Elisabeth Ohlin “nails” thesis on pharmacotherapy in PD

On August 25th Elisabeth Ohlin finally “nailed” her thesis to the wall in the BMC A10 kitchen. The ritual ceremony concluded a long journey into the side effects of L-DOPA medication in PD. A journey that has seen some exciting new findings.

Congratulations on your thesis! How does it feel to have finally reached the finish line?

Well, the job is not really finished yet... The defense is scheduled in 3 weeks, but writing up the thesis is of course a big part of the job, which has now come to an end! It feels great to have a printed copy and to finally nail it!

What has inspired you to pursue a career in experimental neuroscience?

Difficult question, a lot of inspiration from everywhere really, neuroscience has always fascinated me. To get this far has mainly been colleagues and my supervisor, Angela Cenci-Nilsson, for setting high goals and motivation to our research.

Who have played important roles in helping you get this far?

Of course my supervisor Angela, close colleagues, and collaborators in other countries. But also the support from friends and family. Without them it would not have been possible.

Could you very briefly explain the theme of your thesis?

I have investigated the effects of pharmacological treatment in Parkinson’s disease on the small blood vessels in the brain, in areas that are affected by the disease. We have been working both with rats and post mortem human brain material. We have found changes in the growth of blood vessels, which could have important implications for future treatment of the disease.

Where do you go from here?

I will continue with research on the same theme, starting here in Lund finishing off some projects and some new ones that have sprung from the results of my thesis work. Then new challenges lie ahead and I don’t plan to stay in Lund for that.

NEWS IN BRIEF

DANIELLA RYLANDER AWARDED 100 000 SEK PRIZE

Bagadilico’s Daniella Rylander recently received a healthy sum of money from the Swedish Parkinson Foundation for her groundbreaking research on Parkinson medication.

The Elsa and Inge Andersson 100 000 SEK prize gives Daniella a better chance of bringing her exciting research results closer to the clinic. “The prize means a lot for my future research on Parkinson’s disease. The money will go towards investigating specific changes in the parkinsonian brain after nerve cell transplants”, says Daniella while adding; “I wish that our research improves when it comes to communicating with society and health care institutions so that people become aware that there are real ambitions and hopes for treating PD.”

Last year Daniella Rylander caught the headlines when she presented new and important findings on the side effects of dyskinesia in her PhD thesis.

PARKINSON’S SYMPOSIUM DRAWS HUNDREDS TO LUND

On August 24th the Swedish Parkinson Academy arranged a half-day gathering, the Olle Engkvist Symposium, giving visitors a cross section of the the Parkinson research taking place in Lund today.

Since its foundation in 2007 the Swedish Parkinson Academy has been responsible for strengthening research that is closer to the patient. Aside from sponsoring the national Parkinson registry, the SPA has taken part in developing new measurement methods for patient symptoms, contributed to discover previously unknown genetic changes in PD, and much more.

Patrik Brundin, Vice Coordinator for Bagadilico, believes that the SPA has played a key role in elevating PD-research in Lund over the past couple of years; “Events such as this one are important in many regards; it keeps patients informed about what we do, it keeps us up to date about the patients’ thoughts on what is important to them, it motivates scientists to work harder and it also increases opportunities for private donations benefitting our research”.

SIGN UP FOR BAGADILICO/MULTIPARK RETREAT!

We are planning the annual retreat with BAGADILICO and MultiPark that will take place on December 5-7. It is a back-to-back retreat with day one focusing on BAGADILICO and day three focusing on MultiPark. We are trying to plan day two with activities of interest to both groups, although, there will be some common activities all three days. For example, we have confirmed Gerald Stern to speak on the history of Parkinson’s disease late in the afternoon on day one.

We will be staying at the same hotel as last year, Hotel Skansen (Click Here) in Båstad and you will be sharing a room with a work colleague.

Please e-mail Diana Jerman (Diana.Jerman@med.lu.se), no later than the 19th of September, to register for the retreat. Diana would like you to supply the following information: 1) If you are coming/not coming to the retreat. 2) How many nights you will be staying and with whom you are sharing a room. 3) If you have any dietary requirements.
Translated from Latin acoustophoresis means migration with sound. The term, coined by Bagadilico’s Thomas Laurell, refers to a possibly revolutionizing cell sorting technique where cells are separated by a standing ultrasound wave. This seemingly simple technical platform is at the core of a newly launched biomed-tech company called Acousort, founded by Thomas Laurell, Patrik Brundin, Hans Lilja and Lund University Development AB.

In the company’s new offices at Lund Life Science Incubator freshly appointed CEO Tomas Deierborg welcomes me with a plate of pasta Bolognese in his left hand. The lively Deierborg speaks with enthusiasm about the company’s potential and the broad applications of the acoustophoresis platform. The technology has already made sound waves across the globe with several big multinational companies knocking on the door during the company’s first few months in existence.

Tomas Deierborg explains the basic idea behind acoustophoresis.

- Phoresis literally means to migrate. In other similar techniques, electric forces move particles in electrophoresis and magnetic forces in magnetophoresis. In acoustophoresis the active force moving the cells or particles is radiation forces created by a standing ultrasound wave. The cells are sorted by their specific characteristics; cell size, density and compressibility. As the cells exit the channel their acoustic fingerprints help us control which outlet they are sorted into.

From Stem Cells to Milk

The acoustophoresis technology is in essence a generic method with the potential to streamline many different processes. The technique has already attracted interest from a large food quality control company about the possibility of developing a cell separation device to detect mastitis in cows. When a cow has an udder inflammation cells are released into the milk that shouldn’t be there. With a quick analysis through a chip using acoustophoresis, these cells could be detected in a matter of minutes.

- We see great possibilities in developing applications for this technology not only in the field of experimental medical science and this is a telling example of that. We don’t want this milk in our caffe latte’s, that milk truck has to go somewhere else, says Tomas Deierborg, as he draws up a meter-long version of the acoustophoresis chip on the meeting room whiteboard.

At the other end of the spectrum the founders of the company see big potential in the field of experimental neuroscience. A possible future application is in cell transplants for Parkinson’s disease, an area that holds many collaborative opportunities within
the Bagadilico environment. With an acoustophoresis cell-sorting chip, differentiated stem cells could hopefully be efficiently separated from other cells. Today, this process is made in a number of different steps and is far more complicated. Cells have to be tagged with certain markers and the method is quite labor intensive. An express solution where the wanted cells are collected in one simple step would save a lot of time and money.

Also, the acoustophoresis seem to be kinder to the cells than the established technologies used today. The company is now performing a study to see how different cells are affected by the radiation of the sound waves.

- In a FACS machine, the machine most commonly used for cell sorting today, we know that cells are put under a lot of stress as they go through a high flow rate and become electrically charged. Nerve cells are lost in the process and we hope to eliminate that with our technology. What we can see from our current study is that cells don’t seem to be affected at all going through the acoustophoresis chip, even if we maximize the strength of the sound radiation. This is an essential part of our future commercial competitiveness, explains Tomas Deierborg.

**The BioMedTech IKEA of the future?**

At the heart of the Acousort project lies an aspiration to one day make a real difference in the everyday medical care of patients. One of the venues pursued within the company is the development of an acoustophoresis chip with an add-on that could very quickly, through a simple blood sample, diagnose for example cancer or neurodegenerative diseases. In two quick steps the blood cells would be separated from the plasma and the relevant protein detected, completing a process that today is time-consuming and demands advanced expertise. What we have here instead, quite simply, is a lab-on-a-chip.

- This is our hope, of course, says Tomas with noticeable excitement in his voice. We think that there is a possibility that this technology platform could offer real and important solutions in hospitals and laboratories in the future. Maybe we will become the next IKEA in the medical business, he says half-jokingly.

- You can imagine that the heads of the health centers go around in our lab-on-a-chip store and pick up different chips for different purposes.

**Thomas Laurell is the man behind the technology.** The first chips were developed in his lab already in 2000. He knows how difficult it is to build a new BioMedTech company from scratch but remains cautiously optimistic about the future.

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**Taking a leap.** A decade ago Thomas Laurell developed the first acoustophoresis chip. With the founding of Acousort AB he begins to see the fruits of his labor.
In a new study, headed by young researcher Elisabet Ohlin, the Basal Ganglia Pathophysiology Team maps the role of a growth factor that controls the birth of new blood vessels in the brain. Through experiments in rats and comparative studies of human brain tissue the scientists have been able to link an increased expression of the growth factor protein with the development of motor complications. The uncontrollable movements, known as dyskinesia, are a well-documented side effect of the standard medication in Parkinson’s disease, L-DOPA.

Research on dyskinesia has many times over proven that the influx of dopamine from L-DOPA, replacing the dopamine lost in Parkinson’s disease brain cell death, rewires the brain in a number of ways. Unregulated high concentrations of dopamine in the basal ganglia, a major motor center in the brain, are known to be the main trigger of dyskinesia, the involuntary movements experienced by most Parkinson’s patients.

As the brain adjusts to the externally provided flow of dopamine certain signaling pathways in the brain become over-activated. The excess firing between neurons ultimately cause the jerky movements known as dyskinesia.

How different mechanisms and pathways are interlinked remains a matter of great debate among scientists. The new research findings represent another hat tossed into the ring, offering new clues about a previously overlooked role of the microvascular system.

**Blood vessel growth tied to dyskinesia**

The amount of blood supplied to the brain every day is vast. The total length of blood vessels in the brain combines to more than 600 km and the area for oxygen exchange in the normal brain can be translated into 20 square meters. Small blood vessels, known as capillaries, are ultimately responsible for this process.

The new study follows up on research findings presented by the group already in 2006, results that demonstrate a significant increase in the growth of these blood vessels in the basal ganglia, upon chronic treatment with L-DOPA.

Elisabeth Ohlin, post graduate and first author of the study, has long been fascinated by the role of the microvascular system in brain diseases.

- This area of research requires further attention in my opinion. The brain’s microvascular system has been overlooked in some brain diseases where it could play an important role, for example Parkinson’s disease. Our research group is the first to have looked for an answer in how L-DOPA treatment affects the blood vessels in the brain.

- The main finding was that we for the first time were able
to see blood vessel changes in post mortem brain material from the basal ganglia of dyskinetic patients but not in the material from those patients who had remained free from dyskinesia. In material from two different patient sets, we found changes in the microvasculature and the important blood vessel growth factor, called VEGF, indicating ongoing blood vessel growth, Elisabet Ohlin explains.

In the critical proof-of-principle experiment of the study the researchers were able to causally link the involuntary movements to a growth-promoting effect of the L-DOPA medication on blood vessels in the basal ganglia. When introducing a small molecule inhibitor of the over-activated blood vessel growth factor VEGF, the research group was able to mitigate dyskinetic symptoms in Parkinson’s disease rat models treated with L-DOPA.

- We have long suspected that a chronic stimulation of blood vessel growth can be harmful and create an unfavorable environment in the brain. The growth factor inhibitor that we used in the rat experiments blocks blood vessel growth in the entire body, and is therefore not an option for long-term treatment of Parkinson’s disease. However, it is important to have proven that targeting non-neuronal mechanisms can reveal new clues to the treatment of PD-patients.

- It is the first time the effect of an anti-dyskinetic treatment is identified at the microvascular level, which makes it very new, but also exciting in view of the new targets for treatments that could come from these findings.

Our long-term aspiration is to further identify brain vascular mechanisms that are altered over time with the hope of reducing not only dyskinesia but also the aggravation of other symptoms that occur during the course of the disease, concludes Elisabet Ohlin from her BMC laboratory in Lund.

**Breaking new ground.** For the first time in Parkinson’s disease research history, Elisabet Ohlin and her colleagues have been able to prove a connection between L-Dopa treatment and blood vessel growth in the parkinsonian brain. Experiments in rats where the growth factor was inhibited showed clear improvements as the dyskinetic movements subsided significantly.

“It is the first time the effect of an anti-dyskinetic treatment is identified at the microvascular level!”