Parkinson’s Disease Stem Cell Therapy – A Creative Environment

Replacing cells, tissues or entire organs by transplantation are well-established treatments for several live-threatening medical conditions. To replace brain cells via transplantation is a more difficult thought and forms a challenge not only to scientists, but also clinicians and ethicists, as well as to all of society.

Parkinson’s disease (PD) is an example that cell replacement in the brain is possible. This is a chronic neurodegenerative disorder where mainly a well-defined population of cells, dopaminergic (DA) neurons is lost. As a result, patients suffer from different motor and non-motor symptoms. As the disease progresses and DA neurons continue to be lost, pharmacological treatments become less effective and severe side effects arise. Currently, there is no treatment available in the clinic to stop the disease progress or reverse the symptoms. PD creates a large health burden for patients, their family and society.

Therefore, there is a great need to develop new, innovative and more effective therapies such as cell transplantation strategies to replace lost DA neurons by new, functional cells. Studies in PD animal models have shown that neuronal replacement and partial reconstruction of neuronal brain circuitries is possible, and pioneering fetal cell transplantation trials in PD patients have been performed in Lund and elsewhere (Lindvall et al., 1990). Although this approach in the clinic has shown mixed results (Brundin et al., 2010, Paul, 2006), there is clear proof of principle that it can be extremely effective in some patients (Politis et al., 2010). Despite these encouraging results, work with human fetal tissue presents a number of ethical and logistical problems and does not represent a realistic therapeutic option in the future.

AIM & NOVELTY

We will establish a translational cell therapy platform for PD. This interdisciplinary and creative environment will address pre-clinical, clinical and ethical issues related to the different stages of translation using renewable and novel cell sources for cell replacement therapy.

Outline: To ensure further progress and clinical translation of cell therapy for PD, new bankable cell sources need to be identified and developed according to clinical safety, efficacy criteria and national and EU regulations. All our team members have a special interest and experience in PD and/or stem cells, and several members of our team are involved in a clinical multicenter trial using fetal cells for PD (EU funded, TransEuro). Our ideas integrate basic science aimed at developing the novel cell sources for clinical use, pre-clinical validation and up-scaling as well as clinical translation including evaluating health science issues and several ethical issues of CNS stem cell therapy.

NOVEL CELL TYPES

Stem cells are currently the most promising alternative to fetal cell therapy for PD. We address two cell types with the potential of entering clinical trials in the foreseeable future:

1. Human embryonic stem cells (hESC) are pluripotent stem cells that can be differentiated into DA neurons (Kirkeby et al., 2012). The advantage is that ES cells proliferate indefinitely and can thus be expanded in large bankable quantities. The challenge is that it has proven difficult to fully control their proliferation, stability, and differentiation. Human ESC are prone to forming tumors after grafting (Pera, 2011) and therefore associated with serious safety issues hampering their translation into the clinic (Lindvall, 2012, Lindvall, 2012). Proposed approach: We will optimize the current hESC protocols and carry out systematic long-term in vivo studies to prove efficacy and safety of the generated cell preparations. The composition of the cell preparations will be standardized and characterized with respect to phenotype identity of the DA progenitors and to make sure that they do not contain any proliferative or tumorigenic elements. If so, techniques have to be developed to remove these contaminants.

2. Induced DA neurons (iN-DA cells). Recent findings from Parmar’s group and others show
that human fibroblasts can be directly programmed into functional DA neurons without going via a proliferative stem cell intermediate (Caiazzo et al., 2011); (Pfisterer et al., 2011). These findings open up the possibility of generating subtype-specific neurons of human origin for clinical use from patients themselves or from HLA-matched donors. The challenge: The current protocols are not acceptable from a clinical perspective as they use doxycycline-regulated lentiviral vectors with a risk to affect endogenous gene expression. This can lead to transformation events including uncontrolled proliferation. The doxycycline-regulated systems contain elements of bacterial origin that may cause host immune reactions. In addition, incomplete reprogramming events can result in partially reprogrammed “hybrid” cells. Proposed approach: To circumvent these issues, we will develop second generation iN cells using a non-integrating, self-regulating system that efficiently converts the fibroblasts to neurons and then shuts off the reprogramming factors individually in each cell. We also evaluate the use of the nonpathogenic Sendai viruses for delivery of reprogramming factors (already used in clinical trials).

IN VIVO SAFETY AND EFFICACY
Both cell types (hESC and iN-Da cells) have to be adapted to GMP2 certified protocols in collaboration with clinicians. We will test their safety (assessment of tumor formation), authenticity (marker expression), innervation capacity (using GFP-labeled cells), neurotransmitter release (combined amperometric and optogenetic approach) and functionality (several behavioral tests) in relevant animal models in comparison to fetal cells. Combined, these results will provide a safety assessment and evaluation of the therapeutic potential that will serve as a check point for clinical use, form the base to devise the surgical procedure for graft placement and indicate patient selection criteria.

UPSCALING AND GMP PRODUCTION
The next step is focused on the translation of the optimized and validated cell derivation protocol to GMP2-certified cell preparations and includes up-scaling of the production under GMP2 conditions. We will extrapolate cell numbers needed for clinical effect based on animal data and clinical experience from fetal grafts. Which of the two alternatives – hES or iN-DA cells – we will select for this work will depend on the outcome of the previous steps.

DESIGN OF CLINICAL STUDY PROTOCOL
We will create the first road map on how to develop novel cell types, in particular hESC and iN-DA cells for clinical use. The entire team will meet for extended discussions twice a year and external experts will be invited when required. This will shape the work in this project from the start in order to guide the basic science and pre-clinical evaluation work such that issues critical for clinical application are adequately addressed at an early stage. Specifically, we will establish the safety and minimum efficacy requirements for these cell types to be able to enter phase 1 studies. We will identify national and EU regulatory requirements regarding stem cell treatment and preparation etc. to bring this cell product to clinical testing according to GLP3, GMP2 and GCP3 requirements. Furthermore, we will define the best graft placement and procedure related surgical protocols for optimal graft dispersal and innervation (surgical technique, placement, number of tracts). There are unique medical risks connected with stem cell therapies. To design a clinical trial suitable for testing safety and tolerability of novel stem cell therapies of the brain and adequate patient information is a major challenge. Many of our previous experience with clinical trials will have to be adapted to a new stem cell product. Our team of pre-clinical, clinical and health scientists and ethicists will together prepare and disseminate recommendations on patient selection, patient evaluation with respect to safety and

1 GLP=Good laboratory practice; 2 GMP=Good medical practice; 3 GCP=Good clinical practice
primary and secondary outcome parameters to measure product efficacy in future clinical trials.

ETHICAL ASPECTS
We will focus on identifying those ethical concerns that are specific to the novel stem cell types in question and connected with the various stages of translation. This includes cell type specific issues (genetic modification, tumor risk etc as outlined above), cell processing, cell delivery method. Stem cell therapies are much observed by the media and this may create unrealistic expectations and therapeutic misconceptions. We investigate societal and patient perception of the specific cell type, the risk, and a phase-1 trial design and compare patient preferences versus the one of familial caregivers in an empirical study. These preferences are dependent on the information about the use of a certain cell type for cell therapy being received and understood. The informed consent procedure will therefore play a crucial role for the first in-humans trials, which this project will pave the way for. We will try out different sets of information, investigate how much of this information is understood and misunderstood, what needs to be added to provide correct and not misleading information about potential benefit and potential risks of harm. The guidelines and ethical issues developed in this part will serve as the foundation for the first-in-human trial using the respective novel stem cell as a cell replacement therapy for PD.

TREATMENT EFFICACY FROM A PATIENT PERSPECTIVE
We need to identify outcome measures that are meaningful not only to researchers and clinicians, but also to patients and caregivers. We will therefore work in partnership with end-users in order to ensure that our key outcomes are relevant out of a patient perspective. As a mean, we will early on establish a “user board”. An unmet challenge is also to explicitly identify/develop tools that mimic real life challenges (e.g. outdoor mobility) in standardized settings to certify that potential treatment effects translate into “real-world” settings. Pilot tests are then needed well advance of a clinical trial in order to determine the acceptability, feasibility and reliability of such assessments. To in depth investigate the patient perspective, qualitative methods (e.g. interviews) will be used as a complement to quantitative methods that include both objective measures and patient-reported outcomes measures. Taken together, our measurements will tap the complexity of a health condition such as PD by covering both functions, activities of importance in daily life and participation, i.e. “involvement in life situations” (International Classification of Functioning, Disability and Health, ICF, WHO, 2001).

REFERENCES
Lindvall O. Why is it taking so long to develop clinically competitive stem cell therapies for CNS disorders? Cell stem cell. 2012 Jun 14;10(6).
TEAM DESCRIPTION

We will establish a creative environment to bring CNS stem cell therapy for PD to the clinic. We join several enthusiastic, open-minded scientists from different areas in collaboration with other scientific centers worldwide in order to explore new avenues of translational research together in direct interaction with each other.

Vision statement: As a mean to reach our goals, we will establish a creative environment that is inspired by the work of Prof. Nils-Eric Sahlin (Sahlin, 2001). Our platform will rest upon the nine “ingredients” identified as important to foster a creative climate: generosity; a sense of community; expertise; diversity; trust and tolerance; equality; curiosity; freedom of spirit and being a “small scale” environment.

Expertise: The members of our multidisciplinary team are chosen based on the current needs that the clinical translation of CNS stem cell therapy for PD is facing. The team consists of basic scientists, translational experts, a medical ethicist, neurologist, neurosurgeon and a health scientist (see CVs for details). Importantly, all members of the team are early in their career or have only recently established their own research groups. The whole team will work together on all aspects of the project already from the beginning. This is to ensure the necessary critical dialogue and two-way flow between the clinic and the laboratory. By doing so, we will certify that basic science and pre-clinical evaluation work adequately address issues critical for clinical application. This is essential in order to streamline the translation of CNS stem cell therapy towards clinical applications.

All members joined here are experts in PD and/or cell therapies and the clinicians are involved in several phase 1 studies exploring novel therapies for PD.

Experience: Lund has a longstanding interest and world leading expertise in cell therapy for PD. Additionally, several members of our team (MP, GP, HB) are currently active in an EU funded multi-center clinical trial using fetal tissue for transplantation in patients with PD (www.transeuro.org.uk), as well as in another EU consortium (MP, KH) aiming at developing stem cell therapy for neurodegenerative diseases (www.neurostemcell.org). We are in an optimal position to perform both the basic and translational science as well as the pre-clinical evaluation of iN-DA and hESC. Although dealing with an entirely new technique and cell source, the current project will greatly benefit from the knowledge within the above mentioned EU funded programs.

Successful funding: In addition, several team members (MP, GP, HB, JJ, KH) have recently been successful in obtaining one of the VR grants for “Future therapies” to translate iN-DA cells to the clinic (K2012-99X-22324-01-5). This grant acknowledges that our work is highly relevant, feasible and we form a team of experts. It also proves that our team is able to obtain funding for the proposed research. Thus, we have an excellent starting position for this creative environment.

Individual profile and task within project

A: Malin Parmar is responsible for the pre-clinical development of the novel cell types (iN-DA, hESC) in vitro and in vivo. She is a specialist in neurobiology and expert in reprogramming of human fibroblasts into dopamine neurons (Pfisterer et al., 2011). She pioneered the direct conversion of human fibroblasts into subtype specific neurons. Her group has published several protocols on hES cells (Kirkeby et al., 2012, Kirkeby et al., 2012). Malin Parmar is the lead scientist for tissue collection and standardization of dissection of human fetal brain for clinical use in the TransEuro trial; and scientist and training/networking director of Neurostemcell, an EU funded consortium for development of stem cell therapy for PD and Huntington’s disease. Malin Parmar has her own research group “Developmental neurobiology” at EMV, LU since 2009.
B. Johan Jakobsson is responsible for developing a clinically applicable vector technology for iN cells using self-regulated expression strategies and non-integrating delivery systems. Johan Jakobsson is an expert on viral vector-technology and one of his main interests is the development and refinement of viral vectors. His group has previously developed vectors that regulate gene expression based on the endogenous microRNA-machinery (Akerblom et al., 2012, Sachdeva et al., 2010). In this project, he will use state-of-the art vector technology to generate safe, clinically relevant vector constructs capable of reprogramming fibroblast into neurons. He leads his own research group research group “Molecular Neurogenetics” at EMV, LU since 2009.

C. Gesine Paul is responsible for the clinical translation of the stem cell types with regard to safety and efficacy requirements in cell development from a clinical point of view. She is responsible for the design of the clinical study protocol including the patient information. Gesine Paul is a specialist in neurology at SUS-Lund and specializing in movement disorder patients, especially patients with PD. Gesine Paul is docent in Neuroscience and has a background in pre-clinical research, especially cell therapies for PD (Paul, 2006, Paul et al., 2001). She is experienced in clinical trials and is currently clinical investigator and national clinical coordinator in several translational clinical phase I/II trials on novel therapies for PD (sNNO031-001-3, www.Neuronova.com) and clinical investigator in TransEuro. She has the unique strength that she has during several years combined patient care, clinical research and preclinical research and thus can naturally serve as an interlink between preclinical research and its clinical implementation. She started her own research group “Translational Neurology” at IKVL in 2011. The fact that Gesine Paul has an understanding of pre-clinical neuroscience, works as a neurologist with PD patients and is participating/leading phase I clinical trials makes her an excellent coordinator for a translational program. Furthermore, she is experienced in team work, both in the clinic and the laboratory, has taught leadership and communication for medial students (T1) and attended leadership workshops. We therefore suggest Gesine Paul as coordinator for our creative environment.

D: Hjalmar Bjartmarz is responsible for the determination of the surgical requirements to be used in the clinical trial and actively involved in upscaling and the design of the clinical study protocol. Hjalmar Bjartmarz is a consultant Neurosurgeon and head of the Stereotactic and Functional Neurosurgery unit. He has a long experience of operating patients with Movement Disorders. He also participates in a multicenter study on icv administration of a growth factor in Parkinson patients (sNNO031), in TransEuro, the European multicenter consortium on transplantation of human fetal cell to Parkinson’s patients and is involved in the design of a Gen therapy trial.

E. Kristina Hug is responsible for leading the ethical issues connected with the different stages of translation. She has recently finished her PhD (June, 2012) at the Department of Medical Ethics, LU. Her thesis title was: “Building the Bridge from Bench to Bedside: Ethical Issues in Translational Stem Cell Research”. Kristina Hug is teaching biomedical research ethics at LU and has been working on EU-funded projects on “Ethical and societal aspects of Parkinson’s and Huntington’s diseases” (Neurostemcell) as well as on “Ethical and legal aspects of human embryonic stem cell research” (ESTOOLS and EuroStemCell).

F. Maria H Nilsson is responsible for leading the determination of outcome measures to be used in a clinical trial that tap different aspects of PD including body functions, activity and participation. She is also in lead of defining/developing tools that mimic real life challenges and that are relevant out of a patient perspective. Maria H Nilsson is an experienced health scientist that has been working with PD patients for many years. Maria’s PhD-thesis (defended in Nov. 2009) evaluated the effects of a neurosurgical treatment (Deep Brain Stimulation) in PD. Since then her research has involved she several methodological studies targeting outcome measures in PD. She has recently worked on prioritized aspects for outcome measurements
using concept mapping in PD patients (Sjodahl Hammarlund et al., 2012)

Associated panel of experts:
This project will build on our established collaborations. In addition, it will maintain close links to TransEuro (EU-FP7 funded program to take fetal dopaminergic cell transplants back to the clinic for PD patients) coordinated by Dr. R. Barker, Center for Brain Repair in Cambridge, as well as Neurostemcell, which aims to develop stem cell based therapies for clinical use in patients with PD and Huntington’s disease. Additionally, Prof. Olle Lindvall, Lund University and Prof. Håkan Widner, Skånes University Hospital, will act as advisors on translational issues of the program.

Prof. Nils Eric Sahlin has published work on creative environments. We have consulted his literature to establish criteria for our environment and we would like him to monitor the development of our collaborations with respect to whether we are succeeding to keep our environment creative.

Cited references:
Curriculum Vitae

Name: Malin Pernilla Parmar
Date of birth: 1973-12-11
Citizenship: Swedish
Telephone, work: + 46 46 222 0620
Mobile phone: + 46 709 823901
E-mail: Malin.Parmar@med.lu.se
Web: Developmental Neurobiology

Academic Degrees
2008 Associate Professor (Docent) in Neurobiology
Medical Faculty Lund University
2003 PhD in Medical Sciences, developmental biology.
Medical Faculty, Lund University. Degree awarded 2003-09-26.
1998 Bachelor of Science, Simon Fraser University, Canada

Current position
Associate Professor (Docent) and group leader at the Department of Experimental Medical Science: Wallenberg Neuroscience Centre and Lund Stem Cell Centre, Medical Faculty, Lund University

Previous Positions
2007-2012 Assistant Professor (Forskarassistent). Fully financed by the Swedish Research Council
Faculty of Medicine, Lund University, Sweden
2005-2006 Postdoc position, financed by Swedish Research Council
Faculty of Science, Institute of Stem Cell Research
Edinburgh University, Scotland, UK.
2003-2005 PostDoc Position
Faculty of Medicine, Lund University, Sweden
1999-2003 PhD Position, financed by National network in Neuroscience
Faculty of Medicine, Lund University, Sweden
1998-1999 Project Student, Terry Fox Laboratory, University of British Columbia, BC, Canada

Career breaks
Since my Phd was awarded I have had two careers breaks (total 488 days) for parental leave when my children were born (2004 and 2008)

Prizes and Awards
2012 ERC Starting Grant (€1 500 000)
2012 Invited speaker ISSCR 2013
2008 NeuroFortis Young Investigator Award (€12.500)
2004 Bente Rexed award for young researchers (€1000)
Other significant activities

2013-2015: Editorial Board for Experimental Neurology
2012: Appointed member of editorial board for Lund Medical Faculty Monthly, responsible for "Basic Science".
2009 – Currently: Training and Networking Director for 7th framework EU program NeuroStemcell: responsible for activities and training of PhD students and postdocs within the network, organizing scientific workshops and meeting as well as communication with other EU networks and public.
1999 – Currently: Involved in teaching (PBL tutor, lecturer, examination and course leader) at the medical, biomedical programs and PhD program at Lund University
2008 - Currently: Co-Director of Research School in Stem Cell Biology, LU
2009 – Currently: External expert and writer for the Swedish National Encyclopaedia (NE)
2010 – Currently: Member of International Policy group, Lund University

Tutoring experience
Main supervisor for 4 PhD-students and 5 postdocs (3 current, 2 completed)
Co-supervisor for 4 finished and 4 current PhD-students:
Main supervisor for 12 masters students

Selected invited Presentations
ISSCR, Boston, 2013
NeuroStemCell/TransEuro Clinical workshop, London, 2012
Université Libre de Bruxelles, Brussels, Belgium, 2012
International course in tissue transplant and cell therapy (TPM), Barcelona, Spain, 2012
Quebec symposium on neurodegenerative disease therapeutics, Canada, 2012
Postgraduate Neurosciences Meeting, Cambridge, UK, 2011
Plenary speaker at Nov2K, Karolinska Institute, Stockholm, Sweden, 2011
NECTAR annual meeting, Freiburg, Germany, 2010

Selected publications:
CURRICULUM VITAE

Name: Johan Einar Jakobsson
Personal number: 761013-4632
Place of birth: Halmstad, Sweden
Citizenship: Swedish
E-mail: johan.jakobsson@med.lu.se
Web: www.med.lu.se/expmed/molecular_neurogenetics

ACADEMIC DEGREES

2001 **Master of Science** in Molecular Biology, Lund University, Sweden
2005 **PhD** in Medical Sciences, Neurobiology, Medical Faculty, Lund University,
    *Title of thesis: “Development of Lentiviral Vectors for CNS gene therapy”*
    *awarded 23rd Sept. 2005 - Supervisor: Prof. Cecilia Lundberg*
2010 **Associate Professor** (Docent) in Neurobiology, Medical Faculty Lund University

CURRENT POSITION

Associate Professor (Docent) and group leader at the Department of Experimental Medical Sciences and
Lund Stem Cell Centre, Medical Faculty, Lund University

PREVIOUS POSITIONS

2008-2009 **PostDoc position financed by Hjärnfonden/Lund PostDoc program**
    Faculty of Medicine, Dept of Experimental Medical Research, Lund University, Sweden
2005-2008 **PostDoc Position financed by Swedish Resarch Council**
    School of Life Sciences, Global Health Institute
    EPFL, Lausanne, Switzerland
2001-2005 **PhD Position**
    Faculty of Medicine, Dept of Experimental Medical Research, Lund University, Sweden

CAREER BREAKS

Parental leave for Ingrid Jakobsson, May-Oct 2011

TUTORING EXPERIENCE

*Main supervisor for 3 current PhD-students*
- Rohit Sachdeva (registered 2009)
- Malin Åkerblom (registered 2010)
- Liana Fasching (registered 2011)

*Co-supervisor for 3 current PhD-students*
- Olof Torper (registered 2009)
- Ulrich Pfisterer (registered 2010)
- Francesco Bez (registered 2012)

*2008-currrently: Main supervisor for 8 masters students*
LOCAL AND NATIONAL NETWORKS
Wallenberg Neuroscience Center: www.med.lu.se/wnc
Lund Stem Cell Center: www.med.lu.se/labmedlund/lund_stem_cell_center
BAGADILICO Linneus network of excellence: www.med.lu.se/bagadilico
MULTIPARK strategic research area: www.med.lu.se/multipark
SWEDBO Swedish organization of Developmental Biologists www.swedbo.se

INTERNATIONAL COLLABORATIONS
Luigi Naldini, TIGET, Milano, Italy
Didier Trono, EPFL, Lausanne, Switzerland
Carmen Sandi, EPFL, Lausanne, Switzerland
Florence Cammas, IGBMC, Strasbourg, France
Anders Persson, UCSF, USA

NATIONAL COLLABORATIONS
Anders Björklund, Wallenberg Neuroscience Center, Lund
Olle Lindvall, Lund Stem Cell Center, Lund
Deniz Kirik, Wallenberg Neuroscience Center, Lund
Angela Cenci, Wallenberg Neuroscience Center, Lund
Malin Parmar, Wallenberg Neuroscience Center, Lund
Åsa Petersen, Wallenberg Neuroscience Center, Lund
Patric Jern, SciLifeLabs, Uppsala

INVITED PRESENTATIONS
SciLifeLab seminar series, Uppsala, Sweden 2012
NECTAR annual meeting, Freiburg, Germany 2006

PRIZES AND AWARDS
2010 Neurofortis Young Investigator Award (€12,500)
2008 Two years postdoctoral funding from Lund University (€58,000)
2008 Best Poster Award, USGEB meeting 2008, Lausanne, Switzerland (€300)
2007 One year postdoctoral funding from Hjärnfonden (€28,000)
2005 Two years postdoctoral funding, Swedish Research Council (€75,000)

FIVE SELECTED PUBLICATIONS
Gesine Paul, Associate Professor, Neurologist
Translational Neurology, Dept. of Neurology, Institute of Clinical Science
Lund University, gesine.paul@med.lu.se

1. HIGHER EDUCATION/DEGREE
2008 Neurologist, Neurology, Lund University Hospital
1998 Doctor in Medical Science, Humboldt-University, Berlin, Germany
Thesis title: "Neurotrophin dependence of sensory neurons during embryonic development"
Supervisor: Prof. U. Dirnagl, Dept. of Neurology, Charité, Berlin, Germany
Co-supervisor: Prof. A.M. Davies, Dept. of Biological & Medical Sciences, University of St Andrews, UK
1997 Medical degree, MD, Humboldt-University Berlin, Germany

2. POSTDOCTORAL WORK
1999 -2001 (50% research) Charite, Berlin, Germany (Prof. A. Kupsch).
2001-2003 (100% research funded via Marie Curie Individual Fellowship)
Neuronal Survival Unit, EMV, Lund University, Sweden (Prof. P. Brundin).
2004-2006 (50% research funded by Swedish Research Council “Tjänst för kliniska forskare” (25%) VR K2004-33P-15178-01A & “ALF/Yngre forskare ” 25%)
Neuronal Survival Unit, EMV, Lund University, Sweden (Prof. P. Brundin) & Residency in Neurology at Lund University Hospital.

3. QUALIFICATION ASSOCIATE PROFESSOR
2008 Neuroscience, Lund University, Sweden

4. CURRENT POSITION/TIME SPENT IN RESEARCH
2008--to date Specialist in Neurology, Skåne University Hospital, Skåne University Hospital.
Currently 50% research time
since 2011 Group leader, Translational Neurology Group, IKVL, Lunds University, Sweden

5. PREVIOUS POSITIONS
2003-2008 Resident in Neurology (+ 50% research), Lund University Hospital
2001-2003 Postdoc (100%) – Marie Curie Fellowship, Lund University, Lund
1999-2001 Resident in Neurology (+ 50% research), Charité, Berlin, Germany
1998-1999 Clinical internship (AT), Charité, Berlin, Germany
1987-1988 Social practice, Hospital for Neurology and Psychiatry, Berlin, Germany

6. INTERRUPTIONS IN RESEARCH
6/1998-6/1999 12 months of Clinical internship (AT)
7/1999-3/2001 11 months of Residency in neurology
4/2003- 6/2008 31 months of Residency in neurology

7. SUPERVISION EXPERIENCE
Supervisor for 9 master/project students and 3 postdocs
Supervisor for 3 resident doctors and scientific mentor for 1 clinical doctoral student

8. CURRENT CLINICAL STUDIES
2013- National coordinating Principal Investigator in sNN0031-003 a dose-finding
study with icv administration of a growth factor in Parkinson’s disease

2011- National coordinating Principal Investigator: An observational study of safety and tolerability and pharmacodynamic effect, of patients with Parkinson's disease previously treated with sNN0031(sNN0031-002)

2010- Clinical Investigator in TransEUro, a EU-funded multicenter study for transplantation in Parkinson’s disease

2009-2011 Clinical Investigator sNN0031-001, a placebo-controlled, randomized double blind study with icv administration of a growth factor to Parkinson’s disease patients

9. COMISSION OF TRUST
2010 Member of Multipark (strategic research area) Lund University
2009 Member of BAGADILICO (Work package co-leader 2009-2010) (Linnaeus environment, Lund University)
Since 2009 Member of the board (Vice-chair 2009) of the Swedish Parkinson Academy
Reviewer for scientific journals, thesis committee member and grant reviewer

10. SELECTED INVITED PRESENTATIONS LAST 2 YEARS
2011 Paul G. Intracerebroventricular Infusion of PDGF-BB in Patients with advanced PD. 7th German-Scandinavian meeting on Movement Disorders Kiel, Germany.

11. SELECTED PUBLICATIONS LAST 5 YEARS
Curriculum Vitae

Hjálmar Bjartmarz M.D.

Permanent address:
Domarringen 15, 245-51 Staffanstorp, Sweden

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Department of Neurosurgery
Lund University Hostpital, SE-221 85 Lund, Sweden
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Examination:
University of Iceland, School of Medicine, M.D., Candidates Medicinae et Chirurgiae, July 1991.
Swedish board examiniton in Neurosurgery, December 12, 1999.

Certification:
Medical licence to practise in:
Iceland August 12 1993
Norway June 2 1997
Sweden July 9 1998
As Neurosurgeon January 18 2000

Current appointments
January 2000 – present.
Consultant Neurosurgeon, Department of Neurosurgery, University Hospital, Lund, Sweden.

Mars 2003 - present
Head of Image Guided Neurosurgery. (Neuronavigation)

January 2010 – present.
Head of Unit of Functional and Stereotactic Neurosurgery, University Hospital Lund, Sweden.

November 2012 – present
Head of neurosurgical operation theatres

Neurosurgical training:
January 1, 1995 – December 31, 1999, resident in neurosurgery, Lund University Hospital, Department of Neurosurgery, Lund, Sweden
Functional and stereotactic experience
1999 trainee in Functional and Stereotactic Neurosurgery
From January 2000 – present, member of the Unit of Functional and Stereotactic Neurosurgery, University Hospital Lund, Sweden.

Previous employment
At the National University Hospital of Iceland:
Aug 1991 – Aug 1992, resident in medicine and surgery, 1 year
Sept 1992 – Aug 1993, senior resident in surgery at Department of Surgery, 1 year
Sept 1993 – Sep 1994, senior resident in medicine at Department of Medicine, 1 year.
1 ½ years experience as a General Practitioner at different medical centres in Iceland, Sweden and Norway during my vacations between 1988 – 2005.

Administration
Member of the board of Swedish Association of Hospital Physicians in Lund 2003-2013
Member of the board of Association of Icelandic Doctors in Sweden. 2004-2006.
Member of board for Swedish Parkinson Academy 2011 – present.
Member of board for MultiPark project at Lund’s University. 2011 – present

Civil Status
Date of birth: March 16, 1959
Place of birth: Reykjavik, Iceland
Nationality: Icelandic
Immigration status: Icelandic, Swedish and EU citizen
Marital status: Married
Children: Four

Publication
Comparison of accuracy and precision between frame-based and frameless stereotactic navigation for deep brain stimulation electrode implantation.
Bjartmarz H, Rehncrona S.

Segmental cerebral vasoconstriction: successful treatment of secondary cerebral ischaemia with intravenous prostacyclin.
Grände PO, Lundgren A, Bjartmarz H, Cronqvist M.

Intracerebral infections as a complication of deep brain stimulation.
Blomstedt P, Bjartmarz H.
Curriculum Vitae

Name: Kristina Hug

Date of birth: 1975-03-09

1. HIGHER EDUCATION DEGREES

1998. BA, major in Sociology, minor in Political Science. Vytautas Magnus University, Kaunas, Lithuania.


2. DOCTORAL DEGREE


3. CURRENT POSITIONS

University teacher. Faculty of Medicine, Department of Medical Ethics, Lund University. Subject: Medical Ethics

4. PREVIOUS POSITIONS AND RESEARCH EXPERIENCE

2006–2012. PhD position. Faculty of Medicine, Department of Medical Ethics, Lund University. University teacher. (Combined with PhD position). Subject: Biomedical Research Ethics

2010–2012. Researcher. EU-funded research project “Neurostemcell” (European Consortium for Stem Cell Therapy in Neurodegenerative Diseases), Wallenberg Neuroscience Centre, Lund University. Area: Ethical and societal aspects of Parkinson’s and Huntington’s diseases.


2003–2006. University teacher. Subject: Health Law. Faculty of Medicine, Department of Public Health Management, Kaunas University of Medicine, Kaunas, Lithuania.


5. OTHER INFORMATION OF RELEVANCE

2011–present. External ethics advisor for the European Network “ScreenTox” (Stem Cells for Reliable, Efficient, Extended and Normalized Toxicology).

2009–present. Member of the Editorial board of the journal “Stem Cell Reviews and Reports”.

2005–present. Faculty member. Advanced Certificate Program in Research Ethics (E-Education, Vilnius University (Lithuania), the Albany Medical College and the Graduate College of Union University (USA).

2009–present. Visiting lecturer (contributing with lectures in two courses) at the Karolinska Institute, Stockholm, Sweden.

2010. Anne McLaren Award, in memory of the late Dame Anne McLaren, member of the Ethics Advisory Panel, recognising an outstanding multi-disciplinary contribution within EU-funded research project “ESTOOLS” activities to human embryonic stem cell research.

6. MOST RECENT PUBLICATIONS

Hug K, Hermerén G. When can we start first-in-human trials and what patient groups should be asked to participate in such trials? The cases of Parkinson’s and Huntington’s diseases: Ethical and epistemic considerations. *Journal of Clinical Ethics* (in print).

Hug K, Hermerén G. Differences Between Parkinson’s and Huntington’s Diseases and Their Role for Prioritization of Stem Cell-Based Treatments. *Current Molecular Medicine* (accepted for publication).


7. LANGUAGES: Lithuanian (native), English, Swedish, French and Russian (fluent), German (good), Spanish (beginner).
Maria H Nilsson (650424)

1. **HIGHER EDUCATION/DEGREE**

<table>
<thead>
<tr>
<th>Institution and location</th>
<th>Degree</th>
<th>Year</th>
<th>Field of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lund University, Sweden</td>
<td>RPT</td>
<td>1993</td>
<td>Physical therapy</td>
</tr>
<tr>
<td>Lund University, Sweden</td>
<td>BSc</td>
<td>2002</td>
<td>Physical therapy</td>
</tr>
<tr>
<td>Lund University, Sweden</td>
<td>MSc</td>
<td>2003</td>
<td>Physical therapy</td>
</tr>
</tbody>
</table>

2. **DOCTORAL DEGREE**

- Lund University, Sweden PhD 2009 Physical therapy


3. **POSTDOCTORAL WORK/Position**

   Department of Health Sciences, Lund University.
   Principal investigator: Professor Susanne Iwarsson
   CASE- Centre for Ageing and Supportive Environments, August 2010-July 2012. This position was attained in open competition, and was mainly funded by the vice chancellor of Lund University (LU).

4. **QUALIFICATION AS ASSOCIATE PROFESSOR**

   Application is submitted.

5. **CURRENT POSITION**

   Senior Lecturer (promoted in 2010), Department of Health Sciences, Lund University, Sweden. 2006- (ongoing)

6. **PREVIOUS POSITIONS**

   *Clinical position:* Department of Neurosurgery, Lund, Skåne University Hospital. 1993 (February) - 2011 (December)

7. **DOCTORAL STUDENTS**

   I am currently the co-supervisor of three PhD students (2 physical therapists: Beata Lindholm, Stina Bladh, and 1 occupational therapist: Björg Thordardottir), and they were all enrolled in 2011. All PhD-projects concern people with Parkinson’s disease.

8. **OTHER INFORMATION**

   *Nominations and awards:* I was nominated by the Department of Health Sciences for the program named Academic Traineeship. The vice chancellor of Lund University accepted me as a participant for the 2-year program (2009-2011). The aim of the program was to prepare its members for an academic leadership position. In 2010, I attained an award (100 000 SEK) for best PhD thesis within the field of Parkinson’s disease (Elsa and Inge Anderssons award, September, 2010). Institution: The Parkinson Foundation in Sweden. In 2010, I attained a “medal of honour” by the Swedish Parkinson Disease Association in September 2010.

   *Board member:* The Swedish Movement Disorders organization for health sciences (VfMD) 2009-2011, 2011-ongoing.
   *Current Membership of a European network:* In 2011, I was nominated (by the national physiotherapy organization, LSR) and thereafter selected by the European steering group (i.e. Guidelines: evidence based physical therapy for people with Parkinson’s disease) to participate in the Reading group.

   *Total number of original articles:* n=15, *Submitted articles:* n=5, *Published abstracts:* n= 8, *Invited speaker, international invitations (last 5 years):* n=5.
9. RELEVANT PUBLICATIONS last 5 years


14) Bladh S, Nilsson MH, Carlsson G, Lexell J. Content analysis of four fear of falling rating scales by linking to the International Classification of Functioning, Disability and Health (ICF). Accepted for publication in PM&R (The journal of injury, function and rehabilitation).

** Within the PhD-thesis