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Annotated list of publications

My complete list of publications contains about 650 publications with *h*-index: 150 (Scopus) and 172 (Google Scholar). Total citations: 71074 (Scopus), 90919 (Google Scholar), as of October 2023. See: https://scholar.google.com/citations?user=W8CXjsMAAAAJ&hl=en&oi=ao

This list contains a selection of my publised papers, original articles and reviews, organised under 8 main themes:

1. **Studies related to the anatomy of the dopamine neuron systems**
2. **Development and use of rodent models of Parkinson´s disease**
   2a: *The 6-OHDA lesion model of Parkinson´s disease*
   2b: *Development and use of serotonin neurotoxins*
   2c: *The AAV-a-synuclein overexpression model and its use in studies of PD pathogenesis*
3. **Studies of axonal regeneration and reconstruction of neural circuitry by neural transplants in brain and spinal cord**
4. **Development of dopamine cell replacement therapy for Parkinson´s disease**
   4a. *Dopamine neuron transplants in rodent models of Parkinson´s disease*
   4b. *Development of human ES cell-derived dopamine neurons for clinical use*
   4c. *Dopamine cell replacement in patients with Parkinson´s disease*
5. **Neural grafting in animal models of Huntington´s disease and cognitive decline**
   5a. Neural grafting in animal models of Huntington´s disease
   5b. Transplantation of cholinergic neurons in animal models of cognitive decline
6. **Studies on the neuroprotective effects of NGF, GDNF and Neurturin in the brain**
   6a. Nerve Growth Factor (NGF)
   6b. GDNF and Neurturin
7. **Studies aimed at new therapies for L-DOPA-induced dyskinesia**
8. **Studies aimed at the development of gene therapy for local delivery of L-DOPA**

1. Studies related to the anatomy of the dopamine neuron systems

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. These studies spanned over an extended decade and were finally summed up in two highly cited reviews, one in Handbook of Chemical Neuroanatomy, published in 1984, that has received over 1500 citations over the years, and one in volume 4 of Handbook of Physiology in 1986. Still relevant as entries to, and a comprehensive summary of, the classic work in this field.

1. Lindvall, O., Björklund, A.: The glyoxylic acid fluorescence histochemical method: a detailed account of the methodology for the visualization of central catecholamine neurons. *Histochemistry* 39:97-127, 1974.
2. Lindvall, O., Björklund, A.: The organization of the ascending catecholamine neuron systems in the rat brain as revealed by the glyoxylic acid fluorescence method. *Acta Physiol. Scand*. Suppl 412, 1974.
3. Lindvall, O., Björklund, A., Moore, U., Stenevi, U.: Mesencephalic dopamine neurons projecting to neocortex. *Brain Research.* 81:325-331, 1974.
4. Björklund, A., Lindvall, O.: Dopamine in dendrites of substantia nigra neurons: suggestions for a role in dendritic terminals. *Brain Research.* 83:531-537, 1975.
5. Lindvall, O., Björklund, A., Divac, I.: Organization of catecholamine neurons projecting to the frontal cortex in the rat. *Brain Research* 142:1-24, 1978.
6. Björklund, A., Divac, I., Lindvall, O.: Regional distribution of catecholamines in monkey cerebral cortex, evidence for a dopaminergic innervation of the primate prefrontal cortex. *Neurosci. Lett*. 7:115-119, 1978
7. Lindvall, O., Björklund, A.: Organization of catecholamine neurons in the rat central nervous system. In: Handbook of Psychopharmacology. L.L. Iversen, S.D. Iversen, S.H. Snyder (Eds), Plenum Press, 1978, Vol. 9, pp. 139-231.
8. Lindvall, O., Björklund, A.: Dopaminengic innervation of the globus pallidus by collaterals from the nigrostriatal pathway. *Brain Research* 172:169-173, 1979.
9. Björklund, A., Skagerberg, G.: Evidence for a major spinal cord projection from the diencephalic A11 dopamine cell group in the rat. *Brain Research* 177:170-175, 1979.
10. Lindvall, O., Björklund, A., Skagerberg, G.: Selective histochemical demonstration of dopamine terminal systems in rat di- and telencephalon: new evidence for dopaminergic innervation of hypothalamic neurosecretory nuclei. *Brain Research* 306:19-30, 1984.
11. Skagerberg, G., Lindvall, O., Björklund, A.: Origin, course and termination of the mesohabenular dopamine pathway in the rat. *Brain Research* 307:99-108, 1984.
12. Björklund, A., Lindvall, O.: Dopamine-containing systems in the CNS. In: Handbook of Chemical Neuroanatomy, Vol. 2. Elsevier Science Publ. B.V., pp. 55-122, 1984.
13. Björklund, A., Lindvall, O.: Catecholaminergic brain stem regulatory systems. In: Handbook of Physiology - The Nervous System, Vol.4: Intrinsic regulatory systems of the brain, pp.155-235,1986.
14. Björklund A, Dunnett SB.: Dopamine neuron systems in the brain: an update. *Trends Neurosci.* 30(5):194-202, 2007.

2. Development and use of rodent models of Parkinson´s disease

2a. *Characterisation and standardisation of the 6-OHDA lesion model*

The 6-OHDA lesion model, developed in the 1960ies by our colleagues at the Karolinska in Stockholm, became an essential experimental tool in our regeneration and neuroprotection studies studies. An important part of this work was focused on the characterisation and standardisation of the 6-OHDA lesions for long-term functional studies in rats and mice.

1. Brundin, P., Isacson, O., Gage, F.H., Prochiantz, A., Björklund, A.: The rotating 6-hydroxydopamine lesioned mouse as a model for assessing functional effects of neuronal grafting. *Brain Research* 366:346-349, 1986.
2. Cenci, M.A., Kalén, P., Mandel, R.J., Björklund, A.: Regional differences in the regulation of dopamine and noradrenaline release in medial frontal cortex, nucleus accumbens and caudate-putamen: a microdialysis study in the rat. *Brain Research*, 581:217-228, 1992.
3. 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
4. Cenci, M.A., Björklund, A. Transection of corticostriatal afferents reduces amphetamine- and apomorphine-induced striatal Fos expression and turning behavior in unilaterally 6-hydroxydopamine-lesioned rats. *Eur.J.Neurosci.* 5:1062-1070, 1993.
5. 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.
6. Lee, C.S., Sauer, H., Björklund, A. Dopaminergic neuronal degeneration and motor impairments following axon terminal lesion by intrastriatal 6-hydroxydopamine in the rat. *Neuroscience* 72: 641—653, 1996.
7. Kirik, D., Rosenblad, C., Björklund A. Characterization of behavioral and neurodegenerative changes following partial lesions of the nigrostriatal dopamine system induced by intrastriatal 6-hydroxydopamine in the rat. *Exp Neurol.* 152: 259—277, 1998.
8. Cenci, M.A., Lee, C.S., Björklund, A. L-dopa-induced dyskinesia in the rat is associated with striatal overexpression of prodynorphin- and glutamic adic decarboxylase mRNA. *Eur J Neurosci.* Vol. 10: 2694-2706, 1998.
9. Winkler C, Kirik D, Björklund A, Cenci MA. L-DOPA induced dyskinesia in the intrastriatal model of Parkinson's disease: Relation to motor and cellular parameters of nigrostriatal function *Neurobiol. Dis,* 10:165-86, 2002.
10. Carta M, Carlsson T, Kirik D, Bjorklund A**.** Dopamine released from 5-HT terminals is the cause of L-DOPA-induced dyskinesias in parkinsonian rats. *Brain,* 130: 1819-1833, 2007**.**
11. Grealish S, Mattsson B, Draxler P, Björklund A Characterisation of behavioural and neurodegenerative changes induced by intranigral 6-hydroxydopamine lesions in a mouse model of Parkinson's disease. *Eur. J. Neuroscience* **31**, 2266-2278, 2010.
12. Tronci E, Shin E, Bjorklund A, Carta M. Amphetamine-induced rotation and l-DOPA-induced dyskinesia in the rat 6-OHDA model: A correlation study. *Neuroscience Research* **73**, 168-172, 2012.
13. Björklund A, Dunnett SB. The Amphetamine Induced Rotation Test: A Re-Assessment of Its Use as a Tool to Monitor Motor Impairment and Functional Recovery in Rodent Models of Parkinson's Disease. *Journal of Parkinson's Disease* 2019 9:17–29, 2019.

2b. *Development and use of serotonin neurotoxins*

The selectivity of 6-OHDA for catecholamine neurons is due to the fact that it is effectively taken up by the membrane transporter leading to an accumulation of the drug selectively within dopamine and noradrenaline neurons. This mechanism suggested that similar neurotoxins could be developed for

lesioning of the serotonin neurons in the brain. This idea was picked up be a young anatomist in Hamburg, Hans-Georg Baumgarten. With the help of a chemist in Munich, H.G. Schlossberger, he arranged for the synthesis of number of hydroxylated derivatives of serotonin (5-hydroxytryptamine), including 5,6-dihydroxy-tryptamine (5,6-DHT) and 5,7-dihydroxy-tryptamine (5,7-DHT), which we explored together in a highly productive collaboration. 5,7-DHT, administered intraventricularly or directly into the brain parenchyma, has remained a standard experimental tool for selective damage of serotonin neurons.

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2. Baumgarten, H.G., Björklund, A., Holstein, A.F., Nobin, A.: Chemical degeneration of indolamine axons in rat brain by 5,6-dihydroxytryptamine. An ultrastructural study. *Z. Zellforsch*. 129:256-271, 1972
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7. Björklund, A., Baumgarten, H.-G., Rensch, A.: 5,7-Dihydroxytryptamine: improvement of its selectivity for serotonin neurons in the CNS by pretreatment with desipramine. *J. Neurochem.* 24:833-835, 1975.
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2c. *The AAV-a-synuclein overexpression model and its use in studies of PD pathogenesis*

It was Ron Mandel who introduced the AAV vector technology in our lab. Prior to his move to University of Florida in 1999, Ron Mandel spent a 6 month sabbatical in Lund. He brought with him AAV vectors expressing TH, GCH-1, GDNF and GFP, and he helped us to obtain AAV vectors expression WT and A53T-mutated alpha-synuclein. As a result we became one of the pioneer laboratories to introduce viral vectors as a tool to overexpress alpha-synuclein in the nigrostriatal system in both rats and marmosets. Soon thereafter we set up our own AAV vector production. Since then the AAV-a-synuclein model has remained a standard tool in our experimental work.

1. Kirik D, Rosenblad C, Burger C, Lundberg C, Johansen TE, Muzyczka N, Mandel RJ, Björklund A. Parkinson-like neurodegeneration induced by targeted overexpression of alpha-synuclein in the nigrostriatal system. *J Neurosci.* 22(7):2780-91, 2002.
2. Kirik, D, Annett, LE, Burger, C, Muzyczka, N, Mandel, RJ, Björklund A. Nigrostriatal a-synucleinopathy induced

by viral vector-mediated overexpression of human a-synuclein: A new primate model of Parkinson's disease. *Proc Natl Acad Sci U S A.* 100:2884-2889, 2003.

3. Ulusoy A, Decressac M, Kirik D, Björklund A**.** Viral vector mediated expression of a-synuclein as a progressive model of Parkinson´s Diasese, *Prog Brain Res,* 184:89-111, 2010.
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6. Lundblad M, Decressac M, Mattsson B, Björklund A. Impaired neurotransmission caused by overexpression of α-synuclein in nigral dopamine neurons. *Proc Natl Acad Sci*.109(9):3213-9, 2012.
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15. Tozzi A, de Iure A, Bagetta V, Tantucci M, Durante V, Quiroga-Varela A, Costa C, Di Filippo M, Ghiglieri V, Latagliata EC, Wegrzynowicz M, Decressac M, Giampà C, Dalley JW, Xia J, Gardoni F, Mellone M, El-Agnaf OM, Ardah MT, Puglisi-Allegra S, Björklund A, Spillantini MG, Picconi B, Calabresi P. Alpha-Synuclein Produces Early Behavioral Alterations via Striatal Cholinergic Synaptic Dysfunction by Interacting With GluN2D N-Methyl-D-Aspartate Receptor Subunit. *Biol Psychiatry.* 79(5):402-14, 2016.
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17. Wan OW, Shin E, Mattsson B, Caudal D, Svenningsson P, Björklund A. α-Synuclein induced toxicity in brain stem serotonin neurons mediated by an AAV vector driven by the tryptophan hydroxylase promoter *Sci. Rep*. May 23, 2016.
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19. Faustini G, Longhena F, Varanita T, Bubacco L, Pizzi M, Missale C, Benfenati F, Björklund A, Spano P, Bellucci A. Synapsin III deficiency hampers α-synuclein aggregation, striatal synaptic damage and nigral cell loss in an AAV-based mouse model of Parkinson's disease. *Acta Neuropathol*. 2018 Jul 25.
20. Hoban DB, Shrigley S, Mattsson B, Breger LS, Jarl U, Cardoso T, Nelander Wahlestedt J, Luk KC, Björklund A, Parmar M. Impact of α-synuclein pathology on transplanted hESC-derived dopaminergic neurons in a humanized α-synuclein rat model of PD *Proc Natl Acad Sci, USA,* 2020 Jun 30;117(26):15209-15220.
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22. **Björklund, A,** Nilsson F, Mattsson B, Hoban D, Parmar M. A Combined α-Synuclein/Fibril (SynFib) Model of Parkinson-Like Synucleinopathy Targeting the Nigrostriatal Dopamine System. *Journal of Parkinson's Disease*, 12: 2307 – 2320, 2022

3. 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 Svendgaard (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 reserach 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-innervete 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.

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2. Björklund, A., Stenevi, U.: Growth of central catecholamine neurons into smooth muscle grafts in the rat mesencephalon. *Brain Res*. 31:1-20, 1971.
3. Björklund, A., Nobin, A., Stenevi, U.: Regeneration of central serotonin neurons after axonal degeneration induced by 5,6-dihydroxytryptamine. *Brain Res*. 50:214-220, 1973.
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14. Gage, F.H., Björklund, A., Stenevi, U.: Reinnervation of the partially deafferented hippippocmpus by compensatory collateral sprouting from spared cholinergic and noradrenergic afferents. *Brain Res.* 268:27-37, 1983.

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4. Development of dopamine cell replacement therapy for Parkinson´s disease

In 1980 Steve Dunnett (then 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. Our pioneering studies of the use of fetal midbrain dopamine neurons for cell replacement in animal models of Parkinson´s disease 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. Since 2011 the focus of our efforts have been on the development of hESC-derived dopamine neurons for use in patients, a work that has been led by my former student and collaborator Malin Parmar.

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4b. Development of human ES cell-derived dopamine neurons for clinical use

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5. Cell transplantation for reconstruction of neural circuitry in animal models of Huntington´s disease and cognitive decline

Apart from its potential clinical usefulness for dopamine neuron replacement in Parkinson´s disease, 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 striatal neurons in animals with excitotoxic lesions of the striatum, akin to the pathology seen in patients with Huntington´s disease, and transplants of fetal cholinergic neuroblasts in hippocampus and cortex in animal models of cognitive decline, have been particularly interesting in this regard. These pioneering studies, which spanned over two decades, have given compelling evidence for cell-based circuitry repair and provided a background for the current efforts to use stem cell-derived neuroblasts and cellular re-programming forreconstruction of damaged brain and spinal cord circuitry.

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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. 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 in clinical trials.

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7. Studies aimed at the development of new therapies for L-DOPA-induced dyskinesia

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 the 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.

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8. Studies aimed at 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 embarked on a program aimed to move this local DOPA delivery approach toward clinical trials in PD patients. Supportive pre-clinical data, obtained in the monkey MPTP model, was published in Brain in 2019.*

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