New post-doc att TNU wants to boost neuroscience in Pakistan

Ummar Sajjad, born and raised in Lahore, Pakistan, has recently started his postdoctoral fellowship at the Translational Neuroendocrine Unit (TNU), led by Dr. Åsa Petersén. After receiving his PhD in England he is now hoping to gather knowledge and build networks before his desired return to Pakistan where he wants to develop the country's neuroscience research infrastructure.

What will your role be in the research group?
- My role is to study the relationship between striatal dysfunction and non-motor signs and symptoms such as anxiety, depressive-like behavior and metabolic changes in Huntington’s disease. I will also be working in collaboration with other members of TNU and B.R.A.I.N.S. to set up new assays to quantify endogenous proteins, neurotrophic factors and metabolic markers.

What are your aspirations as a researcher?
- I would like to establish my own neuroscience research group in Pakistan in the future. I believe working as a part of TNU would allow me to attain essential skills that are necessary to excel independent research. It is also an opportunity for me to meet and network with prestigious neuroscientists from across the globe. I believe this will enable me to share ideas and initiate future scientific collaborations that are necessary for scientific contribution.

What is so interesting about working on Huntington's disease?
- I am interested in protein misfolding and its implication on human health. Huntington’s disease serves as a good model system to study protein misfolding. In addition to this, HD is a devastating disorder that affects both patients and their families. Lack of therapeutic options also motivates me to study HD and explore new avenues towards treatment.

NEWS IN BRIEF

SEMINAR ON LIVED EXPERIENCE AND BIOLOGICAL CAUSALITY

Bagadilico, together with the Faculty of Humanities, host a seminar on May 9th titled: ‘Degenerative Brain Disorders – Between Lived Experience and Biological Causality’

Developments in science enable us to predict, detect and visualize both normal and pathological processes in the body. This development has caught the attention of a wide range of scientific disciplines, making it an interdisciplinary area of attention. The seminar will address this development from both a medical and cultural perspective.

If you plan to attend, please register with Niclas Hagen; Niclas.Hagen@kultur.lu.se

BAGADILICO HOSTS EVENING ON HUNTINGTON’S

On Wednesday, May 25th, Bagadilico will host an evening on the hereditary and incurable brain disorder Huntington’s disease. The evening is based on the acclaimed, newly released book: “We were supposed to grow old together”. The book is a personal account of what it’s like to live under the threat of a dreaded disease and the dilemmas posed by modern genetic engineering.

PROGRAM

Moderator: Cecilia Lundberg, professor and coordinator of Bagadilico
6:00 to 6:40: Petra Lilja Andersson, professor, nurse and author, talks about and reads from her book “We were supposed to grow old together”.
18:40 to 19:10: Åsa Petersén, associate professor and physician, talks about the disease and ongoing research in the HD field.
19:10 to 19:40: Jan Wahlström, professor emeritus and physician, will discuss the ethical aspects of genetic testing.
19:40 to 20:00: Coffee and sandwiches are served.
20:00 to 20:45: Panel discussion and Q & A session.
Register with Jens Persson by the 15th of May; Jens.Persson@med.lu.se

BAGADILICO LAUNCHES INTRANET SOLUTION

In the coming weeks Bagadilico’s new intranet will be launched. We will be using Microsoft’s web platform SharePoint, the most popular intranet solution for organizations and companies worldwide. In a broad research environment such as Bagadilico, with over a hundred scientists from various disciplines, it will help us bring research groups closer together. The physical and disciplinary distances between different groups can now be reduced to a few clicks with your mouse.

The benefits for Bagadilico will be manifold. It will give our research environment the transparency that many of you have asked for. Bagadilico’s SharePoint will be your one-stop shop for meeting protocols, announcements, events and project updates within the Work Packages.

More information will follow shortly
On April 11 the stage was once again set for the annual World Parkinson Day. Over 200 participants had gathered at the Lund University hospital to hear some of Bagadilico’s leading scientists present the latest developments in research and treatment. An alert audience listened as the Bagadilico five delivered news on cutting edge research from the BMC laboratories. The topics ranged from gene therapy to the future prevalence of Parkinson’s disease in Sweden.

“Hitchhiking” on Nature - The Future of Gene Therapy

Cecilia Lundberg, Bagadilico’s Coordinator, educated visitor’s in the novel art of gene therapy, a research area that until recently was dubbed fiction by skeptical peers in the neuroscience community. The idea is to deliver new genes to correct defective genes responsible for disease development. Delivering the genes to the right place is a major challenge on its own. With the help of viral vectors gene therapy uses nature’s own viruses to “hitchhike” to the target cell where the therapeutic genes are released. Today we have at least five ongoing clinical studies for Parkinson’s disease. The biggest positives from these trials are that no serious side effects have been detected. When it comes to true therapeutic effects the field is still young but small, yet significant, improvements have been seen in some of these clinical trials.

Blocking Glutamate - A Key Towards Battling Dyskinesia

Angela Cenci-Nilsson revealed her latest research findings connected to the overactivation of glutamate systems in PD. The dopamine in our brains fine-tunes the signal strength of important neural circuits, especially in cortico-basal ganglionic circuits where glutamate and GABA are used as the main neurotransmitters. The loss of dopamine in Parkinson’s disease therefore creates an imbalance between these different signal systems and treatment with L-DOPA provides additional changes. We know today that a dysregulated glutamate transmission contributes to the development of both parkinsonism and dyskinesias. Angela Cenci Nilsson talked about the negative effects produced by excessive glutamate transmission on striatal neurons, and explained how blocking a certain glutamate receptor, namely ‘mGluR5’, could prevent these negative effects and improve the dyskinesias resulting from L-DOPA medication. Several clinical trials are now ongoing to evaluate the effects of mGluR5 antagonists in L-DOPA treated PD-patients. Two phase-2 trials have already reported significant positive results.
Anders Björklund spoke about a new exciting drug, Eltroprazine, that has now reached clinical trials in Lund and Stockholm. The drug aims at controlling the irregular release of dopamine from neuronal serotonin cells. These cells inherit the role of L-Dopa induced dopamine-producer from dopamine neurons when they loose this function as the disease progresses. The serotonin cells, however, can’t self regulate and therefore release excessive amounts of dopamine resulting in dyskinesia, the uncontrolled movements that are a common side effect of L-Dopa medication. The Eltroprazine drug will hopefully be able to regulate these cells and help them become reliable producers of dopamine. The goal is to utilize the inherent dopamine producing functions in serotonin cells so that they can be part of the solution instead of the problem.

What Do We Really Know? - The Puzzle of Parkinson’s

Professor and clinician Håkan Widner raised a very basic question; What do we not know about Parkinson? He talked about the different variations of Parkinson and Parkinsonism, painting a broader picture of the complex disease(s). For example, he pointed out the fact that the same genetic mutations can give very different symptoms depending on the individual carrying them. He concluded that today we don’t have a satisfactory model explaining the origin and the development of Parkinson’s disease.

Håkan also brought up the fact that the total number of Parkinson patients in Sweden is difficult to assess. Today it is believed that there are circa 2250 new cases every year and that the total number today of patients with actual Parkinson’s disease is about 25 000. How the Parkinson prevalence will look in the future is also difficult to predict. However, it is believed that a higher life expectancy in the general population will increase the number of cases in the coming years.

The Root of PD? - Cell-To-Cell Transfer of Alpha-Synuclein

Patrik Brundin took the audience on a journey that began with the earliest stages of Parkinson’s disease. He is currently working under the hypothesis that the disease progress can be explained by the slow spreading of misfolded alpha-synuclein throughout the brain, with the sick protein moving from cell to cell. One theory suggests that this process begins in areas of the brain that affect smell, sleep and bowel movement. Lewy bodies, the clumps of misfolded protein that eventually kill the neuron, are often found in the specific brain regions that control these functions. Professor Brundin’s research group is now focused on finding ways to stop the cell-to-cell transfer of alpha-synuclein, with the long-term goal of developing therapies that can halt Parkinson’s disease at an early stage.
Huntington’s disease has long been strongly linked to the involuntary writhing movements that help set the diagnosis for the disease. Now, Bagadilico researchers have shown that the body’s metabolism can also be seriously affected. A fresh study in the April issue of Cell Metabolism proves that the mutant huntingtin protein that causes the degeneration of motor neurons is also responsible for imbalances in the hypothalamus, causing severe changes in appetite control.

Together with research leader Åsa Petersen, post-docs Sofia Hult and Rana Soylu have been an integral part of the study that has been grabbing headlines in Swedish media lately. The research performed in the TNU laboratory at BMC shows significant changes in the brain’s hormonal control centre, the hypothalamus. In a series of experiments on mice, which had the mutated Huntington’s protein injected into this area of their brains, the animals soon demonstrated a reduced ability to regulate their metabolism.

I talked to Rana Soylu and Sofia Hult about why they have chosen to dedicate their research efforts to Huntington’s disease, what the scientific details of this study tells us and how they see their future research on hypothalamus imbalances affecting Huntington patients.

Why is Huntington’s disease such an interesting field of research?

- It’s a fatal disease that has a devastating effect on both patients as well as their relatives. Although the mutation causing the disease was discovered in 1993 there is still no cure. The fact that it is a monogenic disease where the gene mutation is known makes it easier to study since there are good and reliable animal models. This increases the potential to find a cure or find ways to delay the disease within a near future. It is also interesting since it may serve as a model disease for several other neurodegenerative diseases.

Your research on HD is related to non-motor symptoms connected to the hypothalamus. Why do you think this area of research is still relatively small in comparison to the HD research connected to motor symptoms?

- The clinical diagnosis of HD is set when the affected person shows overt motor symptoms. These involuntary movements have long characterized the disease and this is why many researchers focus on these symptoms. Non-motor symptoms and signs have not gained much attention until the last years. It has now been shown that these non-
motor symptoms often start many years before the onset of motor symptoms. We think that this area of research is going to expand in the near future since it has been shown that many patients suffer more from these disturbances than the motor symptoms.

**From a popular science perspective, what are the main findings in your recent study?**

- We found that there is a causal relationship between the expression of the disease-causing protein huntingtin in the hypothalamus and metabolic disturbances. This shows that not only the basal ganglia are affected in HD, but that there are also major changes in the center for hormones and metabolism in the brain.

**What characterizes the symptoms of the metabolic changes that are described in the study?**

- Different animal models of HD show metabolic disturbances either with increased or reduced body weight. Similarities appear to be increased food-intake and fat accumulation. The transgenic model used in this study, the BACHD mouse, displays increased food intake early on that leads to obesity with impaired glucose metabolism as well as pronounced leptin and insulin resistance. The new hypothalamic specific HD model that we have produced using viral vector delivery displays all these metabolic features, indicating that it is the effect of mutant huntingtin in the hypothalamus that drives this phenotype.

**What long-term future therapies could possibly be on the horizon following your latest research results?**

- Gene therapy focusing on the hypothalamus may be one possibility as well as the use of therapies that modify specific molecules in this area. Hopefully there will be synergy between the fields of obesity, diabetes and depression, where there is very active drug development going on targeting signaling pathways in the hypothalamus, with the HD research field.

**Will you now try to prove connections between the mutant protein and other non-motor symptoms, such as depression, anxiety and other symptoms that also may be early signs of the disease?**

- This is what we are interested in and are working on right now. We are also interested in finding a link between psychiatric and metabolic disturbances. It is possible that the underlying neuropathological mechanisms responsible for these non-motor symptoms share the same cellular pathways and may serve as therapeutic targets for several symptoms at the same time.