On Tuesday, March 13th, Bagadilico hosts yet another Parkinson’s Café. The idea behind our Parkinson Cafés is to promote the direct encounter between the patient and the researcher. The distance between the public and the scientific community is often too wide. We want to bridge this gap and take advantage of the knowledge and expertise within the Bagadilico environment.

The fifth Parkinson Café is visited by two clinical researchers that are in contact with patients on a daily basis, Oskar Hansson and Elisabet Londos.

Oskar Hansson’s research is focused on the development of biomarkers for early and safe diagnosis of Parkinson’s disease and other neurodegenerative disorders. This is of great importance in helping new therapies, designed to slow down disease progression, to become more effective. With more accurate diagnostic tools at their disposal clinicians will be able to identify Parkinson’s disease at a much earlier stage.

Elisabet Londos is an expert in Lewy Body Dementia, a disease in the borderland between Parkinson’s and Alzheimer’s disease. Patients of Lewy Body Dementia often experience stiff movements just as Parkinson’s patients, but no tremors. Many also have sleeping disorders characterized by hallucinations. Elisabet Londos will mainly discuss non-motor symptoms related to cognition, for example, sleeping disorders and Parkinson dementia.

Ample time is reserved for asking questions. Coffee and sandwiches will be served.

The place is Belfragesalen, BMC D15, Lund.

The time is March 13, 18 - 20.30.

If you wish to attend, please register by e-mail to Jens.Persson@med.lu.se (tel: 046-222 0876)

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**News in Brief**

**Lund Signs Contract for New MRI Equipment**

Lund University has now signed a contract for MRI equipment for the Lund Bioimaging Centre. The scanner will be the only one of its kind in Sweden and with its seven tesla strength, the brain and its diseases can be studied in very high resolution. Research groups are already queuing up to get access to the technology at the Lund University Bioimaging Centre, and with the new equipment we can expect to see continued high demand. This major infrastructure investment has been made possible through a collaboration between Lund, Umeå, Uppsala, Stockholm and Linköping universities and Region Skåne.

**Neuroscience Day - May 3rd**

Neuroscience Day in Lund is an annual event bringing together both researchers and research students in the Lund - Malmö - Copenhagen area in an effort to stimulate interaction in an informal setting. This year’s program features poster presentations by young investigators from the Lund/Malmö area and invited lectures by Benoni Edin, Marten Smidt and Torkel Klingberg.

Neuroscience Day concludes with the prestigious Segerfalk lecture, this year presented by Ann Graybiel. She studies the basal ganglia forebrain structures that are profoundly important for normal brain function but are also implicated in Parkinson’s disease, Huntington’s disease, obsessive-compulsive disorder, and addiction. Graybiel’s work is uncovering neural deficits related to these disorders, as well as the role the basal ganglia play in guiding normal behavior.

*Click here for more information*

**Scandmodis Annual Meeting - March 16-17**

Stockholm is host to the Scandinavian Meeting, which is now arranged for the 12th time. It is the biggest annual meeting on Parkinson’s disease in Scandinavia bringing together around 150 participants, mainly doctors and researchers.

This time focus will be placed on the genetics, pathophysiology, current and future treatment of Parkinson’s disease and tremor diagnostics. Furthermore a video quiz about the differential diagnosis and a number of pro-cons discussions of themes related to diagnosis and therapy of Parkinson’s disease will be arranged. 13 international and seven Scandinavian Movement Disorder experts will hold lectures. Bagadilico scientists presenting include Anders Björklund, Gesine Paul-Visse and Patrik Brundin.

**Andras Simon Seminar - March 9th**

On March 9th, 15.00, in Segerfalksalen, Bagadilico hosts Andras Simon’s seminar entitled “Reversible Suppression of Neurogenesis in the Adult Vertebrate Brain”. While functional regeneration is relatively limited in most mammals, non-mammalian vertebrates of certain species can rebuild complex structures. It is largely unknown how animals with outstanding regenerative capabilities sense what and how much is missing, and how they translate that information to the appropriate regenerative responses. These questions will be addressed in the March 9th seminar.
The end of 2012 will see the first cell transplants for Parkinson’s disease take place in over a decade. Researchers around the world will be carefully watching on as the fate of this research field may be hanging in the balance. The first years of the new millennium saw two disappointing American studies cast a long shadow over the entire field when many of the transplanted patients experienced serious side effects. In the wake of the failed U.S. trials it suddenly became a lot harder to motivate the pursuit of such an invasive therapy. Cell therapy for Parkinson’s disease appeared to have no future. But what if these trials were designed to fail? Could perhaps more rigorous preparations, a more careful selection of patients and ten years of further development in this research area justify a new large-scale study? Bagadilico’s Anders Björklund and Roger Barker from Cambridge University thought so. Together they initiated a Europe-wide study that revisits past trials in an effort to develop safer and more efficient methods for neural transplants in Parkinson’s disease. The end result may shape the direction of Parkinson research in the 21st century.

The make-or-break character of the EU-supported project is not lost on the researchers involved. Bagadilico’s Gesine Paul, part of the clinical team responsible for selecting patients in Lund, knows that a lot of hope and expectations are pinned on the study, recognizing that ‘we really have to get it right this time’.

- I believe Transeuro is going to be very important in deciding whether cell therapy for Parkinson’s is going to be a clinical treatment in the future, perhaps even deciding if it’s going to be further explored. Still, we have a lot to be excited about. The proof-of-principle we have seen is that some patients can be relieved of their symptoms and can even be taken off medication, so we know this treatment can actually work. The question we’re trying to address is – how do we select the patients that can benefit the most from this treatment and how can we make it work for more patients?

The ‘BIG’ Study

The designers of the Transeuro study are leaving no stone left unturned. All past cell therapy trials are being meticulously re-examined. Careful attention is given to tissue preparation and delivery. Different operation strategies are being evaluated. The process of selecting patients, with detailed attention to individual patient history, is more thorough than in any previous trial.

The comprehensive preparations surrounding the study also extend to screening for non-motor symptoms, for some of which there are no effec-
tive treatments today. Should the clinical trials show a positive effect on non-motor symptoms, especially cognition, it would give cell therapy an important edge over the standard medications for treating Parkinson’s disease today.

- Non-motor outcomes haven’t ever been addressed in cell therapy the way we are doing now. The problem with non-motor symptoms is that they have always proven more difficult to treat. For example, we know that Deep Brain Simulation (DBS) does not seem to have a significant positive effect on cognition or other non-motor symptoms. It will be very interesting to see if grafting of fetal cells can affect these parameters. Because, even if we can prove that cell therapy is working well, we still have to show that it is working better than DBS, duodopa-pumps or apomorphine-pumps for example, the therapies we are competing with. They are all established treatments with an industry behind them and may also be less invasive and cheaper, says Gesine Paul.

The Point of Cell Therapy

The truth is that the Parkinson research community has long been desperate to find an alternative to the traditional pharmacological treatments on the market today. Levodopa, the hallmark treatment for Parkinson’s disease for over forty years, is known to effectively relieve symptoms for the first 5-10 years, giving patients a markedly improved quality of life. However, as the medication becomes less effective serious side effects, most commonly uncontrolled movements and hallucinations, become more prominent. This puts major restrictions on the long-term benefits of the pharmacological treatment. In effect, the treatment is only a symptomatic therapy. You are basically trying to replace the transmitter that the dopamine-producing brain cells can’t produce anymore. But you can’t replace the actual cells that are lost in PD and today no treatment exists that can prevent them from dying.

This is where the promise of cell therapy enters the fray. Clinical data from open label cell therapy trials have shown that some patients have had a lasting therapeutic effect for more than 15 years after grafting. For many researchers and patients the positive examples of cell transplants over the years provide more hope than any other treatment.

- For me, cell therapy remains, besides growth factor treatments and gene therapy, one of the most exciting treatments in development today. Also, the fact that the effects of the treatment have lasted up to 15 years in some patients gives people hope. That’s a long period of really good life quality and in the end that is what we measure, that is what it is all about for the patient. If we succeed it also might mean that we can reduce medication or even take some patients off medication. And you can ask any patient - if there is any chance that they could minimize their tight medication schedules, they’re normally very happy to try a different treatment, Gesine Paul explains.
Lund Leading the Way

With a strong legacy in cell therapy Lund is helping to lead the way within Transeuro. The historical nerve cell transplants on Parkinson’s patients in Lund in 1987 were the result of Anders Björklund’s pioneering work in the laboratory. For the first time it was shown that transplanted brain cells from embryos could survive and function in the brain. 25 years later a host of researchers from Bagadilico are involved in Transeuro, a multi-center study that builds on the ground breaking efforts in Lund a quarter of a century ago. As Parkinson research in Lund may come full circle at the end of these trials, the many Lund researchers involved in the study tells the story of a research environment that has step-by-step emerged as one of Europe’s strongest in its field.

In her role as a clinical investigator Gesine Paul is constantly in dialogue with patients being evaluated for the study. A few of them will be randomly selected for the first round of transplants taking place later this year. Most patients have already expressed a desire to take part and for most a letter of inclusion would be equivalent to picking the winning ticket in a lottery. Communicating with patients is clearly one of Gesine’s strong suits. Speaking about her patients she lights up and her individual knowledge of each one suggests that her daily patient meetings are all but routine affairs. In Gesine’s eyes her patients are seen as equals, not objects of study. When she sits down with a patient, communication doesn’t travel just one-way. Many of her patients are well versed in the latest scientific developments and a lot of times she gets tips on which new articles to read.

- A lot of patients are very interested in what’s going on in Parkinson research and they actively pursue new information. The dialogue with my patients is very stimulating and they often inspire me with suggestions and tips that they share with me. It is one of the strongest driving forces in my work because it gets really personal the moment you meet a new patient. Every patient has a unique personality and a unique social situation. Over time you get to know them very well and some of them I follow over the course of many years. I always try to set the treatment plan together with the patient. You have to design a special plan for every patient since they are all different.

Looking ahead

About thirty patients will be recruited in Lund for the Transeuro study. The total number for the six European sites involved is 150. Some of the thirty Lund patients will be randomized for grafting at the end of this year. The phase-1 trial will primarily focus on safety issues, to see if patients develop uncontrolable movements, dyskiniesias, which were the most worrisome side effects of the trials in the U.S. a decade ago. If everything goes to plan, a proportion of the remaining patients will take part in a phase-2 trial a couple of years later where the therapeutic value of the transplants will be fully evaluated. Gesine Paul is cautiously optimistic about the results expected from Europe’s decisive cell therapy trial.

- What we have learned from the trials in America is that we have to be patient, we need to give the transplanted cells time to mature. We know from open-label trials before that it takes at least two years before you can actually measure a lasting clinical effect, and that effect can keep improving for up to four or five years after. It has been a mistake in previous trials to prematurely evaluate after only one or two years.

- I don’t think the study is going to be large enough to be immediately approved as a clinical treatment, before then we have plenty of hurdles to pass. But if we can show a clear clinical benefit without severe side effects it would probably be strong enough data to support the continuation of cell therapy research for Parkinson’s disease for a long time, concludes Gesine Paul, as she starts to put away one of many binders labeled Transeuro in her crammed office on the neurology ward.
Imagine if you could read the communication between brain cells at a rate of 200 times per second. Well, you can. Though many neuroscientists would cast a dubious glance in your direction upon hearing this. With amperometry, an electronic measuring technique, you can follow the graphic step-by-step activity of chemical messengers in real time. The method has long been a well-hidden secret to large parts of the scientific community. The intricacies involved in setting up the equipment have prevented the complex apparatus from becoming a household technology in most labs. As the machinery is now starting to become more standardized and the word on the scientific benefits of amperometry is beginning to spread, interest from researchers is rapidly growing on a global scale. So, too, among Lund neuroscientists.

Bagadilico’s amperometry wizard, Martin Lundblad, has, since establishing an amperometry platform within MultiPark, been at the receiving end of an avalanche of requests for new collaborations. It seems his missionary work over the past couple of years, mostly consisting of power-point presentations, has not fallen on deaf ears. The gospel has finally been heard.

Martin’s interest for amperometry developed deep in the American South, more precisely in Kentucky. In Lexington, once named the horse capital of the world, he did his second post-doc under the tutelage of Greg Gerhardt at the University of Kentucky. Dr. Gerhardt, one of the pioneers of in vivo amperometry, is a man with many strings to his bow, labeled by Martin Lundblad as an ‘engineer, a biologist and a psychiatrist’. Inspired by the novelty of the technology Martin brought the method to Sweden where he has since continued to develop it to suit the needs of Lund’s Parkinson research environment.

The exclusive features of the technology are best explained by its speed and precision. The electrode inserted, for example in the brain of a mouse modeled for Parkinson’s disease, can measure the instantaneous release of neurotransmitters from brain cells. The method’s unique features reveal the chain of events that lead up to or follow the release of chemical messengers between neurons. Here lie hidden vast amounts of data that previous, slower methods have not been able to detect. Amperometry allows for millisecond mapping of neurotransmitter activity in a precisely defined brain structure and has the capacity to give clear indications on what mechanisms are involved in the detailed chain reactions taking place in brain connectivity.

- Because you can look at different parameters in these communication patterns, such as speed of neurotransmitter release or uptake, you can localize the origin of the problem with a precision that no other technique can match. For example, in a recent paper where we overexpressed alpha-synuclein in a rat model for Parkinson’s, we were able to identify changes in the uptake of dopamine after only ten days, well before there were any damage to the cell body or any symptoms had developed. These early changes in neurotransmitter activity have never before been registered, explains an enthused, yet mild mannered, Martin Lundblad.

New Paper Proves Method

The publication Martin is referring to, “Impaired neurotransmission caused by overexpression of a-synuclein in nigral dopamine neurons”, was published in the January issue of PNAS. The revelatory finding in the paper concerns a discovery, by method of amperometry, that shows how the misfolded protein alpha-synuclein, implicated in the disease progression of Parkinson’s disease, affects the transmission of dopamine between neurons. The fact that this happens before cell death or any development of symptoms suggests that the
damaged protein disturbs the synaptic processes involved in dopamine release very early on in the pathology. The finding could therefore be a key in the search for the pathogenesis of Parkinson’s disease.

In the development of neuroprotective treatments it is vital to ‘catch’ the disease as early as possible. This discovery presents new targets and screening opportunities in the development of such therapies.

As the amperometry technology is starting to cause ripples across the field of neuroscience, the race to further develop the method continues. Part of Martin Lundblad’s job is dedicated to advancing the method and break through new frontiers. His latest improvement involves connecting amperometry with optogenetics, a new method that utilizes delivery of light sensitive proteins to specific neurons and activating them by laser light.

- This method is very hot right now and it enables us to perform experiments that have not been possible with existing techniques. I believe I will be the first person to connect the optogenetic method with the modern amperometry in my upcoming experiments, explains Martin Lundblad.

Since amperometry is a research technique that is still not being used in many labs the potential for uncovering unique data is almost infinite. The inner details concerning the physiology of neurotransmitters are still, to a large extent, unchartered territory. Martin believes that when people realize that these things actually can be measured the use of the technology will take off exponentially. He concludes that we have ‘only just scratched the surface here’.

Today, the method remains a rather exclusive one, only offered to scientists connected to laboratories specifically focused on in vivo electrochemistry. With the MultiPark technical platform for in vivo amperometry this is now available to most Bagadilico scientists. In addition, due to Martin’s close collaboration with Dr Gerhardt, new technology not yet on the market is available to him and the users of the platform, adding further excellence to the Lund research environment. A host of Bagadilico groups have already initiated projects with Martin Lundblad and the list is growing longer week-by-week.

Driven by Desire

The once aspiring meteorologist, a dream held by Martin during his childhood years, first fell under the spell of neuroscience as an exchange student in Copenhagen. Lost in a book about the brain Martin had a ‘wow’ moment he still remembers today.

- It was an epiphany, no doubt. It was the coolest thing. Part of the allure was that it was so difficult. The challenge of it, what attracted me to neuroscience in the first place, was the grand puzzle. Trying to connect the dots, figuring out how the different processes affected each other. And that fascination remains today.

The excitement is revealed by his body language when talks about the amperometry experiments that he conducts today. Being at the forefront of a new technology allows him to be part of history on a daily basis.

- When I see the results of my experiments, I’m often the first one ever to read that specific data. That’s an awesome experience. The experiments are also very graphic. I can follow the developments on my screen as they happen. That’s also very exciting. Even when the results are negative, it’s still new data, so it’s useful anyway. Quite simply, I’m a lucky guy.

To learn more about amperometry or to book an appointment with Martin Lundblad - visit the ‘Amperometry Platform Page’ on the MultiPark website. Click Here