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Annotated list of publications

This list is a selection of my publised papers, original articles and selected reviews, organised under five main themes:

- Studies related to the anatomy and function of the dopamine system, and animal models of Parkinson´s disease;

- Development of dopamine cell replacement therapy, experimental and clinical;

- Experimental studies on the neuroprotective effects of NGF, GDNF and Neurturin in the brain;

- Studies aimed at new therapies for L-DOPA-induced dyskinesias;

- Studies aimed at the development of gene therapy for continuous local delivery of L-DOPA.

My complete lst of publications contains about 540 papers, with a total citation of 43300 (20600 when self citations are excluded), and a *h*-index of 121 (as of March 2011).

1. Studies related to the dopamine system and animal models of Parkinson´s disease

The main focus of my postdoctoral work was to sort out the detailed anatomical organization of the dopamine and noradrenaline neuron systems in the brain using the brand new glyoxylic acid histofluorescence method. This method, which I developed in collaboration with my former PhD student and close collaborator Olle Lindvall, allowed for the first time the visualisation of the dopamine neuron system in its entirety, and allowed us to map anatomically the previously unknown dopamine projections to cortical and limbic areas. We were also the first to identify and map the dopaminergic projections to the habenula and the spinal cord, and reveal the special dendritic projections from the nigra compacta neurons that allow dopamine to be released from dendrites in the pars reticulata.

My PD model work has focused on a detailed functional characterisation and standardisation of the 6-OHDA lesion models in rats and mice, which has been of great help in our regeneration and neuroprotection studies. And more recently, my lab has pioneered the development of the a-synuclein overexpression model of PD, using the AAV vector technology.

a. Anatomy

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9. Skagerberg, G., Lindvall, O., Björklund, A.: Origin, course and termination of the mesohabenular dopamine pathway in the rat. *Brain Research* 307:99-108, 1984.

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12. Cenci, M.A., Kalén, P., Mandel, R.J., Björklund, A.: Regional differences in the regulation of dcpamine and noradrenaline release in medial frontal cortex, nucleus accumbens and caudate-putamen: a microdialysis study in the rat. *Brain Research* 581:217-228, 1992.

b. The 6-OHDA lesion model

13. Cenci, M.A., Campbell, K., Wictorin, K., Björklund, A.: Striatal c-fos induction by cocaine or apomorphine preferentially occurs in output neurons projecting to the substantia nigra in the rat. *Eur.J.Neurosci.,* 4:376-380, 1992

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15. Campbell, K., Björklund, A. Prefrontal corticostriatal afferents maintain increased enkephalin gene expression in the dopamine-denervated rat striatum. *Eur.J.Neurosci.*6:1371-1383, 1994.

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c. The AAV-a-synuclein model

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21. Grealish S, Mattsson,B, Draxler P, Björklund A (2010) Characterisation of behavioural and neurodegenerative changes induced by intranigral 6-hydroxydopamine lesions in a mouse model of Parkinson’s disease. *Eur J Neurosci,* 31(12):2266-2278.

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2. Neural grafting in animal models of neurodegenerative diseses and cognitive decline: Development of dopamine cell replacement therapy for patients with Parkinson´s disease

During the 1970ies I embarked on a new line of research based on the idea that immature neurons or neuroblasts could be made to survive and integrate in the damaged adult brain, and that they could be made to substitute anatomically and functionally for neurons lost to damage. This early part of this work was performed in collaboration with a gifted MD/PhD student, Ulf Stenevi (later Professor of ophthalmology at Goteborg University), and a young neurosurgeon, Niels Svendgaard (later Professor of Neurosurgery at Karolinska Hospital in Stockholm). In 1980 Steve Dunnett (the a young PhD student in Susan Iversen´s lab in Cambridge, UK) and Rusty Gage joined the lab. This was an exciting time, and together with two very gifted PhD students, Patrik Brundin and Ole Isacson, we performed a series of studies in animals models of neurodegenerative diseases and cognitive decline that led to the first clinical trial of dopamine neuron transplantation in PD patients, performed in 1987. Over the years the Lund program, led by Olle Lindvall, has been in the forefront of the development of cell replacement therapy for PD.

Apart from its potential clinical usefulness, intracerebral cell transplantation is a fascinating tool to explore the plasticity of the brain and its capacity for regeneration and repair, and restoration of functional neural circuitry after damage. Our work on transplants of fetal cholinergic neuroblasts in hippocampus and cortex has been particularly interesting in this regard. Current research in my lab is aimed at applying this knowledge, and our experimental skills, to the rapidly developing stem cell field.

a: Experimental: neural grafting in animal models of Parkinson´s disease

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3. Björklund, A., Stenevi, U.: Reconstruction of the nigrostriatal dopamine pathway by intracerebral nigral transplants. *Brain Research* 177:555-560, 1979.

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b. Experimental: neural grafting in animal models of Huntington´s disease

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3. Experimental studies on the neuroprotective effects of NGF, GDNF and Neurturin in the brain

My interest in neurotrophic factors and neuroprotection started in the mid-1980ies when Rusty Gage was working as a postdoc in my lab. Using highly purified NGF that we obtained from Silvio Varon´s lab in San Diego, we were the first to report the neuroprotective effect of NGF on axotomised basal forebrain cholinergic neurons in the rat brain, and went on to show that this trophic effect of intracerebrally infused NGF was also effective in reversing age-related atrophy and functional impairments in the forebrain cholinergic system. This work, continued by Mark Tuszynski and his collaborators in San Diego, has led to the first trials of NGF delivery in patients with Alzheimer´s disease.

When GDNF was discovered in 1993 we were quick to obtain samples of recombinant GDNF, and later also neurturin, from Genentech and, in parallel with two other labs in the USA, we were first to show the profound neuroprotective effect of GDNF and neurturin in the 6-OHDA lesion model. Over the subsequent years we published a series of papers that charcterised the neuroprotective and regenerative effect of GDNF in detail in the rat model, and were also first to use lentiviral and AAV vectors to deliver GDNF to the striatum and nigra by gene therapy, an approach now actively pursued clinically by Ceregene and AMT.

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4. Studies aimed at new therapies for L-DOPA-induced dyskinesias

It was a postdoctoral student, Chong S. Lee (then in Don Calne´s department in Vancouver, now Professor of Neurology in Seoul) who brought the interest in L-DOPA-induced dyskinesia to my lab. Together with a former PhD student of mine, Angela Cenci, we pursued Chong´s idea that L-DOPA-induced dyskinesia could be well and reproducibly generated in rats, using the unilateral 6-OHDA lesion model, provided that the neurological assessment was performed in a more refined way than had been done previously. This turned out to be a success, and Angela Cenci has since made a fantastic job in the development and and validation of this model to the point that it now has become a standard tool in dyskinesia research. My own research using this model has focused on two aspects: the ability of dopamine cell replacement therapy to reverse L-DOPA-induced dyskinesias; and the role of the serotonin neurons (as a source of dysregulated dopamine release) in the induction and maintenance of L-DOPA- and graft-induced induced dyskinesia.

Our most interesting discovery is the observation that silencing of the serotonin neurons (and hence dampening of dopamine release from serotonin terminals) can completely block dyskinesia in the rat and monkey PD models. This approach, which has been actively sponsored by MJFF, is now tested in a PhaseI/II clinical trial in collaboration with an American biotech company, PsychoGenics.

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5. Studies aimed at the development of gene therapy for continuous local delivery of L-DOPA.

The idea to deliver DOPA or dopamine locally in the brain by ex vivo or in vivo gene therapy goes back to the late 1980ies. Our first attempt was made in collaboration with Jacques Mallet´s lab in Paris, based on the use of cell lines engineered to secrete DOPA or dopamine. In the two studies we published together using this approach we could show that DOPA producing cells were more effective than dopamine-producing ones, but that the level of DOPA production obtained with this ex vivo approach was not enough to give any behavioral improvement in the rat 6-OHDA model.

The advent of high titer, highly prurified AAV vectors made the difference. The study we published in PNAS *2002, in collaboration with Ron Mandel and his colleagues at University of Florida, was a turning point: for the first time we could obtain sufficient levels of DOPA production in the dopamine-depleted striatum to achieve full functional recovery in the 6-OHDA lesion model. And in a subsequent study, published in* Brain *in 2005 we could show that AAV-mediated DOPA delivery was efficient in reversing L-DOPA-induced dyskinesias in this model. Based on these results we have now embarked on a program aimed to test this local DOPA delivery approach in PD patients.*

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