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Annotated list of publications

My complete list of publications contains about 570 papers, with h-index of 141 and a total citation of 59299 (Google Scholar as of December 2014).

This list is a selection of my published papers, original articles and reviews, organised under eight main themes:

1. Studies related to the dopamine system and animal models of Parkinson’s disease
2. Studies of axonal regeneration and reconstruction of neural circuitry by neural transplants in brain and spinal cord
3. Development of dopamine cell replacement therapy in Parkinson’s disease
4. Neural grafting in animal models of Huntington’s disease
5. Transplantation of cholinergic neurons in animal models of cognitive decline
6. Studies on the neuroprotective effects of NGF, GDNF and Neurturin in the brain
7. Studies aimed at new therapies for L-DOPA-induced dyskinesias
8. Studies aimed at the development of gene therapy for continuous local delivery of L-DOPA.

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

The focus of my postdoctoral work was to sort out the anatomical organization of the dopamine and noradrenaline neuron systems in the brain using the 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.

A second line of studies has been focused on the characterisation and standardisation of the 6-OHDA lesion models in rats and mice, which has been used in our regeneration and neuroprotection studies. Over the last decade my lab has pioneered the development of the a-synuclein overexpression model of PD, using AAV vector technology.

a. Anatomy


**b. The 6-OHDA lesion model**


**c. The AAV-a-synuclein model**

1. Kirik D, Rosenblad C, Burger C, Lundberg C, Johansen TE, Muzychka N, Mandel RJ, Björklund A. Parkinson-like neurodegeneration induced by targeted overexpression of alpha-synuclein in the nigrostriatal...
During the 1970ies I of Neurosurgery at Karolinska and ophthalmology at Göteborg University, now diseased).

**2. Studies of axonal regeneration and reconstruction of neural circuitry by neural transplants in brain and spinal cord**

My interest in neuronal regeneration in the CNS was triggered by the American neurologist Robert Katzman. In 1969-70 he spent a sabbatical in Bengt Falck’s lab at the Department of Histology in Lund. Using the Falck-Hillarp histofluorescence technique Bob made the serendipitous observation that the nigral dopamine neurons exhibited a surprisingly abundant and extensive axonal sprouting after axotomy. He asked me to join in the study of this phenomenon, which led me in onto an exciting series of studies on axonal regeneration of axotomised monoamine neurons in the brain and spinal cord, performed in collaboration with a gifted MD/PhD student, Ulf Stenevi (later Professor of ophthalmology at Göteborg University), and a young neurosurgeon, Niels Svendsgaard (later Professor of Neurosurgery at Karolinska Hospital in Stockholm, now diseased).

During the 1970ies I and Ulf 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 line of research was further developed in collaboration with a leading neurophysiologists, Menahem Segal, in Israel, and with Rusty Gage when he worked as a postdoc in the lab.

Our studies demonstrated a remarkable capacity of the central serotonergic, noradrenergic and cholinergic systems to regenerate, re-grow of long distances, and re-innervate previously denervated targets in the adult rat brain and spinal cord. In further studies using transecting lesions of the septo-hippocampal cholinergic pathway we showed for the first time the possibility to use intracerebral implants to achieve effective, functional and anatomical accurate regeneration of a transected pathway in the brain.

16. Gage, F.H., Björklund, A., Stenevi, U.: Local regulation of compensatory noradrenergic hyperactivity in the

3. Development of dopamine cell replacement therapy in Parkinson’s disease

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 an interesting 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.

\textit{a. Dopamine neuron transplants in animal models of Parkinson's disease}


33. Cenci, M.A., Campbell, K., Björklund, A. Neuropeptide-mRNA expression in the 6-hydroxy-dopamine-


### b. Development of cell replacement therapy in patients with Parkinson’s disease


4. Neural grafting in animal models of Huntington’s disease


5. Transplantation of cholinergic neurons in animal models of cognitive decline


6. 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 characterised 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.

a. NGF


b. GDNF and Neurturin


20. Vaudano E., Rosenblad C., and Björklund A. (2001) Injury induced c-Jun expression and phosphorylation in the dopaminergic nigral neurons of the rat: correlation with neuronal death and modulation by glial-cell-line-


7. 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 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, an effect that we have explored, together with our partners in London, also in patents affected by graft-induced dyskinesia.


8. 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 purified 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.