research on how people with Down’s syndrome engage in exercise, CIDDRG PhD student Kate McAlister began looking at how the mitochondria work in people with Down’s syndrome and whether their function could be related to the development of Alzheimer’s disease. Mitochondria are the body’s ‘energy factories’ – tiny little structures found inside cells. To do this, Kate measured people’s ability to exercise using a treadmill test and then separately measured how people’s mitochondria recover their ability to produce energy after exercise by asking people to perform a weight lifting task in the MRI scanner.

PhD student Sally Jennings is using another kind of brain imaging called EEG, which records brain activity using a cap of electrodes that are very sensitive to changes in activity on the brain’s surface (the cortex). Using this technology, Sally is looking at how the brain’s responses to sounds and images change as people with Down’s syndrome get older. She is also looking at how these changes relate to the volunteers’ performance on psychological tests to see if certain changes in brain activity are related to changes in memory or other cognitive processes.

Finally, PhD student Maddie Walpert has been conducting a study that aims to determine whether changes in the retina might be related to the development of Alzheimer’s disease in people with Down’s syndrome. The retina is the layer of cells at the back of the eye that absorbs light to help us to see, and has often been called a ‘window to the brain’. Research has shown that the rate of thinning in the retina is much faster in people with Alzheimer’s disease. Using a very simple eye scan, like those performed at an optician’s, Maddie has measured the thickness of the retina in more than 50 people with Down’s syndrome, in the hope...
of whether changes in the retina with age can be used to detect early changes associated with Alzheimer's disease.

All of these projects are now nearing completion, and while it is still a little too early to make any firm conclusions about their findings, the results so far are extremely interesting, and we hope they will lead to more exciting research in the very near future.

In the meantime, the Dementia in Down’s syndrome group has started two new, related brain imaging studies, which are being co-ordinated by Dr. Concepcion Padilla, and are being funded by Alzheimer’s Research-UK and the USA National Institutes of Health (NIH). In these studies we will follow up more people from the original brain imaging study.

In addition to this, Concepcion will be looking for a further group of volunteers with Down’s syndrome, aged 25 and older, to participate in this collaborative project that the research group are running together with several groups in the United States. This comprehensive project aims to recruit 200 volunteers with Down’s syndrome (across all the sites in the United States and Cambridge) who are willing to have several brain scans, blood tests, and cognitive examinations over a period of four years. If you are interested in taking part in this research, you can contact Concepcion by email at cfp31@medschl.cam.ac.uk, or by calling her on 01223 746 127.

If you would like to receive regular updates about the research studies being conducted by the Dementia in Down’s syndrome group, you are welcome to sign up for our newsletter, which we issue twice each year. To join the mailing list, please provide us with your contact details and let us know if you would prefer an electronic or paper copy of the newsletter by emailing us at dh-admin@medschl.cam.ac.uk, or by calling our administrator Agnes Hctoer on 01223 746007.

The research carried out by the Livesey lab at the Gurdon Institute, a part of the University of Cambridge, is dedicated to understanding how the brain develops and how alterations in genetic information causes the initiation of diseases, particularly Alzheimer's disease and other dementias.

One of the genetic models we employ is Down’s syndrome, which is caused by having an extra copy of chromosome 21. Chromosome 21 contains hundreds of genes; however one that is particularly interesting when thinking about Down’s syndrome and Alzheimer’s disease is APP. The gene APP codes for a protein called Amyloid Precursor Protein or APP for short, which is normally chopped up into smaller fragments. Some of these fragments are what make up the “plaques” that are found in the brain of people with Alzheimer’s disease, the most common form of dementia.

Changes or mutations in the APP gene slightly alter the APP protein, and are one cause of an inherited, early onset form of Alzheimer’s disease. We know that people with Down’s syndrome are more prone to getting early onset Alzheimer’s disease. However, people with Down’s syndrome don’t have changes to the APP gene, but instead have an extra copy of APP, because of its location on chromosome 21. Because of this, brain cells with an extra APP gene have more APP protein and make more APP fragments. Research suggests having more APP protein may play a role in developing early onset Alzheimer’s disease. However, it is important to note that not everyone with Down’s syndrome will develop Alzheimer’s disease. So why do some people with an extra chromosome 21 develop Alzheimer’s disease, while others don’t?

Is having three copies of chromosome 21 and the APP gene sufficient to initiate Alzheimer’s disease in the brain cells of people with Down’s syndrome? Or are there other components that are required for Alzheimer’s disease to develop, like lifestyle, diet and general health? If we can dissect these questions, our findings will improve our understanding of the causes of Alzheimer’s disease in people with Down’s syndrome.

To help us answer these questions, our group developed methods to make human brain cells in our laboratory. This is possible because of the work of Dr Shinya Yamanaka (Japan) and Professor John B Gurdon (United Kingdom), the 2012 Nobel Prize laureates in Physiology/Medicine. By using special factors called the “Yamanaka factors”, we can convert skin cells (mature cells) into stem cells (immature cells). When given the correct cues, the immature stem cells have the ability to develop into all tissues of the body, for example the brain cells affected in Alzheimer’s disease.
The stem cells we generate are treated with the Livesey lab protocol to firstly form a sheet of tightly packed cells that gives rise to brain specific stem cells, which collect together like a “rosette”. These rosettes give rise to brain cells that populate the front of the brain known as the cortex. This part of the brain is important for our memory and cognitive skills and is especially affected in dementia. Through this process we can look at brain cells from individuals with and without Down’s syndrome and the effects of an additional copy of the APP gene. We have already shown that the brain cells derived from an individual with Down’s syndrome exhibits aspects of Alzheimer’s disease in a dish within a short period of time, in our case over a period of 90 days.

Can we conclude that the extra copy of APP alone is the true cause of early Alzheimer’s disease in brain cells from individuals with Down’s syndrome? There are many genes on chromosome 21, genes that can contribute to the initiation of Alzheimer’s disease and genes that may be protective. To expand on our previous findings, we have teamed up with Professor Tony Holland, a group leader at Cambridge Intellectual and Development Disabilities Research Group (CIDDRG) at the University of Cambridge. This long-term collaboration helps to study the links between Alzheimer’s disease and Down’s syndrome. Our lab is currently making brain cells from individuals that the Holland group see regularly for check ups. Do we observe differences in the brain cells we grow in the lab? Could that explain what is observed clinically? This can tell us about the contribution of the environment and lifestyle, factors other than the genetic information of our cells.

This new method of studying brain cells, gives us the opportunity to use many techniques that cannot be used in a person. Importantly, by making brain cells of a given individual, we can directly test how relevant our findings are for a real person. This is a major advantage of studying human diseases using stem cells to generate brain cells.

We are grateful for the support we receive from the Wellcome Trust, Alzheimer’s Research UK, the Alborada Trust, Stem BANCC, the Gurdon Institute (our home) and the University of Cambridge as a whole. We are thankful to all individuals that have volunteered to be part of our study; none of this would be possible without you.