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Annotated list of publications

My complete list of publications contains about 675 papers, with *h*-index: 145 (Scopus) 165 (Google Scholar); total citations: 63875 (Scopus) 83260 (Google Scholar), as of March 2020, using "Bjorklund A" and "Lund" as search items.

This list is a selection of my publised 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 and animal models of cognitive decline**
5. **Studies on the neuroprotective effects of NGF, GDNF and Neurturin in the brain**
6. **Studies aimed at new therapies for L-DOPA-induced dyskinesias**
7. **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 a the characterisation and standardisation of the 6-OHDA lesion models in rats and mice, which has been used in our regeneration and neuroprotection studies. Ovre the last decade my lab has pioneered the development of the a-synuclein overexpression model of PD, using AAV vector technology.

1a. Anatomy

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.
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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. 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.
6. Lindvall, O., Björklund, A.: Dopaminengic innervation of the globus pallidus by collaterals from the nigrostriatal pathway. *Brain Research* 172:169-173, 1979.
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8. 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.
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.
10. 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.
11. 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.
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.
13. Björklund A, Dunnett SB.: Dopamine neuron systems in the brain: an update. *Trends Neurosci*. 30(5):194-202, 2007.

1b. The 6-OHDA lesion model

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2. 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.
3. 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.
4. 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.
5. 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.
6. **Björklund A**, Dunnett SB. (2019) 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.

1c. Studies on the pathogenesis of PD using the AAV-a-synuclein model

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.

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4. 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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8. Decressac M, Mattsson B, Björklund A. Comparison of the behavioural and histological characteristics of the 6-OHDA and α-synuclein rat models of Parkinson's disease. *Exp Neurol*. May;235(1):306-15, 2012.

9. Decressac M, Kadkhodaei B, Mattsson B, Laguna A, Perlmann T, Björklund A. α-Synuclein-Induced Down-Regulation of Nurr1 Disrupts GDNF Signaling in Nigral Dopamine Neurons. *Science Transl Med*. Dec 5;4(163): 163ra156, 2012.

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11. Decressac M, Mattsson B, Weikop P, Lundblad M, Jakobsson J, and Björklund A. TFEB-mediated autophagy rescues midbrain dopamine neurons from α-synuclein toxicity. *Proc Natl Acad Sci, USA,* May 7;110(19):E1817-26. doi: 10.1073, 2013.

12. Kadkhodaei B, Alvarsson A, Schintu N, Ramsköld D, Volakakis N, Joodmardi E, Yoshitake T, Kehr J, Decressac M, **Björklund A**, Sandberg R, Svenningsson P, Perlmann T. (2013) Transcription factor Nurr1 maintains fiber integrity and nuclear-encoded mitochondrial gene expression in dopamine neurons. *Proc Natl Acad Sci U S A*. 2013 Feb 5;110(6):2360-5. doi: 10.1073/pnas.1221077110.

13. Decressac M, Volakakis N, **Björklund A**, Perlmann T. (2013) NURR1 in Parkinson disease--from pathogenesis to therapeutic potential. Nat Rev Neurol. 2013 Nov;9(11):629-36.

14. Caudal D, Alvarsson A, **Björklund A**, Svenningsson P (2015) Depressive-like phenotype induced by AAV-mediated overexpression of human α-synuclein in midbrain dopaminergic neurons *Experimental Neurology* 273, 243-252

15. Volakakis N, Tiklova K, Decressac M, Papathanou M, Mattsson B, Gillberg L, Nobre A, **Björklund A**, Perlmann T. (2015) Nurr1 and Retinoid X Receptor Ligands Stimulate Ret Signaling in Dopamine Neurons and Can Alleviate α-Synuclein Disrupted Gene Expression. *J Neurosci*. 35(42):14370-85.

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17. Alvarsson A, Caudal D, **Björklund A**, Svenningsson P (2016) Emotional memory impairments induced by AAV-

mediated overexpression of human α-synuclein in dopaminergic neurons of the ventral tegmental area *Behavioural Brain Research* 296, 129-133

18. Wan OW, Shin E, Mattsson B, Caudal D, Svenningsson P, **Björklund A** (2016) α-Synuclein induced toxicity in brain stem serotonin neurons mediated by an AAV vector driven by the tryptophan hydroxylase promoter Sci Rep. May 23.
19. Thakur P, Breger LS, Lundblad M, Wan OW, Mattsson B, Luk K, Lee VMY, Trojanowski JQ, **Björklund A** (2017) Modeling Parkinson's disease pathology by combination of fibril seeds and α-synuclein overexpression in the rat brain. *Proc Natl Acad Sci U S A*. 2017, Sep 26;114(39):E8284-E8293.
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21. 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

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 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.

1. Katzman, R., Björklund, A., Owman Ch., Stenevi, U., West, K.A. Evidence for regenerative axon sprouting of central catecholamine neurons in the rat mesencephalon following electrolytic lesions. *Brain Res*. 25:579-596, 1971.
2. Björklund, A., Stenevi, U.: Growth of central catecholamine neurons into smooth muscle grafts in the rat mesencephalon. *Brain Res*. 31:1-20, 1971.
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6. Svendgaard, N.-Aa., Björklund, A., Stenevi, U.: Regenerative properties of central monoamine neurons as revealed in studies using iris transplants as targets. *Adv. Anat. Embryol. Cell Biol*. 51:1-77, 1975.

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18. Stenevi, U., Björklund, A., Svendgaard, N.-Aa.: Transplantion of central and peripheral monoamine neurons to the adult rat brain: techniques and conditions for survival. *Brain Research* 114:1-20, 1976.

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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. 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 myformer student and collaborator Malin Parmar.

3a. Dopamine neuron transplants in animal models of Parkinson´s disease

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15. Dunnett, S.B., Björklund, A., Schmidt, R.H., Stenevi, U., Iversen, S.D.: Intracerebral grafting of neuronal cell suspensions. IV. Behavioural recovery in rats with unilateral implants of nigral cell suspensions in different forebrain sites. Acta Physiol.Scand., Suppl. 522, 29-38, 1983.
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4. 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, 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 have provided a background for current efforts to use stem cell-derived neuroblasts and cellular re-programming for brian and spinal cord circuitry repair, and they have also provided compelling evidence for cell-based circuitry repair.

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4b Transplantation of cholinergic neurons in animal models of cognitive decline

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5. 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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5b. GDNF and Neurturin

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6. 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 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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7. 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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