On November 5th, the Swedish Research Council announced its decisions on the ‘General Calls’ for Medicine and Health in 2012. A total of 1.4 billion SEK was awarded to 365 applicants across the country. A host of Bagadilico researchers were among the recipients, solidifying Lund University’s continued position of strength in Parkinson’s research.

Malin Parmar was one Bagadilico scientist who received ten million SEK over five years for her groundbreaking research on cell therapy with reprogrammed fibroblasts. Another was Anders Björklund, who was awarded six million SEK over three years for research on new disease-modifying drugs for Parkinson’s disease. Deniz Kirik, too, landed a five-year grant of ten million SEK for his research on RNA editing for Huntington’s disease. Malin, Anders and Deniz were all awarded funds within a new scheme introduced this year, entitled ‘Therapies of the Future’. Mats Ulfendahl, Secretary General of the Swedish Research Council, comments.

- This is a very exciting call that ties together basic and applied research. One important aspect of this funding scheme is that the applicants were asked to explain how they intended to handle the serious ethical issues that arise when new therapies are introduced. The applications were judged by international expertise and the ones that were awarded funds held the highest scientific quality while at the same time addressing key ethical dilemmas.

Patrik Brundin and Jia-Yi Li complete the Bagadilico awardees line-up, bringing the total tally to just above 38 million SEK. For the full list of grants awarded in Medicine and Health in 2012, CLICK HERE (Excel File).
Huntington’s disease is a simple disease. Simple in the sense that it's caused by a single genetic mutation. Trying to stop the disease process however, occurring in every cell in the body, is infinitely complicated. So where does one begin to tackle a task of such Sisyphean proportions? A good place to start could be the areas in the brain where Huntington’s disease creates the most damage. Trying to ameliorate the early psychiatric symptoms of the disease has shown to be of top priority for patients who often suffer from depression and personality changes. With a fresh grant from the Swedish Research Council, Deniz Kirik and Åsa Petersen will lead a team of experts in finding a way to replace the malicious mutation with a healthy gene expression in key parts of the brain. With meticulous precision they will attempt to recode the abnormal DNA with a synthetically produced genetic sequence, stopping the disease dead in its tracks.

The method used here is called RNA-editing. In essence, it is a molecular level game of cutting and pasting in the RNA in order to remove the mutant encoding that overexpresses the huntingtin protein. When allowed to run its course the genetic mutation produces an abundance of huntingtin protein that clumps together, eventually damaging neurons.

If it would be possible to correct the segment of the RNA made from the mutant DNA, the protein synthesized from that new and healthy RNA make-up would be normal. You wouldn’t then have to correct for the later problems that the mutant protein generates because you now solve the problem at the beginning of the process. Put simply, if there is no mutant protein, there is no disease, explains Deniz Kirik, who last month landed a five-year grant of ten million SEK for his research on RNA-editing for Huntington’s disease (HD).

In theory, this technique could be a key stepping stone towards a cure for HD. However, the vast intricacies of the brain does not allow for a simple delivery of such a method. There are still a lot of unknowns when it comes to RNA transcription processes. Why and when the cell machinery decides to cut and paste is still largely shrouded in mystery. In order to bypass the cells’ malfunctioning processes Deniz Kirik and Åsa Petersén will have to trick them to use their genetic sequence instead, delivered by viral vectors. Herein lies the real challenge.

REVOLUTIONARY APPROVAL

Gene therapy is a field that has been making big strides of late. On November second the Amsterdam-based company uniQure received the first market authorization for a gene therapy in the western world. The treatment is for patients with lipoprotein lipase deficiency, a very rare inherited disease, where patients are unable to metabolize the
fat particles carried in their blood. The decision by the European Commission may open the floodgates for gene therapy based treatments and make financing more readily available.

- **Running clinical trials** is one thing. Getting approval to put it in a pharmacy is another thing. This is a major step because when we develop these treatments as an alternative to well-known medical treatments of today the common question is - Can they ever be drugs on the market? The answer used to be we don’t know. Now, the answer is we know and yes they can be, says Deniz Krik in a voice suggesting both excitement and relief.

TRUE TO TRANSLATION

In spite of this research project’s experimental originality, the translational roadmap is staked out with unusual clarity. Together with the laboratory testing on mice, the study is integrated with state-of-the-art imaging, continuous clinical observations and a comprehensive ethical program.

- **There is already** an ongoing project with Niclas Hagen where they have been talking to HD patients trying to understand the ethical issues concerning the disease. So, Niclas', Susanne Lundin's and Max Liljefors’ role here will be to revise and improve the patients consent forms. Some of the statements currently in these forms are not well thought through so there is a clear need for improvement. Today, the patients actually sign a document that they may not fully understand.

On the clinical side of things Åsa Petersén and Håkan Widner will recruit and observe patients in order to understand how the disease progresses. When the time comes for clinical trials the data collected will help the team evaluate the efficacy of the therapy and how it may alter the natural course of the disease.

- **In the process of** this, if our experimental research is successful and it proves the concept that we can make a difference in correcting these proteins in the brain, we will be able to move this clinical cohort that we have characterized into a second study design. Here, they will be offered to receive the gene therapy aimed at correcting their mutant protein and we will then follow them closely.

At present, the clinical trial for this gene therapy solution is scheduled to take place inside the five-year window of the current project. As always, clinical trials are a costly enterprise but Deniz Krik is confident that the project’s solid structure will attract financiers when the time comes.

- I’m **really convinced** that we can get there. If we can show that the animal studies are successful, that we have a clinically followed cohort and also prove that we can make clinical grade vectors it will probably not be too difficult to obtain funding for the actual clinical trial.

The initial target areas for the therapy are likely to be the hypothalamus, the cortex and the striatum, parts of the brain that in HD code for different abnormalities in behavior. The end game here is to help patients to be cognitively functioning individuals that can cope with their disease in a better way. Catching patients early on in the disease may present them with a path towards a more normal life, outside the nursing homes.
On November 27th the elevators in BMC’s farthest wing were working overtime trying to keep up with a steady stream of people. Parkinson Café visitors were anxious to get out of the early winter cold and on to the top floor. The TRANSEURO-themed café had been fully booked weeks in advance and the room was filled with a collective anticipation. Seasoned café participants came prepared for the concluding Q&A. With notebooks readily placed in laps and scribbled pieces of paper sticking out of back pockets, visitors turned their attention to moderator Göran Hermerén as he took the stage.

Upon a brief introduction of the TRANSEURO basics the floor was given to neurologist Håkan Widner, an experienced clinician who has the senior responsibility for TRANSEURO in Lund. Håkan explained that the main goal of TRANSEURO is to take a critical approach to the viability of cell therapy as a future treatment for Parkinson’s disease. He posed some thought provoking questions at the onset. Can we replace cells that die as a result of our most common neurological diseases? What are the therapies of the future for neurodegenerative diseases like Parkinson’s and Alzheimer’s?

Participants learned that as part of the European study TRANSEURO, five patients with Parkinson’s disease will undergo brain cell transplants at Skåne University Hospital in Lund, in early 2013. These are the first operations of their kind in Europe for over 10 years.

Giving a historic background to cell transplants for PD, a technique first developed in Lund, Håkan continued to tell a fascinating tale of continuous scientific breakthroughs. Under the leadership of Professor of Neurology...
Olle Lindvall, brain researchers in Lund had already developed the method of transplanting nerve cells in the early 1980s. In 1987, brain surgeon Stig Rehncrona operated on the very first patient. The study was significant in history marking the first repair of the human nervous system. The news was cabled out to all the world’s media and the Swedish researchers soon graced the front page of the New York Times.

- Since the advances made in the 1980s and 1990s, the research field has encountered many obstacles. In the early 2000s, two American studies produced negative results, which meant that cell transplants for Parkinson’s disease came to a dead end, said Häkan Widner, explaining the broken promises of a therapy that gave many patients so much hope 25 years ago.

- The results of TRANSEURO will play an important role in the immediate future of cell therapy as a viable treatment. We have scrutinized the failed American studies in an attempt to optimize the technique, improve patient selection and conduct more personalized follow-up. We are hopeful that the results will be different this time, concluded Professor Widner.

Veteran neurosurgeon Stig Rehncrona then entered the stage. The audience now got a quick lesson in the development of brain surgery for PD over the years. From lesions, via DBS to the regenerative approaches put to use within the TRANSEURO program. The structure being used for precise delivery in the upcoming operations is a stereotactic frame once developed in Lund and later refined by Stig himself.

- A somewhat sloppy nurse once dropped the stereotactic frame that we were going to use for an impending operation. Since the patient was already in place I had no use but to take the original frame from the monter in the hospital museum. Sometimes you have to think on your feet. And sure enough, we sterilized the frame and the operation went without any complications, said Stig Rehncrona, the anecdote bringing down the biggest laughter of the evening.

Dr. Rehncrona has been responsible for all 20 transplants performed in Lund since 1987. In total he has made almost 300 insertions of brain cell tissue to target areas in patient brains. Together with Hjalmar Bjartmarz he will be overseeing the upcoming transplantations where they will use an insertion instrument developed by Stig himself together with Janos Legradi.

The final talk was given by experimental scientist Malin Parmar who is at the forefront of developing future alternatives to using fetal brain cells in transplantations. The fetal cells come with major logistical problems and also an ethical debate, perhaps more heated outside Sweden’s borders. One of the earliest alternatives considered has been the use of embryonic stem cells. However, Malin explained, these cells have, in some cases, shown to continue dividing uncontrollably in the host brain, eventually causing tumours.

- One way to bypass this problem is to use a technique that we have developed in my lab where we turn the patients own skin cells directly into nerve cells. The technique, that we originally stumbled upon, is an unexpectedly simple one. It involves activating three genes in the skin cells, genes that are already known to be active in the formation of brain cells at the fetal stage, Malin explained.

Unlike other reprogramming methods, where skin cells are turned into pluripotent stem cells, known as IPS cells, direct reprogramming means that the skin cells do not pass through the stem cell stage when they are converted into nerve cells. Skipping the stem cell stage may help to finally eliminate the risk of tumors forming after the cells are transplanted. Using the patients own skin cells as a basis for reprogramming could also help the transplanted cells integrate better into the brain as the genetic match-up will be the same.

Malin concluded with saying that all options are still on the table and we are yet to find the one given alternative that offers an ethical, logistical and efficient solution to our problems. Somewhat surprisingly she ended on a 200 year old fairy tale metaphor.

- It’s kind of like the dilemma that Goldilocks was facing. The porridge is not yet the perfect temperature and the bed is still slightly uncomfortable to lie in.

The concluding discussion session was a lively affair. Questions and comments came from all over the place, topically as well as spatially. One question concerned the gray areas of medical tourism for stem cell treatments. A unified panel condemned the practices taking place in Germany, China and most recently the Ukraine, underlining the potentially life threatening aspects of this shady business and the overall negative influence it has for the research field as a whole.

- What is the Christmas gift of the year in this field in five years, asked one café visitor.

- A machine that produces nerve cells safe for transplantation, said Malin.

- Something that cures and slows down the disease process, Häkan filled in.

The final comment of the night brought chuckles in the auditorium as one man asked what dopamine releasing pleasures the panel would recommend.

- All joking aside, the effects of physical exercise is a heavily under researched area in Parkinson’s disease. It’s an area that could provide great benefits that we are hoping to look closer at in the coming years, concluded Häkan Widner, as the night drew to a close.