KEY GRANT TARGETS DYSKINESIA PUZZLE

The Parkinson’s Disease Foundation recently announced $1 million in funding for 14 global research projects designed to improve the lives and futures of people touched by Parkinson’s disease. Bagadilico’s Tomas Björklund is one of the recipients, receiving a grant of $165,000 over two years. Tomas will now start looking for a solution to dyskinesia, a common side effect of the gold-standard medication for Parkinson’s disease.

Using his PDF International Research Grant, he will study how particular brain cells may become overly active, leading to dyskinesia. Based upon his results, he will identify targets for treating dyskinesia in people with Parkinson’s disease.

- There is suspicion that brain cells called cholinergic interneurons are involved levodopa-induced dyskinesia (LID). Our research aims to better understand how these cells contribute to LID. We will work with rats with PD-like symptoms that are receiving levodopa treatment. We will observe what happens when we first activate and then quiet cholinergic interneurons. In this way, we can find out whether signaling these cells really worsens LID, as we hypothesize, explains Tomas Björklund.

- In another set of experiments, we will compare the actual cholinergic interneurons from the brains of rats with and without LID, looking at which genes are turned on and off in the cells. These experiments may provide clues as to which genes scientists should target to treat LID in people. Thus, this project is expected to provide new insights into the role of cholinergic interneurons in LID and suggest new targets for therapy to control this debilitating side effect, concludes Tomas Björklund.

PDF President Robin Anthony Elliott noted, “By supporting these 14 talented scientists, PDF is ensuring that a special few daring ideas will not be left on a laboratory bookshelf. Instead, they will be explored for their potential to improve the lives and futures of the people who live with Parkinson’s – the focus of our mission, our passion and our purpose.

NEWS IN BRIEF

MONEY AWARDED TO TWO ‘CREATIVE RESEARCH ENVIRONMENTS’ FOCUSED ON PD

LU’s Medical faculty’s recently awarded funds to stimulate and support translational research through increased integration of basic research, clinical research and health sciences research. A handful of ‘Creative Research Environments’ (CRE’s) will now be established in an effort to stimulate cooperation across traditional boundaries and to give measurable advantages to incoming researchers in the form of actual results, publications, grants and not least implementation of results. Small scale and creativity are the tenets of the concept and a creative environment should consist of 4-6 researchers, gathered around an issue or a specific research problem.

Two of the new CRE’s have a clear focus on Parkinson’s disease. One is entitled “Parkinson’s Disease Stem Cell Therapy” and is spearheaded by Malin Parmar. This research project will attempt to establish a translational cell therapy platform for PD. The research team will address pre-clinical, clinical and ethical issues related to the different stages of translation using renewable and novel cell sources for cell replacement therapy.

The other PD related CRE is called “Lumping and splitting cognitive and psychiatric deficits in Parkinson’s disease”. Read more about it in a feature article in this newsletter.

YOUNG INVESTIGATOR TALK HELD ON HIPPOCAMPAL NEUROGENESIS

On May 23rd Bagadilico arranged a Young Investigator Talk on adult-born hippocampal neurons following epileptic seizures and inflammation. PhD student Depti Chugh explained that animal studies have shown that neurogenesis increases dramatically following several neurological diseases, including epileptic seizures. The talk centered around the potential positives and negatives that may come from new neurons being born into the hyperexcitable environment that follows a seizure.

Keep an eye out for the next ‘Young Investigator Talk’. As of yet, no new date has been set.

NEW MOUSE MODEL TRACKS ALPHA-SYNUCLEIN AGGREGATION IN VIVO

Strong evidence has suggested that the aggregation of alpha-synuclein contributes to the pathogenesis of Parkinson’s disease. In this study, Jia-Yi Li and colleagues describe a novel transgenic mouse model, in which they express wild-type human a-syn fused to green fluorescent protein (GFP). The model allowed researchers to observe, in real-time, the spreading of a-syn in multiple brain regions. With increasing age, the mice exhibited reductions in motor skills and the ability to smell.

The discovery illustrates, for the first time, that we can now use mouse models to track a-syn aggregation in vivo. This novel model manages to mimic a unique set of aspects of PD progression combined with the possibility of tracking a-syn aggregation in the neocortex of living mice. Therefore, this a-syn-GFP-mouse model can provide a powerful tool that will facilitate the study of a-syn biology and its involvement in PD pathogenesis.
“Think outside the box”. Over the past decade, this worn-out expression has served as a cop-out blanket statement describing any ambition to be remotely original or innovative. Even though the catch phrase of the IT-revolution appears in the application for a new project on cognitive deficits in PD, initiator Hannah Lindgren insists that it's not just linguistic cosmetics. Giving weight to her argument is a broad interdisciplinary palette of co-applicants, stretching far beyond Lund's traditional PD research community. This, of course, also represents an unprecedented challenge for Hanna, who will have her work cut out for her in trying to tie together a truly kaleidoscopic group of researchers. The end game? To at long last bring Lund's PD research on cognitive and psychiatric symptoms to the next level.

This ‘Creative Research Environment’, funded by the Medical faculty, follows a pendulum shift that's been going on in the global PD research community in recent years. As it's becoming evident that cognitive symptoms in many ways poses a heavier burden for patients than the characteristic motor symptoms, researchers quite simply have to follow suit. It is hardly surprising that the movement problems have gotten a head start, research-wise. These symptoms are clearly visible to the naked eye and they are, most likely, less complex to understand from a neurobiological standpoint.

- The underlying pathologies creating the cognitive and psychiatric symptoms are simply more heterogeneous. We are dealing here with a number of interlinked neurotransmitter systems that seem to be involved in creating these problems. Also, the alpha-synuclein pathology that leads to the spread of lewy-bodies is of key interest in Parkinson’s related dementia. What we now need to do is try to understand how these processes are tied to each other and for this we need new preclinical models. That’s partly what we will try to develop in this new research environment.

The project, initially spanning over three years, takes a bold aim in its effort to bridge gaps between fractions of researchers not accustomed to working together. Especially interesting is the inclusion of in-depth expertise from the area of major depression and neurocognitive function, both from a preclinical and a clinical point of view. Years and years of experience in this field of research will now be applied to the parkinsonian brain, by way of Anders Tingström’s and Mikael Johansson’s groups.

Is it perhaps possible that some general mechanisms involved in depression and cognitive decline in other disorders also apply to PD? Bringing in fresh eyes is expected to spark new ideas that don’t necessarily follow traditional trains of thought in the PD research community. Long term, the hope is that unconventional approaches may help establish new research lines that can shed light on the underlying processes that lead to cognitive decline.

New therapies are in desperate need. The few treatments that ex-
Hanna Lindgren, who recently arrived back from a two-year post-doc stint in Wales, is a natural fit to take leadership on this venture. From the rain-plagued moorlands on the Irish Sea she brings with her new skills in pre-clinical modeling for cognition in PD.

- I now have the ability to test different aspects of cognition in PD in rodents and that knowledge simply wasn’t here in Lund before. To that, I also brought a lot of new equipment that can help us understand more about cognitive decline. It seems like all the pieces of the puzzle are now here. The timing is right, says Hanna.

Assembling that puzzle, however, is a time- and money-consuming journey. And Hanna knows it.

- Of course it’s a massive undertaking. We don’t kid ourselves about that. But it’s time that we start to focus also on this very important area of PD. Not least for the patients. There’s been a major focus on dopamine in the broader PD research community, and in Lund as well. And that’s all good, but we have pretty decent medication for the motor-symptoms today, while on the cognitive side we have virtually nothing.

Now we have the basic infrastructure to get this going and since it’s a long journey, it’s about time that we set off on it.

The cognitive impairments in PD affect a wide variety of functions that have substantial impact on the quality of life for patients. For example, patients may suffer from depression, working memory deficits, disturbances in executive functions and the general processing of information. These are symptoms that are hard to diagnose but may severely affect work life and close relationships, aspects of everyday life that are likely to be just as important for patients as the troubling motor symptoms.

An essential part of the project will be the development of rodent models for cognitive training and enriched environment. This has previously, in other neurological disorders, shown to promote higher levels of neurotrophic factors resulting in plasticity boosting effects. The researchers now hope to pinpoint areas in the parkinsonian brain that may be receptive to this treatment. These are, to a large extent, unchartered waters in Parkinson’s research. If successful, it could lead to new, non-invasive treatments that may halt cognitive decline in PD patients.

- This part of the mission is closely tied to the work that will be carried out by our clinical node. They will try to better identify the neuropsychiatric symptoms in patients through improved rating scales. Per Odin and Catharina Sjödahl Hammarlund will be very influential here, says Hanna.

Taking the helm of this project, Hanna believes, will help tie her own research closer to the everyday lives of patients. She admits, being a pre-clinical scientist, that it’s easy to get caught up in the “lab bubble”, where you sometimes lose track of the bigger picture. It’s important, she tells me, to be reminded of that it’s ultimately the patients that should inform what research goals we set up.

- For me it’s always been the excitement that comes from understanding things, how things work inside the brain, that has driven my ambition as a scientist. That’s always been number one. But as I get older it seems that the better of the patients is becoming more central to how I identify with being a scientist. This research environment is a great opportunity to put these translational ambitions into practice.

Welsh Connection. The skill-set Hanna acquired during her post-doc in Wales is of key importance for the establishment of the new creative research environment.

**RESEARCH TEAM**

- Hanna Lindgren
- Angela Cenci Nilsson
- Per Odin
- Catharina Sjödahl Hammarlund
- Anders Tingström
- Mikael Johansson
Veronica Francardo’s thesis attracted attention long before it hit the shelves a few weeks ago. A study included in the dissertation, published in late 2010, has been making waves in the Parkinson’s research community. The key finding targets the regulation of a neural pathway that could help ease the troubling side effects caused by L-DOPA medication. The thesis packs another couple of punches with exciting discoveries on neuro-protection that may lead to new therapies in the coming years.

Veronica is relieved to finally see the light at the end of the tunnel.

- Well yes, it’s been hard. It was a bit stressful to finish the last project in time but I made it and now I’m very happy, and proud of course.

Delving into the mysteries of the brain was never a given for young Veronica, growing up in the seaside town of Trieste, Italy. Friends and family had no real interest in medicine, certainly no professional training in the field. What once sparked her interest eludes her, there seems to be no one given moment, but the fascination for the body and mind was always there, she remembers.

- It’s a curious thing really. I’ve always been very interested in the brain in particular and diseases in general. I guess it is something of an instinct. Later on it put me on the path to start an education in biotechnology, which then led me to neuroscience.

It is hardly a surprise that the headline-grabbing study that kicks off the thesis is about L-DOPA induced dyskinesia (LID). Working under Angela Cenci-Nilsson, a European authority on the subject, Veronica had a unique opportunity to develop mouse models tailored for her specific experiments.

She already knew that a specific molecular pathway (Ras-ERK) was involved in the development of LID. The problem is that this pathway also plays numerous key roles in cellular processes, including cell survival. Now, the challenge was to find a safe way to shut down the “negative” signaling while keeping other important channels of communication intact. And they found one, Ras-GRF1, a specific activator of the signals involved in LID. Both in mouse and monkey models of Parkinson’s disease, the turning off of Ras-GRF1 resulted in a significant reduction of dyskinesia. Studies to bring these findings closer to clinical implementation are already underway.

In another key study Veronica examines the modulation...
of that very same molecular pathway (RasERK), this time focusing on its role in neuroprotection. Through gene therapy delivery of GDNF in a PD mouse model, Veronica and her colleagues showed that nigrostriatal restoration induced by this neurotrophin is associated with a prolonged activation of RasERK pathway both in dopaminergic neurons and neurites.

- Here we looked at the other side of the coin, proving examples where the activation of this important pathway is a beneficial plastic response to neuroprotective/neurorestorative interventions. GDNF is regarded as the most potent neurotrophic factor for nigrostriatal dopamine neurons and the closest to clinical application. Investigations of molecular mechanisms underlying the neuroprotective effects of this neurotrophin in vivo are of crucial importance to improve the potential of GDNF gene therapy in the treatment of PD.

The thesis closes with a discovery that may see its clinical application in the not too distant future. Here, focus lies on battling the characteristic motor symptoms of PD. What puts this discovery on a potential fast-track to the clinic is that the examined compound, a Sigma-1 receptor agonist, is already tried, tested and used as a pharmacotherapy for other disorders, such as schizophrenia and depression.

Once again, we are dealing with an attempt to stimulate the brain’s own capacity to boost plasticity and restore functions of damaged nerve cells. Through her experiments in PD mouse models Veronica was able to observe motor improvements and partial neuroprotection in five weeks-treated animals. Despite its wide therapeutic implementation in other diseases, Sigma-1 receptor agonists have never before been tested in animal models of PD. The discovery, strengthened by the proven clinical viability of the substance, clearly holds some future promise for Parkinson patients.

Veronica will now stay on for another year under the tutelage of Angela Cenci Nils-son. Beyond that point, she has no idea where the unpredictable world of scientific employment may lead her. It’s safe to say, however, that a summer visit to her native hometown at the northernmost tip of the Adriatic Sea is well deserved.
Bagadillico researchers at Lund University have succeeded in preventing very early symptoms of Huntington’s disease, depression and anxiety, by deactivating the mutated huntingtin protein in the brains of mice.

“We are the first to show that it is possible to prevent the depression symptoms of Huntington’s disease by deactivating the diseased protein in nerve cell populations in the hypothalamus in the brain. This is hugely exciting and bears out our previous hypotheses”, explains Åsa Petersén, Associate Professor of Neuroscience at Lund University.

**Huntington’s is** a debilitating disease for which there is still neither cure nor sufficient treatment. The dance-like movements that characterise the disease have long been the focus for researchers, but the emotional problems affect the patient earlier than the motor symptoms. These are now believed to stem from a different part of the brain – the small emotional centre called the hypothalamus.

“As now that we have been able to show in animal experiments that depression and anxiety occur very early in Huntington’s disease, we want to identify more specifically which nerve cells in the hypothalamus are critical in the development of these symptoms. In the long run, this gives us better opportunities to develop more accurate treatments that can attack the mutated huntingtin where it does the most damage”, says Åsa Petersén.

**As the role of** the hypothalamus in Huntington’s disease is gradually mapped, knowledge might be gained from drug research for other psychiatric diseases. It is likely that similar mechanisms control different types of depression, according to Åsa Petersén.

**Publication:**

“Hypothalamic expression of mutant huntingtin contributes to the development of depressive-like behavior in the BAC transgenic mouse model of Huntington’s disease”

Journal of Human Molecular Genetics

Sofia Hult Lundh, Nathalie Nilsson, Rana Soylu, Deniz Kirik and Åsa Petersén
Jan Lexell, with an impressive track record in rehabilitation for stroke, gave concrete examples of different physical training initiatives for Parkinson’s disease and how these efforts could be streamlined for better effects across the board for patients. A recurring position during the night, reiterated also by Professor Lexell, was how neglected research on rehabilitation have long been in Parkinson’s disease. However, he seemed to be able to discern trends in a positive direction, but stressed that a coordinated effort from the research community was still necessary.

We still do not know today exactly how the Parkinson brain’s plasticity is affected by physical exercise. What is known is that exercise generally affects the formation of new blood vessels and brain cells. Jan Lexell emphasized that we now need to understand how the parts of the brain affected by Parkinson’s disease is influenced by physical exercise, pointing out that the goal is ultimately to be able to customize the right kind of exercise appropriate for each individual patient.

The next speaker, Tomas Dei-erborg, has just teamed up with Jan Lexell on a project where they are looking at mouse models of Parkinson’s, trying to understand how the disease relates to various physical activities. The broader scientific community has already proven that with physical activity the number of connections between nerve cells and the level of communication between them is increased.

Tomas could reveal, through experiments, that both memory and learning ability was positively affected in the mice that were allowed to participate in different training situations and lived in enriched environments. Jan’s and Tomas’ research is still in its infancy and the two hope to learn a lot more about the impact of physical exercise for Parkinson’s patients by studying the mice in more advanced experiments.

The final speaker of the night, Christer Nilsson, talked about the relationship between the brain’s cognitive ability and movement disorders. Christer, an expert in cognitive medicine, underlined that thinking capacity can be significantly affected in Parkinson’s disease, but that this is manifested very differently from one patient to another. Therefore, Parkinson patients need to meet with several specialists, both in the phase of diagnosis and while being treated. Different aspects of memory, attention, executive functions and emotions must not be ignored and can be treated.

As Parkinson’s research progresses it is becoming more and more unequivocal that we are dealing with a multifaceted disease. If we can better understand how the death of nerve cells in this disorder affects communication pathways involved in cognitive functions, new opportunities to develop both general and targeted therapies might arise. Some of these treatments will be in the form of physical and mental training, hopefully improving quality of life for patients.