**NECTAR 2021 Podcast**

**Episode 1: Anders Björklund and Stephen Dunnett**
**Host: Stevie A Bain**

**00:00 Stevie:** Welcome to the NECTAR 2021 podcast. Nectar 2021 is hosted by Dr. Tilo Kunath at the University of Edinburgh and will be jointly held with the 16th international symposium on neural transplantation and repair, INTR. The conference is sponsored by Guarantors of Brain, CARE - the campaign for Alzheimer's research in Europe, Blue Rock Therapeutics, Roslin Cell Therapy, ProteinTech and Cell and Gene Therapy Catapult. NECTAR - the network for European CNS transplantation and restoration was founded over 25 years ago with the aim of bringing together European groups who share the common goal of protecting, repairing, and restoring the central nervous system from damage caused by degenerative disease or injury. In this first episode of the Nectar 2021 podcast, I talked to the pioneering researchers who founded the network.

**01:05 Anders**: My name is Anders Björklund, I'm a professor of neuroscience at Lund University in Sweden. My field of research is Parkinson's disease. But I have over several decades being involved in the development of cell-based therapies, particularly for Parkinson's.

**01:26 Stephen:** I'm Stephen Dunnett. I started as a mathematician but very quickly switched into neurobiology, psychology, and animal models of human disease. And I've spent my life looking at cell therapies and other therapeutic approaches to two diseases, Parkinson's disease and Huntington's disease.

**01:47 Anders**: Steve and I have been collaborating over many years. And our work, our joint work, started around 1980, has formed much of the basis of, what's now being attempted for cell transplantation in Parkinson's.

**02:04 Stevie:** So how exactly did NECTAR begin?

**02:07 Anders:** This goes back to 1989. I think one should also give a little of the background for what was happening in 1989. The idea of transplanting cells to the nervous system emerged in the 1970s, in the 1980s we saw also the first attempts to apply this idea in patients.

**02:33 Stevie:** Just for a bit of an explanation, what exactly was the hope of that surgery?

**02:40 Anders**: Yeah, the idea is based on the possibility to replace the lost dopamine neurons with new cells that would take over the function from the cells that are lost to the disease. So degeneration of dopamine neurons is a cardinal symptom of Parkinson's disease patients. And the first attempt along those lines were made by our colleagues in Stockholm who had an interest in the function of chromaffin cells taken from the adrenal medulla. And they did two patients, who received implants of adrenal medulla cells into the caudate nucleus in one case and the putamen in another case,and followed them over a couple of years. Their results were negative basically. When it was picked up by Mexican

neurosurgeon Ignacio Madrazo who reported in 1987 what seemed to be sensational results obtained by putting in adrenal chromaffin cells into patients and that caused media stir, one can say. The attention was remarkable. And over the next 2-3 years, over 300 patients were operated in United States, with a technique that after just a few years turned out to be futile. Any changes that were seen in these patients had disappeared within two or three years. Now the important consequence of this is that in Europe, we became worried about this very rapid, in many ways, uncontrolled development that happened in the United States. And we wanted to assemble interested scientists and get together and make sure that progress in this field could be made cautiously and based on solid scientific data I should say.

**04:40 Stephen:** We were working on animal models in particular of Parkinson's disease. When we were looking at a number of different models, it was the dopamine depletions in the rat brain that was our first and most effective results. And we were pursuing placement of the lost brain dopamine cells with true dopamine cells which only survive in the transplantation in the adult brain when taken from the developing embryo. Now clearly in the early days, transplanting from human embryos was thought to be problematic. It's since been addressed. But at that stage, we probably had the most experience anywhere of looking at the effect of different types of cells implanted in Parkinson's models on a whole range of motor and sensory motor functions. And that was absolutely clear to us that embryonic cells worked much better than did adrenal medulla. And we felt quite strongly that we need to build up the experimental basis to get it working reliably and well, and to understand the principles of how to rebuild a damaged brain rather than simply trying serendipity, trying every cell type you could try. But that was the driver for us in Europe to say, let's get together, all the labs in Europe and focus on, first of all, building up the experimental basis for the therapies. Secondly, discussing the ethics of alternative sources of tissue so that we could at least consider embryonic tissues which we knew experimentally, is what worked best. And thirdly, we wanted a framework within which we could compare the results of different approaches and different centres. So a third focus of NECTAR was to establish not only common standards for going forward but commons standards of testing, common standards of reporting.

**06:59 Stevie:** Yeah, I can see there, the clear impetus for this as well because like you're saying, the importance of clinical trials, experimental data, but also the ethical implications. So that was the reasoning behind it. But how did you actually come together?

**07:15 Anders**: We contacted colleagues throughout Europe. Both basic scientists, clinicians, neurosurgeons, neurologists. We had the first planning meeting, which was in Munich and 1990. Organised by young neurologist there, Wolfgang Oertal.

**07:36 Stephen:** Now a very senior neurologist.

**07:39 Anders:** Well, he was young at the time.

**07:41 Stephen:** Yes. We all were. Relatively speaking.

[laughs]

**07:47 Anders:** But one could say, well, in some ways, many of those who gathered in those days were young people who were keen to go into this new field of research. One should remember that cell transplantation in the brain was an unconventional and rather brave idea. But I think it appealed to the young mind, those who saw the possibility of developing something that comes close to repair. At the Munich meeting, we agreed on the main purposes of the new organisation. And we were also invited by Mike Peschanski, he invited us to come to a place outside of Paris in 1991. And that was formally speaking the first NECTAR meeting. I think in retrospect, the first and most important impact NECTAR had was the introduction of ethical guidelines for use of both foetal tissue but also of transplantation to the brain.

**08:56 Stephen:** And in parallel, a number of European countries were all at a governmental level considering that they needed regulatory framework for this field. I think, because of NECTAR's early involvements in these regulatory matters we avoided the kind of reckless activities and reckless use of foetal material that otherwise could have happened. It's worth saying, in subsequent years, alternatives to foetal tissue are emerging as looking as effective, particularly approaches based on stem cell sources which originally were themselves derived from human embryos. But nowadays, there are techniques of inducing a pluripotentiality in cells without them having embryonic origin. So increasingly, this field that was developed based on the only cells that worked at a time, which were of embryonic origin. Increasingly, we now have alternatives that I'm sure we're going to see progressively take over as viable, practical clinical alternatives that circumvents what was such a major problem 20, 30 years ago.

**10:26 Anders:** Yeah, the other field where NECTAR was early in taking initiatives was in how to assess patients in trials that were aimed at restorative therapies. It's clear that restorative therapies, including cell transplantation, is different from the more classic drug trials in that the patients have to be followed over a longer time period, the effects are emerging gradually. And there is also a clear possibility for placebo effects link to the interventional surgeries. So NECTAR established a working group for this, that worked out a detailed protocol for how assessment ideally should be made. And I think this protocol has become a little of the gold standard. It also engaged the clinicians early on in the field because one could say that the field developed in two parallel ways. One was the experimental work which has been very active throughout the years. In parallel, there have been these initiatives to explore the cell and, later on, gene therapy approaches clinically in small clinical trials. And cell therapy remains experimental still today. There isn't established therapy that can be offered freely to patients. That's why it's important also to make sure that the experimental work, the clinical initiatives, are closely interacting and feeding on each other.

**12:18 Stevie:** Yeah, it's very interesting and its obviously – in the years that NECTAR has been going there's obviously been a lot of changes happening in the field and a lot of progress. But I was just wondering - and you've both sort of touched on this earlier in different ways, but looking back on those first few NECTAR meetings so maybe not the very first one, but you know, maybe the first five, six, when things are getting up and running, how things have evolved and changed since then?

**12:49 Stephen:** Some things have remained the same. The meetings remain focused on translation, developing methods from the lab to the clinic. They are experimentally focussed. As a group, we have always been strongly encouraging lab members, not just the lab chiefs, the younger members, and less experienced members of the community are encouraged to come along and give very short presentations only 2 or 3 slides, but snapshots of their work. And so we have these allotted data blitz sections which is often the first opportunity for young members of the lab to present their work outside the internal workings of the lab. The changes - we started off as a group, of both experimentalists and clinicians focused on dopamine cells for Parkinson's. Fairly soon, in the first five or six meetings, we started saying, we know it can work in animals and there's growing evidence of it working under some conditions in patients, if it can work, the dopamine cells in Parkinson's, are there other conditions? And then in the later 1990s into the early 2000s, there was a parallel focus on another disease of the same system, of the brain, which is Huntington's disease. In course of this, a lot of the focus of the early meetings was on fundamental scientific issues, the challenges that we were confronting. And as we started addressing aspects like that, it became apparent that those problems and solutions applied beyond Parkinson's and Huntington's disease. So as the years have progressed we've started asking, are there possible applications in spinal cord injury? In dementias? In multiple sclerosis? Or even outside the brain in things like the retina? Increasingly, we have been looking at complementary therapies like gene therapy, sometimes as an alternative to regenerative medicine, to repairing the brain, but more often it's actually that different approaches complement each other. So we can think of genetic manipulation of cells, enhancing the survival of cells to be transplanted. Regenerative medicine is now widely seen as a major therapeutic strategy for future health care. When we started, very few people believed it could work. It was very much a radical new alternative. That was, there was a lot of scepticism to. I think the field has now moved mainstream and as a consequence, I think although it remains a small organisation, NECTAR is widely seen as a pioneer. And so we get more people from outside our specific community wanting to participate.

**16:05 Anders:** I think stem cell research has been an important driver for the emergence of the regenerative medicine field. The possibilities that they offer us as tools, as models but also as sources for material that could be used for brain repair. And stem cell research has also gradually moved into NECTAR and become an important part of the programme. There has been an emphasis on keeping these meetings not growing too much. The typical is, I think, something between 100 and 150 participants. Which means that the interaction and the networking is effective. And it becomes also attractive for young people to establish their own networks and get to know colleagues in the field. And it's also, I think the NECTAR meetings have been important in promoting exchange between labs, promoting the career of young people who can then move to postdoc positions in other labs and at the same time retain the collaborations with the wider community.

**17:32 Stephen:** I think there's another side to that. We can certainly see within many of these larger meetings, and especially as developing new therapeutics often involves companies and big national investments and commercial investments, there is a driver towards confidentiality, secrecy, proprietary rights. An aspect of the ethos of NECTAR, I

think driven by us old guard, the people who, who as a small group have trusted each other and talked freely with each other, we find it important, I certainly do, to encourage an openness of talking openly and honestly about their research. By and large, you get a lot more out of life, the more open you are and the more free in exchange and discussing because we're all trying to solve the same overlapping problems. And the range of problems is more than one individual can track by themselves. I think the ethos of open exchange is still maintained in NECTAR in the way many similar organisations don't succeed.

**18:53 Stevie:** What are your hopes or predictions for the future of NECTAR? So I think last year
it was online as well, and then this year it's going to be hosted, I think for the first time it's going to be in Scotland with -

**19:03 Anders:** Yeah –

**19:04 Stevie:** Tilo Kunath?

**19:05 Anders:** I hope it will continue in the spirit it's been carrying over almost three decades. And that it will be possible to maintain this collegiality and sense of friendship. And I think we need organisations like NECTAR where this spirit is maintained. And with people like Tilo for example, I think we are still in good hands.

**19:33 Stephen:** Agree, entirely.

**19:35 Stevie:** Excellent. And not to put you on the spot, this is maybe a very specific question, but is there anything, you're particularly looking forward for this next meeting coming up.

**19:44 Anders:** Well, to visit Edinburgh, I feel a little abstinence from not having been able to travel. I'm a fan of England and Scotland. So it's something I look forward to be able to visit again.

**19:59 Stephen:** It has felt to me like NECTAR is the one meeting that feels like home. Although I'm retired from the lab, I'm still fascinated by the challenges that we are trying to solve. And I've handed the baton on to students and other colleagues are continuing that work and it's for me, the excitement of just catching up. It never leaves you as a scientist. That search, the challenge of playing with ideas and seeking alternative ways of finding solutions and resolutions to long-standing problems.

**20:46 Stevie:** A huge thank you to Anders and Stephen for such a great discussion. Also, thank you again to our sponsors, Guarantors of Brain, CARE- the Campaign for Alzheimer's Research in Europe, Blue Rock Therapeutics, Roslin Cell Therapy, ProteinTech, and Cell and Gene Therapy Catapult. Be sure to tune in to future episodes of the NECTAR 2021 podcast.