29 - 30 NOVEMBER 2012

N E C T A R

22ND ANNUAL MEETING

LUND, SWEDEN

A message from the NECTAR President Emma Lane

Dear NECTAR members

It is my great pleasure to welcome you to the 22nd Annual Meeting of the Network for European CNS Transplantation and Restoration in Lund. I am sorry that I cannot be with you person this year but having been involved in the program I know that this will be a stimulating and exciting two days, unfortunately the imminent arrival of my first baby prevents me from travelling to Lund.

The local programme committee in Lund have put together an exciting and vibrant program of presentations and datablitz sessions, which I have no doubt will stimulate much discussion and debate. Learning from last year we have increased the number of datablitz sessions so I hope most of you have been accommodated, and the quality, as always has been very high. NECTAR has long been an environment supportive of collaboration, sharing ideas and supporting younger scientists, this conference continues those ideals.

The website, Facebook and Twitter pages have been active this year to share information about the conference and other events, please tweet or comment on the Facebook pages throughout the conference, #NECTAR2012, with your thoughts on talks and data presented. Please use these sites to continue to network and collaborate or simply share new innovations through these media sources. Importantly, if you have any thoughts on the future of NECTAR, how the conference ran, or anything relevant please post, tweet or email me on emma@nectar-eu.net.

Finally I'd like to remind you that Cardiff will be hosting next year's conference in association with the 13th International Symposium on Neural Transplantation and Restoration on September 3rd - 6th 2013 – keep the date in your diaries! Information is already available on the website and we look forward to seeing you in Cardiff.

BEST WISHES

EMMA

INDEX

2012 NECTAR programme

Thursday, November 29th

Topic	Speaker	Time
Welcome	Angela CENCI NILSSON Anders BJÖRKLUND	8.30
Opening lecture Prion-like behavior of alpha-synuclein: implications for neural grafting and the pathogenesis of Parkinson's disease	Patrik BRUNDIN	8.30-9.15
Parkinson's disease – progress in the clinic *Chair person: Roger Barker*		
PD treatment, state-of-the-art with focus on CDS	Per ODIN	9.20-9.50
Update on DBS	Joachim KRAUSS	9.50-10.10
Coffee 10.10-10.40		
Update on PDGF	Gesine PAUL-VISSE	10.40-11.00
Update on Exendin	Tom FOLTYNIE	11.00-11.20
Datablitz – Session 1 *Chair person: Christian Winkler*	*6 speakers* *(4 min+2 min)*	11.20-12.00
Lunch 12.00-13.00		
Update on dyskinesia *Chair person: Angela Cenci Nilsson*		
Functional imaging of LID, the state-of-the-art	Paola PICCINI	13.00-13.30
Gene therapy for LID	Erwan BEZARD	13.30-13.50
Update on Graft-induced dyskinesia	Christian WINKLER	13.50-14.10
Datablitz – Session 2 *Chair person: Daniella Rylander*	*6 speakers* *(4 min+2 min)*	14.10-14.50
Coffee 14.50-15.20		

Huntington's Disease – progress in the clinic *Chair person: Åsa Petersen*		
HD in the clinic state-of-the-art	Anne ROSSER	15.20-15.50
Allele-specific silencing of mutant Huntingtin in HD neural stem cells and in vivo	Nicole DEGLON	15.50-16.10
RNAi in HD	Beverly DAVIDSON	16.10-16.30
Datablitz – Session 3 *Chair person: Claire Kelly*	*5 speakers* *(4 min+2 min)*	16.30-17.00
Short break 17.00-17.10		
Datablitz – Session 4 *Chair person: Claire Kelly*	*5 speakers* *(4 min+2 min)*	*17.10-17.40*
Business meeting		18.00
Conference dinner (Grand Hotel) 19.30		

Day 2 – Friday, November 30th

Topic	Speaker	Time
Models of degenerative disease *Chair person: Paola Piccini*		
Special lecture Pathways to PD neurodegeneration, studies on LRRK2 and alpha-synuclein models	Darren MOORE	9.00-9.45
Transgenic models of HD	Åsa PETERSEN	9.45-10.05
Alpha-synuclein: a tool for new neuroprotective strategies	Mickael DECRESSAC	10.05-10.25
Datablitz – Session 5 *Chair person: Stephen Dunnett*	*4 speakers* *(4 min+2 min)*	10.30-10.55
Coffee 11.00-11.20		

Repair strategies in other fields *Chair person: Elena Cattaneo*		
Cell therapies in Macular degeneration	Peter COFFEY	11.20-11.50
Stem cells in stroke	Zaal KOKAIA	11.50-12.20
Datablitz – Session 6 *Chair person: Elena Cattaneo*	*6 speakers* *(4 min+2 min)*	12.20-13.00
Lunch 13.00-14.00		
Cellular programming and reprogramming *Chair person: Anders Björklund*		
State-of-the-art of stem cells in degenerative disorders	Malin PARMAR	14.00-14.20
Strategies of direct cell reprogramming for generating neuronal cells with therapeutic potential	Vania BROCCOLI	14.20-14.40
Neural differentiation of human pluripotent stem cells	S.C. ZHANG	14.40-15.00
Generation of authentic striatal neurons from human pluripotent stem cells	Elena CATTANEO	15.00-15.20
Coffee 15.20-15.40		
Datablitz – Session 7 *Chair person: Malin Parmar*	*6 speakers* *(4 min+2 min)*	15.40-16.20
Special lecture How to bring stem cells to the clinic	Roger BARKER	16.20-17.05
Close of the meeting	Anders BJÖRKLUND Angela CENCI NILSSON	17.10

ORGANISING COMMITTEES

International Organizing Committee (NECTAR board)

Emma Lane (President)

Roger Barker

Angela Cenci-Nilsson

Maté Döbrössy

Paola Piccini

Gregor Wenning

Christian Winkler

Local Organizing Committee

Angela Cenci-Nilsson

Anders Björklund

Per Odin

Daniella Rylander

Paulina Pettersson

BIOGRAPHY OF SPEAKERS

Roger	**BARKER**	Cambridge, UK
Erwan	**BEZARD**	Bordeaux, France
Vania	**BROCCOLI**	Milan, Italy
Patrik	**BRUNDIN**	Lund, Sweden Grand Rapids, USA
Elena	**CATTANEO**	Milan, Italy
Peter	**COFFEY**	London, UK
Beverly	**DAVIDSON**	Iowa City, USA
Mickael	**DECRESSAC**	Lund, Sweden
Nicole	**DEGLON**	Lausanne, Switzerland
Tom	**FOLTYNIE**	London, UK
Zaal	**KOKAIA**	Lund, Sweden
Joachim	**KRAUSS**	Hannover, Germany
Darren	**MOORE**	Lausanne, Switzerland
Per	**ODIN**	Lund, Sweden
Malin	**PARMAR**	Lund, Sweden
Gesine	**PAUL-VISSE**	Lund, Sweden
Åsa	**PETERSEN**	Lund, Sweden
Paola	**PICCINI**	London, UK
Anne	**ROSSER**	Cardiff, UK
Christian	**WINKLER**	Freiburg, Germany
Su-Chun	**ZHANG**	Madison, USA

Roger Barker

Roger Barker is the Professor of Clinical Neuroscience and Honorary Consultant in Neurology at the University of Cambridge and at Addenbrooke's Hospital. He trained at Oxford and London and has been in his current position for over ten years having completed an MRC Clinician Scientist Fellowship just prior to this. His main interests are in the neurodegenerative disorders of the nervous system in particular Parkinson's disease and Huntington's disease. He combines basic research looking at cell therapies to treat these conditions with clinically based work on defining the natural history and heterogeneity of both Huntington's disease and Parkinson's disease and is the co-ordinator of the EU FP7 TRANSEURO project looking at fetal cell grafting in patients with early PD.

Erwan Bezard

Erwan Bezard is an INSERM Research Director who has authored or co-authored over 120 professional publications in the field of neurobiology, most of which are on Parkinson's disease and related disorders. Listed in the Top 1% of the most cited neuroscientists he is best known for his work on the compensatory mechanisms that mask the progression of

Parkinson's disease and on the pathophysiology of levodopa-induced dyskinesia. His current research interests include the study of the compensatory mechanisms, the levodopa-induced dyskinesia, the basic pathophysiology of basal ganglia circuitry, and the development of new strategies to alleviate symptoms and/or to slow disease progression. He is the director of a new CNRS research unit located in Bordeaux, the Neurodegenerative Disorders Institute that features preclinical and clinical researchers working towards development of therapeutic solutions.

Vania Broccoli

Vania Broccoli is leading the Unit of "Stem Cell and Neurogenesis" at the San Raffaele Scientific Institute in Milan (Italy). He is a neurobiologist interested to unravel the molecular mechanisms that control key processes of brain development such as neural stem cell identity maintenance, neural commitment and migration, neural network establishment and function. Lately, his group has applied new technologies of direct cell reprogramming to convert mouse and human skin fibroblasts into functional dopaminergic neurons. Now, he aims to further strengthen these approaches to establish safe and efficient systems for producing functional human neurons suitable for cell replacement therapies in infantile neurological and neurodegenerative disorders.

Patrik Brundin

Patrik Brundin is a renowned researcher in the field of Parkinson's disease and has published over 300 papers on this and closely related topics. He was part of the research team that first developed a clinical procedure for intracerebral transplantation in this disease. He presently holds a professorship in neuroscience at Lund University, and leads a research group that is active in several areas of investigation related to experimental models of neurodegenerative diseases. From 1995 to 2000, he was president of the Network for European CNS Transplantation and Repair (NECTAR). He presently coordinates numerous national and international research programs and scientific projects that focus on neurological disorders of the basal ganglia. Patrik has recently moved to the US to direct research on Parkinson's at the Van Andel Institute, Grand Rapids, Michigan.

Elena Cattaneo

Elena Cattaneo is Director of the Laboratory of Stem Cell Biology and Pharmacology of Neurodegenerative Diseases at the Department of Pharmacological Sciences, as well as a co-founder and first appointed Director of UniStem, the Centre for Stem Cell Research of the University of Milano. The main research theme of her lab is neural stem cells, and the molecular pathophysiology of Huntington's disease. Prof Cattaneo is a Coalition Investigator of the Huntington's Disease Society of America (H.D.S.A.), and a member of the Board of Directors of several European consortia (including NeuroStemCell and NeuroNE).

Peter Coffey

Pete Coffey is Head of Ocular Biology and Therapeutics at UCLs Institute of Ophthalmology and the Co-Executive Director of Translation at UC Santa Barbara's Center for Stem Cell Biology and Engineering. He is the principal author and co-author of two landmark papers demonstrating the use of human cells to halt visual deterioration in models of age-related macular degeneration. His achievements include the launch of the London Project to Cure Blindness, which aims to develop a stem cell therapy for the majority of all types of age-related macular degeneration, seminal work on retinal transplantation (as described by Döbrössy & Dunnett, Nature Neuroscience 2001). Prof. Coffey has received many honors and awards, including the prestigious Estelle Doheny Living Tribute Award in 2009, Retinitis Pigmentosa International's Vision Award in 2009, the CIRM Leadership Award in 2010, and the New York Stem Cell Foundation Roberston Prize in 2011.

Beverly Davidson

Beverly Davidson is a member of the American Association for the Advancement of Science and the American Society for Neuroscience and American Society for Gene Therapy. Research in her laboratory at the University of Iowa is focused on inherited genetic diseases that cause central nervous system dysfunction, with a focus on (1) recessive, childhood onset neurodegenerative disease, (2) dominant genetic diseases, and (3) understanding how noncoding RNAs participate in neural development and neurodegenerative diseases processes.

Mickael Decressac

Mickael Decressac is a senior postdoc at the Wallenberg Neuroscience Center, Lund University. He received his Master of Sciences and Doctorus Europeus of Neurosciences from the University of Poitiers. During his PhD period, he characterized novel properties of the neuropeptide Y. In 2008, he was at the Brain Repair Centre (University of Cambridge) working with Roger Barker. In 2009, he joined the group of Anders Björklund in Lund where he investigates the mechanism of alpha-synuclein-induced toxicity in vivo and therapeutic strategies in animal models of Parkinson's disease. Dr. Decressac serves as scientific reviewer for *Experimental Neurology.*

Nicole Déglon

Nicole Déglon is research director of the French Atomic Energy Commission (CEA) and deputy director of MIRCen, a pre-clinical imaging platform for drug, cell and gene therapy located in Fontenay-aux-Roses, south of Paris. Dr. Déglon's research interests include the development of viral-based genetic models of neurodegenerative diseases, the treatment of

neurodegenerative diseases from cell transplantation to gene therapy, and investigation of the central nervous system by means of functional and molecular imaging techniques. Dr. Déglon received her education, including a PhD in biochemistry, at the University of Lausanne, Switzerland. Before joining CEA in 2003, she held several research positions at the Gene Therapy Center in Lausanne, at the Salk Institute in San Diego, California, and at the Federal Polytechnic Institute of Lausanne, Switzerland where she developed gene therapy approaches for neurodegenerative diseases.

Tom Foltynie

Tom Foltynie is a Movement Disorders Consultant Neurologist with a specialist interest in Parkinson's disease, Deep Brain Stimulation (DBS) and the development of novel treatments for PD. He was appointed as senior lecturer and honorary consultant in the Unit of Functional Neurosurgery at the Institute of Neurology in May 2008. As well as contributing to the pre-operative, intra-operative and post-operative assessment of PD patients needing DBS, he is developing an academic programme to further explore genetic influences on dyskinesia risk, expression of dystonia and responsiveness to DBS.

Zaal Kokaia

Zaal Kokaia is a Professor of Experimental Medical Research at Lund University. He is currently the Director of Lund Stem Cell Center and head of Laboratory of Stem Cells and Restorative Neurology. He coordinates Strategic Research Area in Stem Cells and Regenerative Medicine (StemTherapy) at Lund University supported by Swedish Government and EU FP7 consortium TargetBraIn. His research interests are generation and characterization of neural stem cell lines from different sources and development of stem cell-based treatments for stroke.

Joachim Krauss

Joachim K. Krauss is an expert both in general and in functional neurosurgery.
Major clinical interests are complex spinal neurosurgery, functional neurosurgery and skull base surgery. Professor Krauss pioneered several new therapeutic concepts.
Over the past years, he received several awards and serves as a reviewer for numerous journals and academic institutions. His academic achievements include board positions in various professional societies. He serves as the Head of the Commission for Technical Standards of the German Society of Neurosurgery, as Secretary of the European Society of Functional and Stereotactic Neurosurgery, as Vice-President of the World Society of Functional and Stereotactic Neurosurgery, and as Head of the Task Force Neurosurgery of the Movement Disorder Society.

Darren Moore
Darren Moore is assistant professor and head of the Laboratory of Molecular Neurodegenerative Research at the Brain Mind Institute, Ecole Polytechnique Fédérale de Lausanne (EPFL). Dr. Moore received his PhD in molecular neuroscience from the University of Cambridge in 2001 in the laboratory of Piers Emson, and conducted post-doctoral research with Ted Dawson in the Department of Neurology and Morris K. Udall Parkinson's Disease Research Center of Excellence at the Johns Hopkins University School of Medicine. Dr. Moore joined the faculty of the Department of Neurology at Johns Hopkins in 2005 as an Instructor and was appointed assistant professor in 2006. Dr. Moore later joined the faculty at EPFL in winter 2008. His laboratory is interested in understanding the cell biology and pathophysiology of gene products associated with familial Parkinson's disease, including the LRRK2, parkin, α-synuclein and ATP13A2 proteins, and the development of novel genetic pre-clinical models of Parkinson's disease.

Per Odin
Per Odin is head of the department of Neurology at the Central Hospital in Bremerhaven, Germany and at the same time has a Professorship in Neurology at the Lund University, Sweden. He has focused his interest on Movement Disorders since 1987 and his main research areas concern continuous dopaminergic stimulation, pump therapies for Parkinson´s disease (PD), non-motor PD symptoms and cell transplantation in PD. He is chair of the Swedish Movement Disorders Society, the Scandinavian Movement Disorder Society, board member of the Competence Network Parkinson, Germany and member of the executive committee of Movement Disorder Society European Section.

Malin Parmar
Malin Parmar is an expert on differentiation and maturation of human pluripotent and multipotent stem cells as well as on the quickly growing field of reprogramming. Together with her lab she has shown in a series of high profile publications how human fibroblasts can be reprogrammed into neurons by expressing a few transcription factors and how dopamine neurons can be generated from human embryonic stem cells. Malin Parmar collaborates with several European consortia including NeuroStemcell and Transeuro and has recently been awarded a starting grant from the European Research Council.

Gesine Paul-Visse
Gesine Paul-Visse is a neurologist and an associate Professor in Neuroscience at Lund University in Sweden. She trained in Berlin, Germany, St. Andrews University, Scotland and UMDS, London, UK and has completed her specialist training in neurology in Sweden. Currently she holds a position as a neurologist at SUS-Lund and is trained to become one of

the movement disorder specialists in Scandinavia. She has during several years combined patient care, clinical research and preclinical research. Her main interest is translational research. She now leads the research group ”Translational Neurology” at Lund University and is mainly interested in the development of novel, innovative therapies for Parkinson’s disease. Currently, she is clinical investigator in several clinical trials aiming to slow disease progression in PD. She is also involved in Transeuro, a FP7 multicenter transplantation trial.

Åsa Petersén

Åsa Petersén is an Associate Professor of Neuroscience at Lund University. She combines a senior researcher position from the Swedish Research Council with a residency in clinical psychiatry in Lund, and is a member of the scientific and bioethics advisory board (SBAC) of the European HD Network (EHDN) as well as of the editorial board of the new Journal of Huntington's disease. She leads the research group Translational Neuroendocrine Research Unit that she formed in 2007. Her research team focuses on non-motor aspects of Huntington's disease (HD) such as psychiatric symptoms and metabolic dysfunction, and the work bridges from development of novel genetic animal models to analyses of human postmortem tissue and MR images. Åsa has been part of pioneering work demonstrating important neuroendocrine changes in HD and her group has recently identified early changes in the hypothalamus relevant for dysregulation of both metabolism and emotion in HD.

Paola Piccini

Paola Piccini is the head of the Centre of Neuroinflammation and Neurodegeneration. She is Professor of Neurology and i.e. Honorary Consultant in Neurology with the Imperial College Healthcare NHS Trust. She has worked extensively in the field of functional imaging for 20 years. Her main research has focussed on movement disorders and predominantly on the use of Positron emission tomography (PET) as a method of investigating aetiology, effects and complications of therapies, particularly new neuroprotective and neurorestorative therapies, in Parkinson’s disease and Huntington’s disease.

Anne Rosser

Anne Rosser is Professor of Clinical Neuroscience and Honorary Consultant Neurologist at the University Hospital of Wales, Cardiff. She is also joint Director of the University's Brain Repair Group. She has worked in the area of neurodegeneration since 1994 primarily on Huntington’s disease (HD) and the development of new therapies for this and related neurodegenerative conditions. Her research activities, based in the School of Biosciences, are focused on cell replacement therapies and the potential of stem cells as a donor source for neural transplantation. As part of these activities she is joint co-ordinator of a UK pilot trial of neural transplantation in HD.

Christian Winkler

Christian Winkler is trained in Hannover and Lund. His research is focused on experimental studies in rodent models of neurodegenerative diseases. His interests lie particularly in restorative therapies in animal models of Parkinson´s disease using cell transplantation and viral vectors with focus on improving the functional efficacy of these therapies, and in investigating L-DOPA- and graft-induced dyskinesia in these animal models with a focus on understanding the molecular mechanisms of these dyskinesias and thereby preventing their development. He was president of NECTAR from 2007 until 2011.

Su-Chun Zhang

Su-Chun Zhang is Professor of Anatomy and Neurology and a research group leader at the University of Wisconsin–Madison. His laboratory intends to address how functionally diversified neuronal and glial subtypes are born in the making of our human brain. They have developed models of neural differentiation from mouse, monkey, and human pluripotent stem cells, including embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs). The specialized neural cells produced from normal human stem cells in his laboratory are being tested for their therapeutic potential in animal models of neurological diseases such as Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis, brain/spinal cord injury, and multiple sclerosis.

PRACTICAL INFORMATION

Venue
AF BORGEN
Sandgatan 2
223 50 Lund
Tel: +46 (0)46 384 905

Speakers' accommodation
Grand Hotel
Bantorget 1
222 29 Lund
Tel: +46 (0)46 280 61 00

Registration

The registration desk will be located on the 2nd floor of AF Borgen, just in front of the conference room. Please follow our NECTAR signs to the conference room.
The registration desk will be open during the following hours:
Thursday, November 29th 08:00 – 18:00
Friday, November 30th 08:15 – 17:30

At the registration desk you can collect you badge and your programme booklet.
Please contact the conference staff throughout the day if you have any questions.

During the conference, the NECTAR meeting staff can be reached under the numbers:
+46 736 67 16 24 – Paulina Pettersson
+46 703 14 67 61 – Anders Björklund

Please wear your badge during the conference. This will also serve as your entrance ticket.

Delegates who have booked their accommodation should deal with their hotels at the hotel desk.

Conference dinner

The conference dinner on Thursday, November 29th is included in the delegate package. The dinner will be held at the Grand Hotel (Bantorget 1) at 19:30, 2nd floor. Please follow the signs guiding you to the dinner room. You are welcome to leave your coat or jacket at the hotel's cloakroom situated on the right hand side of the hotel's main entrance.
Please wear your badge for the dinner, it will serve as your entrance ticket.
Should you have any dietary requirements and you have not specified them in the online registration form, please inform Paulina as soon as possible.

Sponsors' exhibition

The sponsors' exhibition will be located in the coffee break area in front of the conference room.

Lunch and coffee Breaks

Coffee breaks will be served outside of the conference room.
A seated lunch (not a buffet!) will be served in two rooms at the building of AF Borgen. Our main lunchroom is the same room where the coffee breaks will take place during the day. In case all the seats are taken in this room, please proceed downstairs and follow our NECTAR signs to a private room on the ground floor reserved for us.

Instructions for speakers

Considering the packed timetable of the meeting, we kindly ask speakers to present their talks within the allocated time.
PowerPoint projection facilities will be available, and technical assistance will be available throughout the meeting. We kindly ask all speakers to bring their talks on a USB-stick and send the PowerPoint presentations before November 23th to Paulina.Pettersson@med.lu.se.

Oral Presentations (Datablitz sessions)

As in previous years, there will be no poster session, but instead there will be Datablitz presentations; short 4 minute presentations followed by a 1-2 minute discussion. These will be timed by the Chair of the session and will not be allowed to over run so we ask all speakers in these sessions to be particularly mindful of the time and the amount of data covered. We recommend that you do not try and present any more than 6 slides in your datablitz.
Considering this short timeframe, the results will not be able to be discussed in detail, but these presentations are good springboards for discussions during the rest of the conference. We kindly ask all datablitz presenters to bring their talks on a USB-stick or send the PowerPoint presentations before November 23th to Paulina.Pettersson@med.lu.se.

Official Language

The official language of the conference is English.

Wireless Network

AF Borgen offers complementary access to wireless internet in all the public areas and conference rooms. The network we should use is: AF Borgen Wifi, the password: KmH456!!

Website: www.nectar-eu.net

Facebook: NECTAR-eu (for access to the private group, please email your Facebook details to Emma Lane (emma@nectar-eu.net and public page)

Twitter: @NECTAR_EU, #NECTAR2012

TRAVEL TO LUND

Lund is located only 15 km away from Malmö, Sweden's third biggest city, and 60 km from Copenhagen, the capital of Denmark.

By AIR

Copenhagen Airport CPH (Kastrup), Denmark

This is our biggest international airport, located approximately 50 km from Lund. It is the busiest airport in the Nordic countries handling 60 scheduled airlines and serving more than 62,000 passengers per day. Lund is within easy reach by rail or taxi. The railway station is within the terminal building, the train platforms are situated below the arrivals terminal. The journey takes around 35 minutes and a single ticket costs in the region of € 15. After you have passed the arrival gate, please follow the signs saying "Trains to Malmö", this will be your platform (the trains to Lund pass through Malmö which is a bigger city, hence the signs say "Malmö" and not "Lund"). The tickets must be bought before you go down to the platform, either from a vending machine or from a cashier - both are located just by the entrance to the train platform.
During daytime hours the trains leave every 20 minutes, between 01:00 – 06:00 at night there's a train once an hour. For schedules please visit
http://www.oresundstag.se/en/Start/

Malmö airport MMX (Sturup)

Malmö Airport is located 25 km south of Lund. Here you have direct flights to and from London, Amsterdam, Stockholm to mention a few. It takes approximately 25 minutes by taxi or 45 minutes by Airport coach (Flygbussarna, www.flygbussarna.se) to Lund. There are buses every 45 minutes from Lund central station and a return ticket costs around € 19.

Trains, cars & buses from the continent

It is possible to get to Lund from the continental Europe by land, it will however take some time! There are a number of coach operators travelling to Lund who offer their services at very reasonable prices. One of them can be found here:
http://www.swebus.se/swebusexpress_com/.
If you wish to drive to Lund from Denmark or continental Europe, it is most convenient to cross the Sound between Sweden and Denmark by the Öresund Bridge. For more information and prices please visit the bridge's website: www.oresundsbron.com.

TRAVEL WITHIN LUND

If you arrive to Lund by train, you will arrive at Lund Central Station, situated just next to the city centre. Taxis are available from a rank outside the station should you have baggage or prefer not to walk.
Buses in Lund are either green or yellow. The green buses stay within Lund's city boarders while yellow buses will leave Lund and go to e.g. Malmö. It is NOT possible to pay for your bus ticket onboard a bus with cash – you will need to use your credit card or your mobile phone to pay for the ticket.
For schedules of trains and buses in Lund as well as in the whole region of southern Sweden and Copenhagen please visit www.skanetrafiken.se.

Taxis

Taxi Skåne: www.taxiskane.com	+46 (0)46 330 330
Taxi Lund: www.taxilund121212.se	+46 (0)46 121212
Taxikurir: www.taxikurir.se	+46 (0)46 700 000

Disclaimer

The local and scientific organizing committees accept no liability for injuries and losses of whatever nature incurred by participants and/or accompanying persons, nor loss of, or damage to, their luggage and/or personal belongings

LUND HOTEL ACCOMMODATION

Grand Hotel **** Superior

Bantorget 1, 221 04 Lund, Tel: +46 46-280 61 00. www.grandilund.com

"At the Grand, everything is that little bit different. The hotel style is classic and has all the atmospheric charm one expects from a 19th century hotel.
As a guest at the Grand you are well looked after. We deliver the morning paper direct to your door and should you put our your shoes in the corridor in the evening you will get them back smartly polished the following morning without charge. All rooms are equipped with dressing gown, cable TV while a surcharge gives you access to wireless Internet in your room. Our famous buffet breakfast is included in the price of the room."

Single room/night SEK 1.645 (€ 194), 5 minutes walk from the central station. To make a reservation, please email hotel@grandilund.se stating the reference number 34955.

Hotel Lundia ****

Knut den Stores torg 2, 221 04 Lund, Tel: +46 46-280 65 00. www.lundia.se

"Hotel Lundia is situated in the centre of Lund, just one minute from the railway station and regional and local buses. (…) For a hotel to call itself a design hotel requires a major commitment. But we know that we dare to, and can live up to it. Over the past 20 years, Hotel Lundia has been refurbished with the emphasis on design. Today we can say that there is a conscious purpose behind every single piece of furniture, picture and furnishing feature in the hotel."

Single room/night SEK 1.620 (€ 191), 8 minutes walk from the central station. To make a reservation, please email info@lundia.se stating the reference number 45201.

Hotel Concordia ****

Stålbrogatan 1, 222 24 Lund, Tel: +46 46-13 50 50. http://www.concordia.se/

"The historical hotel building is located on a quiet street in Lund, a city that dates all the way back to the 11th century! Here you can feel and experience the typical "lundian" atmosphere. Also, you have all the restaurants, cinemas and cultural activities just around the corner. Lund´s attractive shopping streets, located only 100 meters from the hotel, offers excellent shopping for all ages."

Single room/night SEK 1.175 (€ 138), double room/night SEK 1.375 (€ 162), 12 minutes walk to the conference venue. To make a reservation, please email info@concordia.se stating the reference Paulina Pettersson.

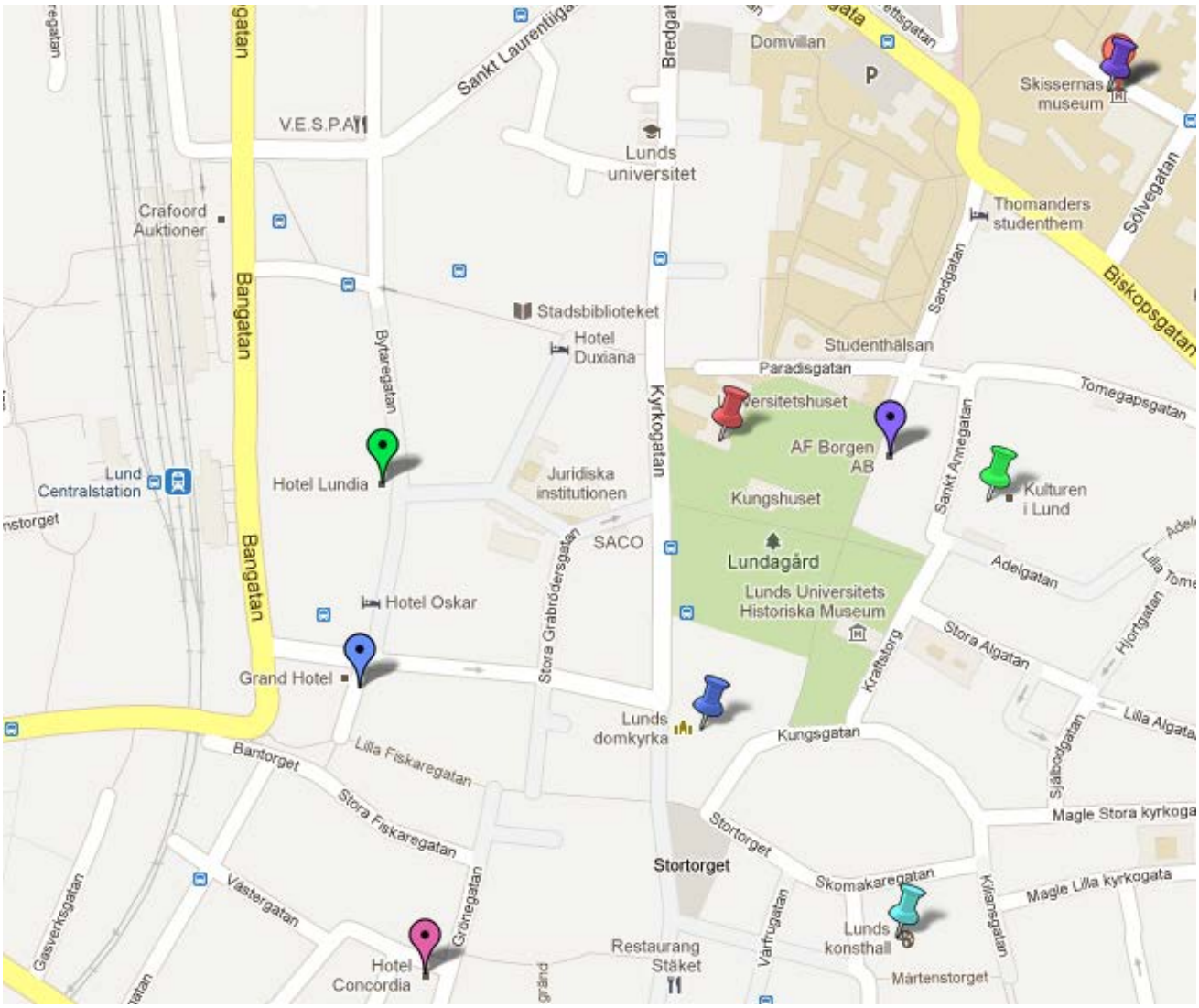
Hotel Sparta

Tunavägen 39, 223 63 Lund, Tel: +46 46-19 16 00. www.spartahotell.se/e/index.html

"If these walls could speak!
Sparta used to be a favourite haunt of local university students. In fact, the name Sparta still brings a nostalgic twinkle to the eye of Lund residents of a certain age. Sparta is located in the middle of IDEON Science Park with the hospital and the University of Economics as close neighbours. (…) To better suit the needs of today's customers, the Hotel and Conference Center has been refurbished and brought up to modern comfort standards."

Single room/night SEK 778 (€ 92), double room/night SEK 950 (€ 112), 8 minutes by bus (nr 6 and nr 1) or 20 minutes on foot to the conference venue. To make a reservation, please email info@spartahotell.se stating the reference Paulina Pettersson.

MAP OF LUND



- Grand Hotel
- Hotel Lundia
- Hotel Concordia
- AF Borgen AB
- Lund Cathedral
- Lund University / Viking rune stones
- Kulturen
- Lund konsthall
- The Museum of Sketches - Museum of Public Art

DO YOU NEED A WALK?

In case you will be staying in Lund for a little longer or just need some fresh air to clear your thoughts, here are some tips of what to see.

Lund Cathedral

Lund Cathedral was built before 1085, the high altar of the crypt was consecrated in 1123. Its history gives a glimpse of the amazing history of Lund and it's the main tourist attraction in the city.

Address: Kyrkogatan, 222 22 Lund
Opening hours: 08:00-18:00 Mon-Fr, 09:30-17:00 Sat, 09:30-18:00 Sun, no admission.

Lund University

The university is what makes Lund tick! It was founded in 1666, making it the second-oldest university on Swedish ground. Today, it is one of northern Europe's most prestigious universities and one of Scandinavia's largest institutions for education and research. The university is spread around town, but some of the most beautiful buildings are located in Lundagård Park, not far from the cathedral and AF Borgen.

Viking rune stones

You'll find them in Lundagård Park surrounded by university buildings. They come from different villages in Skåne and tell stories of how a few Vikings met their death in different places in Northern Europe.

Kulturen

Kulturen is the second oldest open-air museum in the world. There are now more than thirty buildings filling two blocks of the city. The buildings show how people have lived and worked in Sweden through the ages. You will also find some fifteen exhibitions about everything from peasants in Skåne to arts and crafts from all over the world.

Address: Tegérsplatsen, 223 50 Lund
Opening hours: 12:00 – 16:00 Tue – Sun, admission: 90 SEK.

Lund konsthall

Lund Konsthall is a contemporary art venue. They offer exhibitions and events of high international standard, featuring art from the nearby region as well as from the rest of the world. They also engage in continuous research and experimentation with new exhibition formats.

Address: Mårtenstorget 3, 223 51 Lund,
Opening hours: mostly noon – 17:00, no admission.

The Museum of Sketches – Museum of Public Art

The Museum of Sketches was founded in 1934. Its focus is the creative process around the conception of public art – that is to say sketches, preliminary works, and models to the art that meets us in our surroundings. It consists mainly of three main collections – the Swedish, the Nordic and the International collections.

Address: Finngatan 2, 223 62 Lund,
Opening hours: noon-17:00 Tue-Sun, admission: 50 SEK.

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ACKNOWLEDGEMENTS

We would like to acknowledge and thank the following companies and organisations for sponsoring the event.

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DATABLITZ SESSIONS

Thursday 29th November

Datablitz - Session 1 11.20 – 12.00

Chair person: Christian Winkler

1	Olga Baron Hannover	FGF signalling ensures adequate nigrostriatal pathway formation
2	Luis Quintino Lund	Regulating GDNF expression using Destabilizing Domains leads to functional neuroprotection in the 6-OHDA model of Parkinson's Disease
3	Mary Ní Fhlathartaigh Galway	Fibrin as a biomaterial matrix for delivery of GDNF overexpressing MSCs to the adult rat brain
4	Stefanie Seiler Berne	Neuroprotective capacity of Endothelial Progentitor Cells in an in vitro model of Parkinson's Disease
5	Deirdre B. Hoban Galway	Assessment of a type 1 collagen hydrogel as a support matrix for neurotrophin-secreting stem cells in the hemi-Parkinsonian rat brain
6	Barry Snow Auckland	Intrastriatal Encapsulated Porcine choroid plexus cells for Parkinson's disease

Datablitz - Session 2 14.10 – 14.50

Chair person: Daniella Rylander

1	Ludivine S Breger Cardiff	Influence of chronic L-DOPA treatment on graft tolerance in a rat model of Parkinson's disease
2	Tim I. Fieblinger Lund	Dendritic adaptations in striatal dSPNs following dopamine-depletion and L-DOPA treatment

3	Joanna Garcia Freiburg	L-Dopa sensitivity following striatal transplantation: Behavioural and histological analysis in a partial double-lesion model of MSA-P
4	Regina Rumpel Hannover	Neuronal firing activity and gene expression changes in the subthalamic nucleus after transplantation of dopamine neurons in hemiparkinsonian rats
5	Irene Sebastianutto Lund	*In Vitro* Assay To Identify Putative Antidyskinetic Treatments Targeting D1-Receptor-Induced Phosphorylation Of Extracellular-Signal-Regulated Kinase-1/2 In The Dopamine Depleted Striatum
6	Patrick Aldrin-Kirk Lund	Elucidation of the functional contribution by striatal cholinergic interneurons and their involvement in L-DOPA induced dyskinesias using novel designer receptors and transgenic rats

Datablitz - Session 3 16.30 – 17.00

Chair person: Claire Kelly

1	Rana Soylu Lund	The role of mutant huntingtin expression in the paraventricular nucleus of the hypothalamus in the BACHD mouse model
2	M. Umar Sajjad Lund	Development of novel assays to quantify full-length wild type and mutant huntingtin using AlphaLISA technology
3	Luis Azmitia Freiburg	Directly reprogrammed neural cells from human fibroblasts of Huntington's Disease patients
4	Reena Prity Murmu Lund	Early-onset alterations in dendritic spine plasticity in a mouse model of Huntington's disease: mechanisms underlying early cognitive deficits in Huntington's disease?
5	Amy Evans Cardiff	Characterisation of FoxP1 in the striatum

Datablitz - Session 4 17.10 – 17.40

Chair person: Claire Kelly

1	Marcus Davidsson Lund	An unbiased validation assay of trans-splicing efficiency by randomized intron fragmentation
2	Liliane Tenenbaum Lausanne	An adeno-associated virus-based intracellular sensor of pathological Nuclear Factor-kB activation for disease-inducible gene therapy
3	Marija Fjodorova Cardiff	Effect of the environment on dopamine neuron subtypes in ventral mesencephalic grafts in a rat model of Parkinson's Disease
4	Rohit Sachdeva Lund	MicroRNA-9 regulated lentiviral vectors enable targeted transgene expression in microglia
5	Malin Åkerblom Lund	miR-125 distinguishes developmentally-born and adult-born olfactory bulb interneurons

Friday 30th November

Datablitz - Session 5 10.30 – 10.55

Chair person: Stephen Dunnett

1	Hanna S. Lindgren Lund	Impact of cortical alpha-synuclein overexpression on the performance in operant tasks of cortico-striatal function
2	Daniela Kuzdas Innsbruck	Heart Rate Variability analysis in a human-α-synuclein expressing mouse model of Multiple System Atrophy
3	Andreas Heuer Cardiff	Behavioural assessment of 6-OHDA lesioned mice on simple and complex behavioural tasks and the effects of primary fetal tissue grafts
4	Christian Hansen Lund	Novel alpha-synuclein-GFP mouse model displays progressive motor impairment and accumulation of alpha-synuclein with age

Datablitz - Session 6 12.20 – 13.00

Chair person: Elena Cattaneo

1	Claris Diaz Cardiff	The Corridor Test to Assess Sensorimotor Neglect Following Middle Cerebral Artery Occlusion
2	Ilknur Özen Lund	Regenerative potential of pericvascular progenitors in ischemic stroke
3	Christine Kaindlstorfer Innsbruck	Mesenchymal stem cells – the cure for MSA?

4	Laura Jensen Lund	Artificial bio-surfaces for stem cell differentiation
5	Victoria Roberton Cardiff	A new method of testing cells for *in vivo* transplantation in neurological disease
6	Robert Andres Bern	Responses of the Dopaminergic and Endogenous Neurogenic Systems in a Rat Model of Intracerebral Hemorrhage

Datablitz - Session 7 15.40 – 16.20

Chair person: Malin Parmar

1	Asuka Morizane Kyoto	Immune or inflammatory responses by allo- vs. auto-transplantation with primate iPS cell-derived neurons
2	Meltem Özer Hannover	Electrophysiological comparison of in vitro differentiated dopaminergic neurons derived from transgenic TH-EGFP mice and intrastriatal transplanted rat embryo derived mesencephalic neurons in the rat model of Parkinson´s disease
3	Pia Jensen Odense	Influence of oxygen tension on dopaminergic differentiation of human fetal stem cells of midbrain and forebrain origin
4	Jun Takahashi Kyoto	Sorting and transplantation of dopaminergic progenitor cells derived from human pluripotent stem cells
5	Olof Torper Lund	Survival of induced human neuronal cells from fibroblasts and astrocytes, after transplantation into the striatum of the adult rat
6	Daniella Rylander Lund	Dopaminergic ventral mesencephalic neurons can restore activity-dependent synaptic plasticity in the host striatum

DATABLITZ - SESSION 1: THURSDAY 29th November 11.20 – 12.00

1.1 Olga Baron

FGF signalling ensures adequate nigrostriatal pathway formation

Authors: O. Baron[1], A. Ratzka[1], M. Özer[1,2], C. Grothe[1,2]
Affiliations: [1] Institute of Neuroanatomy, Hannover Medical School, 30652 Hannover,
[2] Center for Systems Neuroscience, 30559 Hannover

Fibroblast growth factor 2 (FGF-2) is a relevant neurotrophic factor for mesencephalic dopaminergic (mDA) neurons, whose degeneration or abnormal development is associated with Parkinson's disease and Schizophrenia, respectively. FGF-2 is known to protect the adult mDA neurons from neurotoxic effects and to regulate the adequate development of Substantia nigra pars compacta (SNpc). We previously reported that in FGF-2 deficient mice the disbalanced FGF-signalling leads to an increased/ prolonged neurogenesis in mouse embryos (E14.5). Additionally, we found a decreased ontogenic neuronal cell death in the SNpc of newborn (P0) FGF-2 deficient mice, assigning a reduced nigrostriatal wiring control. Here, we established a suitable model to study the role of target-derived (FB) and intrinsic ventral midbrain (VM)-derived FGF-2 during nigrostriatal pathway formation. An EGFP transgenic mouse strain was applied for the VM explants, which allowed combining and distinguishing of individual VM and FB tissue from wild type and FGF-2 deficient E14.5 embryos, respectively. Loss of FGF-2 in both FB and VM resulted in significantly increased mDA fiber outgrowth compared to wild type cocultures. Further, FGF-2 signalling is necessary in both VM and forebrain since heterogenous cocultures deficient for FGF-2 in FB and VM, respectively, showed similar phenotypes with disorganized wide tracts. Additionally, the loss of target-derived FGF-2 in FB explants resulted in decreased caudo-rostral migration of glia-like cells. Preliminary data shows, that inhibition of FGFRs or supplementation with exogenous FGF results in a corresponding phenotype. Altogether these findings imply an intricate interplay of target-derived and VM-derived FGF signaling during nigrostriatal pathway formation and target innervation, which will be further studied including electrophysiological approaches.

In conclusion, the loss of FGF-2 seems to cause a developmental hyperplasia of SNpc and may result in an inadequate basal ganglia control, which might be causative for the previously described stress induced hyperactive behavioural phenotype.

1.2 Luis Quintino

Regulating GDNF expression using Destabilizing Domains leads to functional neuroprotection in the 6-OHDA model of Parkinson's Disease

Authors: Luis Quintino[1], Giuseppe Manfré[1], Angrit Namislo[1], Erika Elgstrand-Wettergren[1], Christina Isaksson[1] and Cecilia Lundberg[1]
Affiliations: 1- CNS Gene Therapy, Wallenberg Neuroscience Center,Lund, 22184 Lund, Sweden

Using a novel system based on destabilizing domains (DD) that regulates gene expression by targeting specific proteins for destruction we have been able to effectively regulate glial cell-derived neurotrophic factor (GDNF) expression in vivo.
The next step was to determine if regulated GDNF expression could protect nigral neurons in a Parkinsons Disease model. Lentiviral vectors expressing GDNF-DD, wildtype GDNF or regulated yellow fluorescence protein (YFP-DD) were injected to the striatum of of rats. In one group of GDNF-DD was turned on (DD-ON). In another group of GDNF-DD animals the expression was turned off (DD-OFF). Three weeks after vector delivery, the animals were lesioned with 6-hydroxydopamine (6-OHDA) in a striatal lesion protocol. The GDNF and DD-ON were able to protect striatal projections and of substantia nigra neurons. The neuroprotection given by the GDNF-DD resulted in behavior improvements in forelimb akinesia, forelimb assymetry and decrease of drug induced rotations. In all assessments, the DD-OFF group was comparable to the YFP-DD control group, suggesting that the GDNF-DD is tightly regulated under pathological conditions. The results indicate that the DD system is a promissing tool for regulating GDNF in vivo.

1.3 Mary Ní Fhlathartaigh

Fibrin as a biomaterial matrix for delivery of GDNF overexpressing MSCs to the adult rat brain

Authors: Teresa Moloney[1,2], Mary Ní Fhlathartaigh[1,2], Mangesh Kulkarni[2], Kiah McCabe[1], Emma Collins[1] Abhay Pandit[2], Eilis Dowd[1]
Affiliations: [1]Department of Pharmacology & Therapeutics and [2]Network of Excellence for Functional Biomaterials, National University of Ireland, Galway, Ireland.

The development of disease-modifying therapies for Parkinson's disease will probably necessitate the development of a multimodal treatment approach because of the heterogeneous nature of the disease's pathogenesis. Biomaterial platforms offer unique potential upon which to develop multimodal therapies for neurological disorders given their

potential to 1) act as a supportive matrix for cell replacement strategies, 2) provide vehicles to deliver multiple therapeutic proteins and plasmids directly to the CNS and 3) offer adjustable degradation profiles to allow temporally-controlled release of therapeutic factors[1]. This study sought to determine the suitability of a commercially-available fibrin matrix (Baxter's TISSEAL®) as a biomaterial upon which to build such a multi-modal approach.
Male Sprague-Dawley rats received bilateral intra-striatal injections of the fibrin vehicle (n=4) or the fibrin matrix (n=6), or they received mesenchymal stem cells (MSCs) transduced to overexpress GDNF either alone (n=8) or in the fibrin matrix (n=8). Rats were then sacrificed at different time-points and the brains isolated to determine fibrin polymerisation and degradation, MSC graft volume, GDNF release (GNDF immunohistochemistry), and host immune response (microglial and astrocyte immunohistochemistry).
We found that the fibrin matrix was biocompatible with the brain in that it polymerised *in situ*, degraded over time, and did not induce a significant host immune response (relative to vehicle-injected animals). Moreover, when GDNF transduced MSCs were delivered in the matrix, we found that it permitted cell survival and GDNF release into the surrounding striatal parenchyma, and also reduced the microgliotic reaction to the cells.
Therefore this study shows that fibrin may represent a compatible biomaterial for employment as a multimodal platform for CNS therapeutics. Future studies will test the bioactivity of GDNF released from fibrin in a model of Parkinson's disease, as well as investigating the complexing of therapeutic plasmids and proteins to the fibrin platform to target other pathogenic processes.

1.4 Stefanie Seiler

Neuroprotective capacity of Endothelial Progentitor Cells in an in vitro model of Parkinson's Disease

Authors: Stefano Di Santo PhD, Stefanie Seiler Msc, Nicole Porz MD, Angélique Ducray PhD, Andreas Raabe MD and Hans R. Widmer PhD
Affiliations: Department of Neurosurgery, University of Berne, Switzerland

Background: There is growing evidence that stem and progenitor cells exert regenerative actions by means of paracrine factors. In the present study we tested the hypothesis that soluble factors secreted by cultured endothelial progenitor cells (EPC) may support dopaminergic cell functions and survival.
Methodology: EPC were isolated from peripheral blood of healthy human donors. Cells were cultured in hypoxic conditions (1.5% O_2) to stimulate the secretion of growth factors. Primary cultures from fetal rat embryonic (E14) ventral mesencephalon (VM) were treated with EPC derived conditioned medium (EPC-CM). The effect of EPC-CM was monitored by immunocytochemical analyzes for tyrosine hydroxylase (TH) and for a marker of microglial cells (Iba1).

Results: Incubation of primary VM cultures with EPC-CM resulted in a significant increase in TH-ir cell densities and of microglial cells. Strikingly, EPC-CM displayed neuroprotection against MPP+ toxicity which was used as an in vitro model of Parkinson's Disease. Moreover, the effect of EPC-CM on TH-ir cells persisted upon treatment with Ara-C conducted in order to limit microglia expansion.
Conclusions: Our results suggest that paracrine factors derived from EPC promote viability and/or differentiation of dopaminegic cells. Importantly, the effect of EPC-CM seems to involve the expansion of microglia cells. A deeper characterization of EPC-CM constituents and their interactions with microglia cells might represent a cell-free approach to explore novel strategies for the treatment of Parkinson's Disease.

1.5 Deirdre B. Hoban

Assessment of a type 1 collagen hydrogel as a support matrix for neurotrophin-secreting stem cells in the hemi-Parkinsonian rat brain

Authors: Deirdre B. Hoban[1], Benjamin Newland[1,2], Teresa C. Moloney[1,2], Linda Howard[3], Abhay Pandit[2], Eilis Dowd[1,2].
Affiliations: [1]Department of Pharmacology & Therapeutics, [2]the Network of Excellence for Functional Biomaterials, and [3]the Regenerative Medicine Institute, National University of Ireland, Galway, Ireland

The most effective experimental neuroprotectant for Parkinson's disease that has been identified from extensive preclinical studies is the neurotrophin, glial cell line-derived neurotrophic factor (GDNF). However, its efficacy in clinical trials has been hampered by issues related to its delivery. A possible alternative approach for GDNF delivery is through *ex vivo* gene therapy, in which suitable cells, such as bone marrow-derived mesenchymal stem cells (MSCs), are genetically engineered to overexpress the neurotrophin prior to transplantation. However, one factor limiting the use of MSCs for intra-cerebral applications is their inadequate survival in the brain (Moloney *et al.*, 2010a; Moloney *et al.*, 2010b). Thus, this project is seeking to develop a biomaterials-based cell delivery matrix that could attenuate the host response to, and increase survival of, the cell transplant, and also allow for sustained GDNF release from, and bio-functionality of, GDNF-secreting MSCs in the rat brain.
The specific aims of this project were to assess the impact of a bovine type 1 collagen hydrogel on the host response to rat MSCs transduced with a GDNF-encoding retrovirus (GDNF-MSCs), as well as its impact on the survival of, and GDNF release from, the cells in the rat brain. Furthermore we sought to confirm the bio-functionality of the released neurotrophin from the hydrogel using the 6-hydroxydopamine rat model of PD.
Unlesioned or 6-hydroxydopamine-lesioned male Sprague-Dawley rats received intrastriatal injections of 1) the hydrogel vehicle, 2) the collagen hydrogel, 3) GDNF-MSCs in the hydrogel

vehicle, or 4) GDNF-MSCs in the collagen hydrogel (n=5 per group). *Post-mortem*, the impact of the hydrogel on GDNF-MSC immunogenicity and survival, as well as on GDNF-MSC-mediated GDNF release and nigrostriatal neuroprotection was assessed by immunohistochemistry.
Although the collagen hydrogel did not improve the survival of the GDNF-MSCs overall, it significantly reduced the immunogenicity of the cells in the rat brain as evidenced by reduced microgliosis and astrocytosis at the graft site. Moreover, the hydrogel did not impede the diffusion of GDNF into the surrounding striatal tissue, and the secreted neurotrophin was capable of protecting the nigrostriatal terminals surrounding the transplant. Thus, future studies will focus on using collagen hydrogel for temporally dynamic release of pro-survival factors in order to improve the efficacy of this *ex vivo* gene therapy approach for Parkinson's disease.

1.6 Barry Snow

Intrastriatal Encapsulated Porcine choroid plexus cells for Parkinson's disease

Authors: Barry Snow[1], Arnold Bok[1], David McAuley[1], Mark Simpson[1], Lorraine Macdonald[1], Jon Stoessl[2], Hai Lin[3], Wei Wang[3], Xian-Ming Luo[3], Marilyn S Geaney[3], Shaun Wynyard[3], Jian Guan, Robert B Elliott[3], Stephen JM Skinner[3], Paul L-J Tan[3],
Affiliations: 1:Auckland Hospital, 2:University of British Columbia, 3:Living Cell Technology

Intrastriatal growth factor enhancement with either direct infusion or gene therapy is an attractive but as yet unproven therapy for PD. The failure of human studies despite encouraging animal studies may be due to issues with delivery or perhaps the wrong growth factors.
Porcine choroid plexus produces an extensive range of growth and other factors that enhance neuronal growth and survival.
We have developed an encapsulation technique using an alginate membrane that permits prolonged survival of porcine cells in the peritoneum of human diabetes and in the brains of animal models of PD, Huntington disease and stroke without the need for immune suppression. We use cells derived from an isolated herd of pigs that have been certified free of potential pathogens.
Intrastriatal transplants of encapsulated porcine choroid plexus reverses parkinsonism in 6OHDA rat and unilateral MPTP monkey models of PD as demonstrated by improved rotational behaviour and increased striatal TH staining. There is no histological evidence for inflammatory reactions to the implants. The capsules have been shown to be intact and contain viable cells at 6 months after implantation in rats. The monkey models showed sustained clinical improvement out to 6 months.
We are now designing a Phase I study of 4 human subjects with PD. These subjects will have been selected for deep brain stimulation and will be offered a unilateral transplant of

encapsulated porcine choroid plexus cells. They will have close and perpetual monitoring for infection. They will be assessed clinically and with PET before and 6 months after transplant. At that time, they may continue observation or be offered DBS, depending upon their clinical response and the advice of the independent DSMB.

DATABLITZ - SESSION 2: THURSDAY 29th November 14.10 – 14.50

2.1 Ludivine S Breger

Influence of chronic L-DOPA treatment on graft tolerance in a rat model of Parkinson's disease

Authors: Ludivine S Breger [1,2], Korbinian W Kienle[1], Stephen B Dunnett[2] and Emma L Lane[1]
Affiliations: [1]School of Pharmacy and Pharmaceutical Sciences, Cardiff University, Wales, UK
[2]Brain Repair Group, School of Biosciences, Cardiff University, Wales, UK

Parkinson's disease (PD) is the most common neurodegenerative movement disorder. Currently, L-DOPA remains the gold standard treatment, however, it is associated with the development of abnormal involuntary movements called dyskinesia. An alternative approach to the treatment of PD currently investigated in clinical trial is the replacement of the lost striatal dopaminergic innervation by transplantation of foetal ventral mesencephalon (VM) dopaminergic precursor cells. The outcome of previous clinical trials using this approach have been variable and led, in some patients, to the direct development of motor complications, namely graft-induced dyskinesia. The causes of such variability in the efficacy of cell therapy and side effects are still to be determined. Most of the patients entering clinical trials are at an advanced stage of the disease; they have been under L-DOPA treatment for many years and remain under medication after transplantation. However, it has never been resolved whether L-DOPA treatment could affect the survival, the implantation or function of the graft and more generally the success of cell therapy in PD patients. We investigated the effect that chronic L-DOPA treatment prior to and post grafting had on the survival and the function of the graft. 6-hydroxydopamine lesioned rats were treated daily with saline or L-DOPA for the 8 weeks preceding and following VM allograft or xengograft. During this period, the animals were assessed for functional recovery and dyskinesia at regular intervals. The different treatment regimes did not affect the functional recovery but influenced the dyskinesia severity when the animals were assessed post-transplantation. More importantly, L-DOPA treatment seems to lead to an increased inflammatory response surrounding the graft. These results could have a direct impact on clinical trials as it suggests that L-DOPA treatment can influence how well the transplant is tolerated, especially as post-mortem studies reported infiltration of immune cells in grafted patients.

2.2 Tim I. Fieblinger

Dendritic adaptations in striatal dSPNs following dopamine-depletion and L-DOPA treatment

Authors: Fieblinger T[1], Alcacer C[1], Chan CS[2], Plotkin JL[2], Cenci MA[1], Surmeier DJ[2]
Affiliations: [1] Basal Ganglia Pathophysiology Unit, Department of Experimental Medical Science, Lund University, Lund, Sweden; [2] Department of Physiology, Northwestern University Feinberg School of Medicine, Chicago, Illinois 60611, USA.

While the initial events leading to the motor symptoms Parkinson's Disease (PD) and L-DOPA-induced Dyskinesia (LID) are identified – loss of dopaminergic neurons and subsequent treatment with L-DOPA, respectively – the impact following these events on other parts of the brain is largely unknown. The Striatum, receiving direct dopaminergic input from the Substantia Nigra pars compacta (SNc) and being crucially implicated in action selection, is indicated to be one of the most affected brain-regions. However, how the principal striatal neurons (SPNs) adapt to the pathophysiological stages of PD and LID is only poorly understood.
Using multiphoton imaging in combination with whole-cell patch-clamping and two-photon glutamate uncaging we investigated cellular changes in striatal direct pathway neurons (dSPNs), in response to different stages of Basal Ganglia pathophysiology. We find that, in contrast to indirect pathway neurons (iSPNs), dSPNs are largely unaffected by dopamine depletion alone. However, subsequent L-DOPA treatment triggers substantial adaptations in dSPN dendrites. These are (I) a significant reduction in spine-density on dSPN dendrites, (II) increased relative NMDA-currents at the remaining spines and (III) decreased calcium-transients in response to back-propagating actionpotentials (bAPs). Interestingly, Dopamine D1-receptor activation can increase bAP-evoked calcium-transients - however, only after L-DOPA-treatment that induced LID.
Our findings suggest that SPN dendrites are the main site of neuronal adaptation in the Striatum. While dopamine depletion left dSPN-dendrites unaffected, subsequent L-DOPA treatment triggers a complex homeostatic response and aberrant modulation of bAP-evoked calcium-transients by D1-receptor activation seems to be one mechanism underlying LID.

2.3 Joanna Garcia

L-Dopa sensitivity following striatal transplantation: Behavioural and histological analysis in a partial double-lesion model of MSA-P

Authors: A Marsch[1], J García[1,2], R McLean[1], GK Wenning[3], G Nikkhah[1], MD Döbrössy[1], C Winkler[2]
Affiliations: [1]Department of General Neurosurgery, Laboratory of Molecular Neurosurgery, University Freiburg - Medical Center, 79106 Freiburg, Germany; [2]Department of Neurology, University Freiburg - Medical Center, 79106 Freiburg, Germany; [3]Neurological Research Laboratory, University Hospital, Anichstrasse 35, 6020 Innsbruck, Austria

Multiple system atrophy (MSA) is a neurodegenerative disease characterised by progressive autonomic failure, cerebellar ataxia (MSA-C) and parkinsonism (MSA-P) due to neuronal loss in multiple brain areas associated with oligodendroglial cytoplasmic α-synuclein inclusion bodies. There are no effective treatments for MSA, and as the disease advances most MSA-P patients lose their sensitivity to L-Dopa due to the loss of striatal dopaminergic post-synaptic receptors. Based on a unilateral sequential double lesion striatal rat model combining a partial 6-hydroxydopamine (6-OHDA) lesion followed by a striatal quinolinic acid (QA) lesion, the current study examined whether, and to what degree grafting of embryonic E14.5 striatal cells can i.) mediate functional recovery in general, and ii.) promote L-Dopa sensitivity in particular in this model.
The experimental design included three groups (Double Lesion, DL, n=18; Double Lesion + Graft, Tx, n=20; and a naïve Contol, n=10), and four behavioural testing blocks: Baseline (Corridor, Paw-reaching); PL1 (post 6-OHDA lesion but prior to QA and the graft; Corridor, Paw-reaching, Amphetamine-induced rotation, Stepping, and Cylinder); PL2 and PL3 (4 and 8 weeks after grafting, respectively; all the tests were performed). L-Dopa sensitivity was tested using 6mg/kg L-DOPA + 10mg/kg benserazide at PL1-3 in the Cylinder and the Stepping tests at 20 and 40 min after s.c. injection in a double-blind latin square design where we used saline as a counter injection. Apomorphine rotation was carried out prior to perfusion.
Behavioural analysis showed no difference between DL and Tx groups in either amphetamine- nor apomorphine-induced rotation, nor in the Paw-reaching tests at PL1-3. In the Cylinder test we observed a positive response to L-Dopa in the Tx group, but unexpectedly in the DL group also, despite the loss of striatal tissue. However, in the Stepping test we observed a significant and selective graft mediated return to L-Dopa responsiveness in PL2 with a sustained tendency in PL3. Striatal dopamine loss in the DL and Tx rats was 75-80%, and the QA lesion reduced the ipsilateral striatum by about 40%. The striatal grafts had a mean volume of 3.2 mm^3.
The data analysis needs to be further refined incorporating the following additional parameters: i.) position of partial 6-OHDA lesion; ii.) position of QA lesion; iii.) DARPP-32 cell

numbers; and iv.) and the presence or absence of L-DOPA induced dyskinesia assessed post-PL 3. However, after initial assessment, the current study suggests that striatal grafts may restore L-Dopa sensitivity in a partial double-lesion model of MSA-P.

2.4 Regina Rumpel

Neuronal firing activity and gene expression changes in the subthalamic nucleus after transplantation of dopamine neurons in hemiparkinsonian rats

Authors: Rumpel R (1), Alam M (2), Klein A (1), Oezer M (1,3), Wesemann M (1), Krauss JK (2,3), Schwabe K (2,3), Ratzka A (1), Grothe C (1,3)
Affiliations: (1) Institute of Neuroanatomy, Hannover Medical School, Hannover, Germany
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The loss of dopaminergic (DA) neurons in the substantia nigra pars compacta and the resulting DA depletion in the striatum lead to dysfunction of basal ganglia activity with neuronal hyperactivity in the subthalamic nucleus (STN). In Parkinson's disease (PD) patients and in 6-hydroxy dopamine (6-OHDA) lesioned rats the STN firing rate is enhanced, as well as oscillations in the β-frequency band (15-30 Hz). Intrastriatal transplantation of DA neurons has been shown to re-innervate the host brain and restore DA input.
To better understand the effect of striatal transplantation of DA cells on the STN, we combined behavioral and histological findings with electrophysiological extracellular recordings, as well as qRT-PCR analyses of GABAergic and glutamatergic transporter and receptor genes. In animals, which were transplanted with cells derived from the mesencephalon of E12 rat embryos in the striatum, the rotational behavior induced by amphetamine was alleviated; further, STN neuronal firing abnormalities were improved. Interestingly, both behavioral and electrophysiological measures were dependent on the number of surviving tyrosine hydroxylase positive cells. In animals with small grafts (300-1000 cells) the recovery of drug-induced rotational behavior was 50 %, while rats with large grafts (2000-6000 cells) displayed overcompensation of 116 %. Only in rats with large grafts the enhanced firing rate and the coherence of β-oscillatory activity between cortex and STN decreased to the level of naive animals. Although grafted rats displayed restored expression of the GABA synthesizing enzyme Gad67 in the striatum compared to naive rats, the grafts induced a decrease in NMDA receptor subunit expression. Interestingly, the NMDA receptor subunit 2B was also less expressed in the STN, both compared to 6-OHDA-lesioned and naive rats. In summary, DA grafts partially restore functional deficits and neuronal activity of STN in PD rats. However, functional recovery may be compromised by changes in receptor gene expression induced by DA grafts.

2.5 Irene Sebastianutto

In Vitro Assay To Identify Putative Antidyskinetic Treatments Targeting D1-Receptor-Induced Phosphorylation Of Extracellular-Signal-Regulated Kinase-1/2 In The Dopamine Depleted Striatum

Authors: Sebastianutto I., Fieblinger T. and Cenci M.A.
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The dopamine (DA) precursor, L-DOPA, remains the most effective treatment for Parkinson's disease (PD) but causes L-DOPA-induced dyskinesia (LID) in a majority of patients. Previous work has established that induction and expression of LID is paralleled by a sustained activation of extracellular signal-regulated-kinases 1 and 2 (ERK1/2) via D1 receptors in the dopamine-depleted striatum. Here we describe an in vitro approach to identify compounds that inhibit D1 receptor-dependent pERK activation in the dopamine-denervated striatum. Adult rats sustained 6-hydroxydopamine (6-OHDA) lesions of the medial forebrain bundle and were screened on an amphetamine-induced rotation test. Vibratome-cut striatal slices (250 µm) were prepared and kept on a standard aCSF at physiological temperature and under constant oxygenation. Bath-application of the selective D1R-agonist SKF-38393 (10 µM, 7 min) induced an 80-90% increase in the levels of pERK1/2, as measured by Western Blotting. However, the same treatment did not affect levels of pERK1/2 in the unlesioned striatum. Blocking D1R (SCH-23390, 10µM), Protein kinase A (KT-5720, 500nM), or the ERK upstream kinase (MEK; UO126, 10µM) prevented the induced increase of striatal pERK1/2.
Using this in vitro model, we screened different categories of compounds for their ability to inhibit D1R-induced pERK1/2: effectors of ionotropic and metabotropic glutamate signaling (NR2B-antagonist Ro-25-6981; mGluR1-antagonist EMQMCM; mGluR5-antagonist MTEP; mGluR2/3-agonist LY370268) as well as modulators of calcium-related signaling (e.g. L-type calcium channel blocker Isradipine).
Taken together, our results indicate that antagonists of voltage-dependent calcium channels or mGluR5, but not NMDA receptor antagonists, have the ability to inhibit D1R-dependent increase of pERK1/2 in the DA-denervated striatum. We suggest that drugs targeting these molecules and related signaling pathways have therapeutic potential for the treatment of LID.

2.6 Patrick Aldrin-Kirk

Elucidation of the functional contribution by striatal cholinergic interneurons and their involvement in L-DOPA induced dyskinesias using novel designer receptors and transgenic rats

Authors: Patrick Aldrin-Kirk, Marcus Davidsson and Tomas Björklund
Affiliations: Molecular Neuromodulation Labs, Lund University, Sweden

L-DOPA induced dyskinesia (LID) is a major obstacle that limits current therapy in patients with Parkinson's disease. LID may involve modulatory changes in striatal medium spiny neurons (MSNs), which play a critical role in controlling and initiating voluntary movements. Modulation of MSNs may involve several distinct striatal cell populations that could be altered by L-DOPA treatment. Recent evidence suggests that dopamine mediated activation of cholinergic interneurons, potentially through the ERK pathway, may play a pivotal role in the modulation of MSNs during dyskinesia.
Here, we aim to investigate the role of cholinergic interneurons in the healthy, parkinsonian and LID modified striatum of a novel transgenic rat line, using the DREADD (Designer Receptors Exclusively Activated by Designer Drugs) approach. These DREADDs utilize a mutated form of the hM_4D receptor, which has lost the affinity to its endogenous ligand. However, the receptor can instead be modulated by administering Clozapine-N-Oxide (CNO, a naturally occurring metabolite of Clozapine) to induce silencing of expressing cells. Thus, the DREADD system allows for controlled inhibition of specific cell populations with regional specificity when used in combination with Cre/lox AAV vectors. We have previously validated the DREADD receptor system by controlled inhibition of TH-expressing cells in the substantia nigra, producing rats exhibiting reversible Parkinsonism following CNO administration. In the present study, Cre-recombinase is expressed under the Chat promotor of transgenic rats, limiting the expression to cholinergic neurons. We intend to identify the most suitable viral vector for transduction of cholinergic interneurons, using flexed GPF AAVs. Serotypes 1, 2, 5, 8 and 9 are being evaluated in both striatal and septal cholinergic interneurons with this end in mind. GFP expression is then used to compare the transduction efficiency. Once optimized, our DREADD/AAV approach can be used to investigate the role of striatal cholinergic interneurons in dyskinesia.

DATABLITZ - SESSION 3: THURSDAY 29th November 16.30 – 17.00

3.1 Rana Soylu

The role of mutant huntingtin expression in the paraventricular nucleus of the hypothalamus in the BACHD mouse model

Authors: Rana Soylu, Barbara Baldo and Åsa Petersén
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Depression, anxiety, sleep disturbances and metabolic dysfunction are clinically relevant aspects of Huntington's disease (HD). Recent studies suggest that these early non-motor symptoms of HD might originate from hypothalamic dysfunction. Neuropathological studies

have showed loss of neurons producing oxytocin and vasopressin, neuropeptides involved in the regulation of emotion and metabolism, in the paraventricular nucleus (PVN) of the hypothalamus in clinical HD. Furthermore, animal models have recapitulated key hypothalamic and neuroendocrine changes in HD. The BACHD mouse, a widely used animal model of HD, displays both psychiatric-like features and a metabolic phenotype. As it was generated with loxP sites flanking the mutant *huntingtin (htt)* gene, deletion of mutant htt in specific cell populations can be obtained using cre recombinase (cre). Interestingly, in this model the metabolic phenotype can be prevented by deletion of mutant htt in the hypothalamus. However the specific hypothalamic cell type responsible for the metabolic phenotype needs to be further identified.
The aim of this study was to investigate whether selective deletion of mutant htt in PVN neurons of BACHD mice would reverse the metabolic and psychiatric-like phenotype. The BACHD mice were therefore crossed with mice expressing cre under a common transcription factor for PVN cells, Sim 1 (Single-minded 1). Mice were monitored for body weight changes and percentage of body fat composition. The behavioral and motor phenotypes were assessed using Porsolt forced swim test, the elevated plus maze, the sucrose preference test and the open field test. Our data so far show that silencing mutant htt in Sim1 neurons ameliorates the metabolic phenotype in BACHDSim1Δ male mice but not in female mice. These results indicate sex specific differences in the regulation of metabolism in BACHD mice.

3.2 M. Umar Sajjad

Development of novel assays to quantify full-length wild type and mutant huntingtin using AlphaLISA technology

Authors: Muhammad Umar Sajjad[1], Genevieve Pinard[2], Christian Fafard[2], Chantal Illy[2], Åsa Petersén[1] and Deniz Kirik[3]
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Huntington's disease (HD) is a hereditary neurodegenerative disease without a cure. It is caused by an expansion of CAG repeats in the HD gene that encodes the huntingtin (htt) protein. Currently, there are several animal models that recapitulate the disease phenotype and knockdown of mutant htt in several of these models have shown beneficial therapeutic effects. However, there are limited tools for quantification of different forms of soluble full-length (FL) htt in biological samples although they are needed to assess the efficacy of potential therapeutic therapies. Therefore, we decided to establish bioassays that can

detect and selectively quantify wild type (WT) and mutant forms of htt in biological samples with complex matrices.
We developed two-step no wash bioassays to detect soluble forms of FL htt by using the AlphaLISA® technology. In each assay, a pair of antibody was chosen to capture either total or mutant htt. Assay performance was tested in HEK293 cells, WT and BACHD brain homogenates. Brain samples from BACHD mice were incubated with antibody-conjugated magnetic beads to deplete mutant htt in order to allow selective quantification of the WT htt.
The AlphaLISA® platform was efficient at detecting endogenous and overexpressed forms of soluble htt in HEK293 cells and in brain homogenates. Total and mutant htt assays revealed differential htt expression in various brain regions of WT and BACHD mouse models. In addition, our results demonstrated that total htt levels in BACHD brain were only about 40-50% higher than WT mice, indicating that this mouse model does not exhibit overt overexpression of the protein.
In conclusion, the Htt AlphaLISA assays exhibited robust performance, high sensitivity and broad dynamic range. Hence, these assays can be used as a powerful tool to quantify soluble htt variants in experimental studies using both cellular and tissue samples.

3.3 Luis Azmitia

Directly reprogrammed neural cells from human fibroblasts of Huntington's Disease patients

Authors: Luis Azmitia[1], Mariana Klett[1], Philipp Capetian[2], Máté Döbrössy[1], Guido Nikkhah[1]
Affiliations: 1. Molecular Neurosurgery Laboratory, Neurosurgery, section of Stereotactical and Functional Neurosurgery, University Hospital Freiburg, Germany; 2. Section of Clinical and Molecular Neurogenetics, Section of Neurology, Campus SH, University Hospital Lübeck, Germany.

The reprogramming process described by Yamaka et. al., 2007 made a source of cells available that came from a differentiated into a pluripotent state, so called *iPS cells*, involving forced expression of transcription factors, resulting not only in time consumption but a complicated protocol and the risk of genomic alterations due the use of retroviral vectors. We combined an insertion free approach of transfecting 3 plasmids carrying the reprogramming factors by electroporation (Okita et al., 2011) into fibroblasts from Huntington's disease (HD) patients, propagated under basic neuralizing conditions.
After two weeks, cell structures resembling neural rosettes appeared, were aloud to get confluent, picked and harvested leading to a high yield of directly reprogrammed neural cells (drNCs).
These were positive for Nestin, ZO1 and PLZF, as BIII Tubulin. The PCR showed expression of Neurotensin, FoxG1, LHX9 and Pax6. After three weeks exposure to Sonic Hedgehog, FGF8,

Purmorphamin and the inhibition of the Wnt pathway, evidenced an expression of DLX, DSH, OTX2, GAD67 and Darpp32. A PCR from the genomic DNA during the reprogramming process (to check vector integration) was done and the cells were transplanted into rats to evaluate the risk of tumor formation.
This model of direct reprogramming using HD patient derived fibroblasts, gave rise to a neural stem cell and early developmental phenotype with a forebrain commitment. This process was malleable through the addition of growth factors and small molecules, promoting rostralization of an already established cell commitment, including the generation of Darpp32 positive cells. PCR from the gDNA showed no integration of the vector in the drNCs, and the in vivo grafting produced no tumor formation. In summary, the reprogramming protocol offers a valuable tool in the understanding of neurodegenerative diseases.

3.4 Reena Prity Murmu

Early-onset alterations in dendritic spine plasticity in a mouse model of Huntington's disease: mechanisms underlying early cognitive deficits in Huntington's disease?

Authors: Reena Prity Murmu, Anthony Holtmaat, Jia-yi Li
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In Huntington's disease (HD) cognitive symptoms precede the onset of classical motor symptoms, such as chorea, by almost a decade. In addition, cellular dysfunction occurs before the motor symptoms and neuronal loss in striatum and cortex become evident. This suggests that the early symptoms in HD, such as deficits in cognition may be due to a cellular dysfunction rather than a consequence of neuronal death. Abnormalities in dendritic spines are described in HD patients and in several animal models of the disease. Available evidence indicates that altered spine and synaptic plasticity could underlie the motor as well as cognitive symptoms in HD. However, the exact kinetics of spine alterations and plasticity in HD remains unknown. We have used *in-vivo* two-photon imaging technology through a cranial window to track dynamic changes in individual dendritic spines in a mouse model (R6/2) of HD as the disease progressed. *In-vivo* imaging over a period of 6 weeks revealed a steady decrease in dendritic spine density and survival on cortical neurons of R6/2 mice compared to control littermates. Very interestingly, we observed increased spine turnover, with concomitantly reduced persistent-type mature spines in the R6/2 mice throughout the disease. Additionally, we found mutant huntingtin aggregates associated with dendritic spines in R6/2 mice. Alterations in dendritic spine dynamics, survival and density in R6/2 mice were evident before the onset of motor symptoms suggesting that these alterations may underlie the early symptoms of HD. Our findings suggest a novel mechanism of impaired synaptic circuits in HD.

3.5 Amy Evans

Characterisation of FoxP1 in the striatum

Authors: Evans AE[1], Kelly CM[1], Taylor MV[2] and Rosser AE [1]
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Medium Spiny Neurons (MSNs) are the major projection neuron in the striatum and are lost in Huntington's disease (HD). A screen looking at gene expression changes in the developing striatum in embryonic mice (E12-E16) showed the transcription factor *FoxP1* to be the most up-regulated gene over this period. *FoxP1* is also expressed in the adult striatum and thus has the potential to be a marker of both developing and mature MSNs (Tamura *et al.,* 2003). Reliable detection of MSN precursors is of importance for the generation of properly specified MSNs from stem cell (SC) sources for transplantation therapy and for the development of disease models. The production of specific neuronal phenotypes from SCs requires that these cells be "directed" along a specific lineage. Therefore protocols using specific markers at different stages that direct the differentiation towards MSNs *in vitro* are crucial.
FoxP1 is widely expressed during development and has critical roles in heart and lung development. To date the function of *Foxp1* in the brain is unknown. Conventional FOXP1 knock outs (*FoxP1*$^{-/-}$) in mice are embryonically lethal from ~E16 due to cardiac defects (Wang et al., 2004). However, one can analyse the embryos before the onset of lethality. By grafting tissue from the embryonic striatum of E14 *FoxP1*$^{-/-}$ pups into an adult mouse lesioned striatum, we can overcome this lethality and study development *in vivo.* Within the *FoxP1*$^{-/-}$ grafts very few cells stained for DARPP-32, but there was an increase in CTIP2 compared to cells grafted from WT and *FoxP1*$^{+/-}$ pups. This result suggests that *FoxP1* has an important role in the differentiation of MSNs.

DATABLITZ - SESSION 4: THURSDAY 29th November 17.10 – 17.40

4.1 Marcus Davidsson

An unbiased validation assay of trans-splicing efficiency by randomized intron fragmentation

Authors: Marcus Davidsson[1], Marcos Torroba[1], Cecilia Lundberg[2] and Tomas Björklund[1]
Affiliations: [1]Molecular Neuromodulation Labs and [2]CNS Gene Therapy, Lund University, Sweden

Trans-splicing is an alternative form of splicing where two different DNA sequences, generate two different pre-mRNAs (mRNA with retained introns), a donor and an acceptor sequence, that can hybridize through complementary sequences and form one mRNA (containing only the coding exon sequence). This is in contrast to normal (*cis*) splicing, where one pre-mRNA forms an mRNA. *Trans*-splicing has emerged as a potential candidate for correction of a widespread range of inherited diseases but the method could also become a valuable tool in protein tracing and live imaging applications. In *trans*-splicing, only a segment of the mRNA is replaced, meaning that the gene is still under the control of its normal promotor and other endogenous regulatory elements are kept unaltered. However, the efficiency of *trans*-splicing in previous reports has been varying substantially and a thorough investigation of the requirements for efficient trans-splicing is therefore of great interest.
In this assay, we want to establish an unbiased, randomized screening assay for *trans*-splicing efficiency for virtually any gene. To screen an entire intron, we aim to fragment the intron into suitable sizes whilst still representing the entire intron. To do without sequence bias, we used PCR with varying dUTP/dTTP concentrations. The dUTP containing intron was then cleaved with Endonuclease V, yielding fragments with sizes dependent on the dUTP concentration used. These fragments were then cloned into a "splicing- acceptor" vector containing the C-terminal part of GFP. Meanwhile, a "splicing-donor" vector was created containing N-terminal GFP and full-length intron. When *trans*-splicing takes place, full length GFP is created from the two pre-mRNAs. Through cell-sorting by FACS based on GFP expression levels followed by high-number single-cell sequencing, we then aim to link GFP expression to sequences suitable for *trans*-splicing.

4.2 Liliane Tenenbaum

An adeno-associated virus-based intracellular sensor of pathological Nuclear Factor-kB activation for disease-inducible gene therapy

Authors: A. Chtarto[1,2], O. Bockstael[1,2], K. Vermoesen[3], E. Gebara[4], C. Melas[1,2], M. Levivier[5], O. De Witte[1], R. Luthi-Carter[4], R. Clinkers[3] and L. Tenenbaum[1,5,]
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Stimulation of resident cells by NF-kB activating cytokines is a central element of inflammatory and degenerative disorders of the central nervous system (CNS). This disease-mediated NF-kB activation could be used to drive transgene expression selectively in affected cells, using adeno-associated virus (AAV)-mediated gene transfer.
We have constructed a series of AAV vectors expressing GFP under the control of an inducible promoter containing NF-kB -responsive sequences derived from the human JCV neurotropic polyoma virus promoter, fused to a new tight minimal CMV promoter.
As a proof of concept, mouse embryonic cortical neurons were infected with an AAV2/1 vector containing the GDNF cDNA under the control of the NF-kB-responsive promoter (AAV-NF). GDNF became slowly expressed from 9 days post-infection with a peak at 26 days and in 60 days-old senescent cultures, an *in vitro* model for brain aging, neuron survival was enhanced as compared to control cultures infected with a GFP-encoding vector.
The NF-kB-responsive vector was then evaluated *in vivo* in the kainic acid (KA)-induced status epilepticus rat model for temporal lobe epilepsy in which NF-kB activation plays a central pathophysiological role. We demonstrate that AAV-NF, injected in the hippocampus, responded to disease induction, as characterized by microglial and astrocytic activation, by mediating GFP expression preferentially in CA1 and CA3 neurons and astrocytes. As expected, in the cerebellum, no sign of inflammation was present and GFP expression from the AAV2/1-NF vector was not induced.
Altogether, these data demonstrate the feasibility to use disease-activated transcription factor-responsive elements in order to drive transgene expression specifically in affected cells in inflammatory CNS disorders using AAV-mediated gene transfer.

4.3 Marija Fjodorova

Effect of the environment on dopamine neuron subtypes in ventral mesencephalic grafts in a rat model of Parkinson's Disease

Authors: Marija Fjodorova, Eduardo M Torres, Anne E Rosser, Stephen B Dunnett
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Rat embryonic ventral mesencephalic grafts (embryonic age 12-day-old (E12) and E14) contain two dopamine (DA) neuron subtypes: A9 neurons of the substantia nigra pars compacta and A10 neurons of the ventral tegmental area. In previous experiments co-expression of a G-protein-gated inwardly rectifying K^+ channel subunit (Girk2) and calbindin with tyrosine hydroxylase (TH) in dopamine cells allowed for the identification of A9 and A10 type DA neurons, respectively, in dopaminergic grafts. E12 grafts produced 5-fold larger DA cell yields than E14 grafts. In both donor age groups, 83% of TH^+ neurons were co-stained with Girk2. However, in E12 grafts 15% of TH^+ neurons co-labelled with calbindin, whilst in E14 grafts 27% of TH^+ neurons were $calbindin^+$. The aim of this study was to address the effect of the host striatum on the development of DA neuron sub-types in grafts. We looked at E12 and E14 grafts implanted into different cerebral targets to see if the site of implantation affected the survival of the two DA cell phenotypes in the graft. Striatum, nucleus Accumbens (N.Acc), and prefrontal cortex (PFC) all receive midbrain dopamine innervations, whilst the hippocampus receives very sparse DA input and was chosen as a control site. Surviving grafts were seen in all rats. Once again it was confirmed that younger donor age tissue has better survival rates and yields higher DA cell numbers. Preliminary results show that a greater proportion of A9 type DA neurons are found in the striatal and N.Acc grafts and, in both age groups, the same proportion of TH^+ neurons are co-stained with Calbindin regardless of the site of transplantation. The environment has a significant effect on the proportion of A9 type DA neurons in the grafts but not A10 type DA neurons.

4.4 Rohit Sachdeva

MicroRNA-9 regulated lentiviral vectors enable targeted transgene expression in microglia

Authors: Sachdeva R[1], Åkerblom M[1], Quintino L[2], Manfre G[2], Lundberg C[2], & Jakobsson, J[1]
Affiliations: [1] Molecular Neurogentics, Department of Experimental Medical Science, Faculty of Medicine, Lund University, Sweden.; [2] CNS Gene Therapy, Department of Experimental Medical Science, Faculty of Medicine, Lund University, Sweden.

Microglia have been found to play a crucial role in the pathogenesis of several brain disorders. The ability to target genetic modifications to microglia would allow mechanistic investigations as well as provide novel therapeutic strategies. However, specific targeting of microglia using viral vectors and cell specific promoters has thus far been unsuccessful. In this study we used an alternative way to successfully target transgene expression to microglia using lentiviral vectors and miRNA target sites.
We generated a lentiviral vector that contained a housekeeping PGK promoter driving GFP expression along with 4 perfect-match target sequences for microRNA-9. Thus, when microRNA-9 is present in the cell, it will down-regulate GFP expression. We used this construct to generate a reporter mouse using lentiviral transgenesis. When analysing the brains of several transgenic founders we found that microRNA-9 is active in astrocytes, oligodendrocytes and most neuronal populations as indicated by the lack of GFP expression in these populations. However, we found numerous GFP expressing cells with microglia morphology that co-labelled with IbaI. This demonstrates that microglia do not express microRNA-9 while brain cells with an ectoderm origin do.
We then exploited this finding by injecting microRNA-9 regulated lentiviral vectors bilaterally into the striatum of rats. 1 week after vector injection, the rats received a unilateral excitotoxic lesion. When we analysed the brains 3 weeks later, we found numerous GFP expressing microglia in the intact side of the brain. In the lesioned side there were numerous GFP expressing cells with the typical morphology of activated microglia. The great majority of GFP expressing cells co-labelled with IbaI. Noteworthy, we did not detect significant GFP expression in other cell types, such as neurons or astrocytes. In summary, we have generated a microRNA-9 regulated lentiviral vector that allows targeting of resident microglia. This vector should have a broad use both for mechanistic studies as well as novel gene therapy approaches.

4.5 Malin Åkerblom

miR-125 distinguishes developmentally-born and adult-born olfactory bulb interneurons

Authors: Malin Åkerblom[1], Rebecca Petri[1], Rohit Sachdeva[1] and Johan Jakobsson[1]
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New neurons are constantly formed from adult neural stem cells located in the subventricular zone the rodent brain. Here, the stem cells produce neuroblasts that migrate to the olfactory bulb (OB) where they differentiate into inhibitory interneurons.
Interestingly, several recent reports suggest a different functional role for developmentally generated and adult born OB-interneurons. It is therefore expected that the distinct OB interneurons populations have molecular differences. However, up to date, no molecular marker distinguishing these two cell populations has been identified.

MicroRNAs (miRNA) are small, non-coding endogenous RNA regulating mRNA. microRNA-125 (miR-125) is the mammalian homolog of *lin-4*, the first discovered miRNA regulating developmental timing in *C. elegans.* miR-125 is highly expressed in the mammalian brain and cell culture experiments have linked miR-125b to promotion of neuronal differentiation and regulation of synaptic strength and function. However, the *in vivo* role of miR-125 in the brain remains unknown.
In this study, we demonstrate developmentally generated OB interneurons to represent a unique population of cells in the adult brain lacking miR-125 activity. These miR-125 negative cells, born around birth and during the first post-natal week, are predominately found in the superficial part of the granule cell layer of the OB. In contrast, late-born OB interneurons are primarily positioned in the deep layers of the granule cell layer and express miR-125. These results identify miR-125 expression as a molecular marker distinguishing developmentally-born and adult-born interneurons and provides first molecular explanation to the differences of early-born and late-born OB interneurons.

DATABLITZ - SESSION 5: FRIDAY 30th November 10.30 – 10.55

5.1 Hanna S. Lindgren

Impact of cortical alpha-synuclein overexpression on the performance in operant tasks of cortico-striatal function

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Although Parkinson's disease (PD) has traditionally been considered a pure motor disorder, impairments in cognition are increasingly recognized among the non-motor symptoms with significant clinical impact. More specifically, cognitive impairments typically fall within the 'executive' domain, affecting functions such as cognitive flexibility and rule learning. Cortical and subcortical pathological accumulation of intracellular alpha-synuclein aggregates are considered to be a key factor to this cognitive decline.
Rats were pre-trained on an operant version on the classical delayed alternation task before receiving an injection of adeno-associated viral vectors (AAV) encoding for alpha-synuclein into the medial prefrontal cortex. Another subset of animals received excitotoxic lesions of the same prefrontal region and all rats were re-tested on the delayed alternation task twelve weeks post-injection. To evaluate the impact of cortical a-synuclein accumulation on reversal and learning, the rats were also tested in the delayed-non-matching-to-position task and thereafter reversed to delayed-matching to position.

Excitotoxic lesions of the medial prefrontal cortex impaired performance in the delayed alternation and delayed-non-matching-to-sample task, showing a reduced choice accuracy at all delays, suggesting that the deficit is of the a frontal-type executive type rather than of short-term memory. It had however no effect on the reversal to, or on the acquisition of the delayed-matching-to-position task. In contrast, rats with a-synuclein over-expression in the same cortical region showed impaired learning of this task but did reach control performance in the end of the testing period. Post-mortem immunohistochemistry revealed widespread a-synuclein expression in several of the projection areas of the medial prefrontal cortex together with a-synuclein-positive axonal swellings.

5.2 Daniela Kuzdas

Heart Rate Variability analysis in a human-α-synuclein expressing mouse model of Multiple System Atrophy

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Background: Multiple System Atrophy (MSA) is a rapidly progressing, adult-onset neurodegenerative disease. MSA patients present with parkinsonism, cerebellar ataxia and progressive autonomic failure. The major hallmark of MSA is the appearance of glial cytoplasmic inclusions (GCIs) with their main component α-synuclein (αSYN).
The animal model used in this project has constitutive overexpression of human αSYN in oligodendrocytes, mild neuronal degeneration and the according motor phenotype.
The aim of this project is the further characterization of cardiovascular autonomic failure (CAF) in this animal model. The analysis of autonomic parameters (i.e. ECG for deriving heart rate [HR] and its variability [HRV] and body temperature) has been performed in transgenic (tg) animals and age-matched wildtype controls.
Rationale and objective: The rationale of this project is that in human MSA CAF affects the balance between sympathetic and parasympathetic function leading to neurogenic orthostatic hypotension and reduced HRV. We aimed to investigate whether CAF also occurs in the tg PLP MSA mouse model.
Results: We observed a significant reduction of HRV (measured by RMSSD (ms) - a measure of parasympathetic activity) consistent with neurodegeneration of cholinergic neurons in the Nucleus ambiguus.
Conclusion: These findings are of great interest because the reduced HRV and

corresponding neuropathology replicate characteristic CAF features present in human MSA. Our experimental data support HRV as a potential non-motor marker in preclinical MSA studies.

5.3 Andreas Heuer

Behavioural assessment of 6-OHDA lesioned mice on simple and complex behavioural tasks and the effects of primary fetal tissue grafts

Authors: Andreas Heuer, NgocNga Vinh and Stephen B. Dunnett
Affiliations: Brain Repair Group, School of Biosciences, Cardiff University, Cardiff, UK

The 6-OHDA mouse lesion model of Parkinson's disease has received increasing attention in recent years. In the present experiment we aimed to investigate the effects 6-OHDA lesions to the medial forebrain bundle in C57/Bl6 mice on a battery of simple motor tests (drug-induced rotation, rotarod, corridor) and the lateralised choice reaction time task conducted in the mouse 9-hole box. The choice reaction time task allows for the objective assessment of response accuracy, reaction and movement time latencies, as well as motor learning and functional recovery. After assessment of the lesion-induced deficits a subgroup of lesioned mice was engrafted with E12.5 ventral mesencephalic tissue. After histological analysis of lesion extent and graft size, statistical analysis showed that mice which were grafted partially improved on parameters of the choice reaction time task whereas effects of simple motor behaviour failed to reach statistical significance. This study shows the ability of ventral mesencephalic tissue to ameliorate some of the lesion-induced deficits and the power of operant testing over tests of simple motor behaviour in detecting small but significant improvements. Operant assessment via the choice reaction time task offers a powerful tool for the assessment of therapies that are based on cell replacement.

5.4 Christian Hansen

Novel alpha-synuclein-GFP mouse model displays progressive motor impairment and accumulation of alpha-synuclein with age

Authors: Christian Hansen[1*], Tomas Björklund[2], Geraldine Petit[3], Reena Murmu[1], Patrik Brundin[3] and Jia-Yi Li[1]
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Parkinson's Disease (PD) is the second most common neurodegenerative disorder in the world. The cardinal symptoms of the disease are primarily caused by selective loss of dopaminergic neurons in the SNpc, which leads to impairment of locomotor function. The resulting symptoms include rigidity, bradykinisia and resting tremor. Today there is still no medicine that can effectively stop disease progression and the gold-standard medication remains L-DOPA, which was discovered over half a century ago.
Accumulation of the presynaptic protein alpha-synuclein (α-syn) can accelerate progression of Parkinson's disease (PD). Here we describe a novel Bacterial Artificial Chromosome (BAC) transgenic model, in which we have expressed human α-syn fused to GFP under control of the mouse α-syn encoding gene. We observed a strong expression of α-syn-GFP in different brain regions, including dopaminergic neurons of the Substantia Nigra par compacta (SNpc), ventral tegmental area (VTA). Impairment of locomotor activity was observed both in open field assay and rotarod as the mice aged. This effect was dependent on amphetamine induced dopamine release in open field assay, suggesting that dysfunction of the dopaminergic neurons is a slowly progressing process in these mice. In addition, we observed that the transgenic mice develop olfactory deficits as they aged, which is interesting as olfactory deficits is also an early clinical marker of PD.
We confirmed by Western blotting that α-syn-GFP accumulates and aggregates as the mice aged. Furthermore, we could detect increased accumulation and aggregation of α-syn-GFP in the cortex of living aged mice by two-photon microscopy, implying the potential use of the mice to track a-syn aggregation *in vivo*. In conclusion, the data indicate that the novel mouse model can be very useful for research on α-syn biology and involvement in PD pathogenesis.

DATABLITZ - SESSION 6: FRIDAY 30th November 12.20 – 13.00

6.1 Claris Diaz

The Corridor Test to Assess Sensorimotor Neglect Following Middle Cerebral Artery Occlusion

Authors: Claris M. Diaz[1], Rebecca C. Trueman[2], Anne E. Rosser[1] & Stephen B. Dunnett[1]
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Stroke is a leading cause of death and disability in the developed world; therefore it is vitally important that therapeutics are developed for the consequences of this disease. This requires robust preclinical models and assays, which are relevant to the human condition. Striatal damage induced by middle cerebral artery occlusion (MCAO) in the rat is a suitable

animal model for assessing behavioral and motor deficits post stroke in addition to assessing recovery via cellular transplantation. However, robust tasks are required which detect deficits in this model in order to test potential therapeutics. The corridor test to assess sensorimotor neglect has been used to assess deficits in the rat model of Huntington's and Parkinson's disease, but has not been used as an indicator for MCAO lesion deficits. An experiment was performed to assess MCAO lesion deficits utilizing a variety of motor tasks including the corridor test. Six weeks post surgery, MCAO and sham animals underwent two consecutive days of corridor habituation followed by two consecutive days of corridor testing, obtaining two measures for each subject. We found that unilateral MCAO lesions induced deficits in lateral side neglect as assessed with the corridor test. Eight weeks post-lesion, deficits were also assessed using the staircase test, which has previously shown to be a robust method for assessing MCAO rats. Cell counts will be performed to assess the extent of damage to the striatum, to correlate with the behavioral data obtained. These novel results can prove the corridor test to be a robust method for assessing MCAO lesion deficit. All of the work mentioned was performed in context of a larger ongoing experiment.

6.2 Ilknur Özen

Regenerative potential of pericvascular progenitors in ischemic stroke

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Potentiation of endogenous repair mechanisms by stem cells is a promising innovative therapeutic approach, especially for stroke, but also other neurological disorders. Therefore, for development of novel treatments it is crucial to understand the exact identity of adult stem cells in the vascular niche and the mechanisms of neuronal recruitment to injured sites.
Neurovascularization is essential for neuronal regeneration after stroke. The dynamic relationship between angiogenesis and neurogenesis is responsible for creating a perivascular niche for maintaining stem cells. Pericytes are a subpopulation of perivascular cells with multipotential characteristics. We have recently identified a new perivascular stem cell in the adult human brain. We now investigated whether this pericyte-like stem cell represents a common precursor cell that, under ischemic conditions, can contribute to brain repair. We examined the role of these cells in a stroke model using transgenic mice that express GFP under pericyte-specific promoter.

6.3 Christine Kaindlstorfer

Mesenchymal stem cells – the cure for MSA?

Authors: C. Kaindlstorfer, G. Wenning
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Multiple system atrophy (MSA) is a neurodegenerative disease characterised by progressive autonomic failure, cerebellar ataxia (MSA-C) and parkinsonism (MSA-P) due to neuronal loss in multiple brain areas associated with oligodendroglial cytoplasmic α-synuclein inclusion bodies. Currently there are no treatment options providing long-term benefits for patients with multiple system atrophy (MSA), and therefore neuroprotective or regenerative strategies, including cell-based therapies, represent a powerful approach for treating MSA. Mesenchymal stem cells have been investigated in neurodegenerative diseases because of their great potential to differentiate into neural and glial like cell lines on top of their immunoregulatory properties. Therewith, they offer the possibility to regenerate degenerated systems and inhibit neuroinflammation within respective brain areas. Evidence from two experimental and two clinical studies suggests that the application of MSCs can be effective in MSA. The first clinical pilot study was already launched in 2008, and Lee and coworkers postulated that the progression of neurological deficits can be delayed via the application of MSCs. Further experimental evidence comes from an acute-toxin induced model of MSA where it could be shown that the intravenous application of human MSCs resulted in striatal and nigral neuroprotection. Our recent investigations in the chronic transgenic mouse model of MSA, replicating the alpha-synuclein inclusion pathology, supported these results by showing a potent effect on immunomodulation and neuroprotection in the SN. Finally, the first randomized clinical trial was brought into being, investigating autologous application of MSCs in MSA-C patients. It could be demonstrated that MSCs slow the progression of the UMSARS and, both, cerebral FDG-PET and DWI MRI anaylses revealed less decreased metabolsim and gray matter density in the treatment group over a period of 360 days. Despite these promising results, there are limitations and side effects, including the mode of application, that have to be considered in future investigations.

6.4 Laura Jensen

Artificial bio-surfaces for stem cell differentiation

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Cell-based regenerative therapy represents a feasible alternative to current, symptomatic treatment for Parkinson's disease (PD). Successful clinical translation, however, is dependent on finding an accessible source of dopaminergic neurons.
This project aims to test the potential of novel artificial biosurfaces (ABS) as tools for dopaminergic differentiation of stem cells. These ABS differ in their structure and therefore exert a different topographical stimulus on differentiating cells in conjunction with the chemical stimuli provided in the culture medium. Epiblast stem cells (EpiSCs) yield a large number of neurons following 14 days of differentiation, of which approximately 40% are positive for tyrosine hydroxylase (TH). The machinery for dopamine synthesis and -uptake is also functional in EpiSC-derived neurons. Having shown that smooth ABS are conducive to the differentiation of EpiSCs into TH-positive neurons, we are now combining this result with the observation made from a preliminary screening performed in 2008 that the differentiation of human embryonic stem cells into TH-positive neurons is greatly influenced by the topography of the ABS. We will now further our investigations into the efficacy of ABS and the effect of surface topography using EpiSCs. Furthermore, we will determine whether differentiated neurons express the complete transcriptional, biochemical and functional profile of mature dopaminergic neurons.

6.5 Victoria Roberton

A new method of testing cells for *in vivo* transplantation in neurological disease

Authors: Roberton VH, Kelly CM, Rosser AE
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In order to test human donor cells for transplantation in neurological disease, safety, integration and function must first be demonstrated in pre-clinical trials in animal models, usually rodents. To prevent rejection of xenografts, immunosuppressant drugs or immune compromised hosts are generally used. These methods are not considered ideal for the

preclinical assessment of transplanted cells, therefore an alternative method has been proposed by our lab group. Host animals are desensitised to xenogeneic donor tissue via a neonatal i.p. injection, resulting in acceptance of a neural graft of the same tissue type in adulthood. As the parameters of this method and its underlying mechanisms are as yet unknown, current work aims to investigate this further.
In one study we aimed to determine the range of tissue disparity that may be used to inject neonatally and transplant in adulthood. To this end; rat hosts were desensitised to human neural or non-neural tissues to determine whether graft survival may be achieved in both groups. Although survival appears to be greater in hosts injected with neural tissue than non-neural, no significant differences were found between the groups, suggesting desensitisation is not tissue specific. Additionally, we have demonstrated that any tolerance induced through neonatal desensitisation is not just a global reduction in immune response, but is specific to the donor species tissue used to tolerise. This has been achieved by transplanting mouse tissue into rat hosts which had previously been desensitised to human tissue or were treated daily with a conventional immunosuppressant. Graft survival and the host immune response were then compared between groups. The increased immune response and ongoing rejection of mouse transplants in rat hosts tolerised to human tissue can be seen at 6 weeks post transplantation.

6.6 Robert Andres

Responses of the Dopaminergic and Endogenous Neurogenic Systems in a Rat Model of Intracerebral Hemorrhage

Authors: R.H. Andres[1,2], L. Andereggen[1], P. Mordasini[1], A.D. Ducray[1], R. Ibatullin[1], A. Raabe[1], A. Barth[1,3], and H.R. Widmer[1]
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Aims: Intracerebral hemorrhage (ICH) constitutes one of the most devastating forms of cerebrovascular disease with no effective treatment options. In the present study, we investigated remote effects of ICH on the nigrostriatal dopaminergic system and on endogenous neurogenesis, which might be involved in functional and structural brain plasticity after the insult.
Methods: ICH was induced in rats by combining a striatal microtrauma with infusion of 30 ul autologous blood. Amphetamine-induced rotational behavior was assessed after 7, 20 and 30 days, and the numbers of tyrosine hydroxylase (TH) expressing dopaminergic neurons and total neuronal cells in the SN were analyzed at days 2 and 30 post ICH. Effects on endogenous stem cell proliferation in the subventricular zone (SVZ) and hippocampus were assessed using the 5-bromo-2-deoxyuridine (BrdU) incorporation method.

Results: Rats suffering ICH showed an increase in ipsiversive rotational behavior at day 7 post ICH, followed by a partial recovery at days 20 and 30 ($p<0.05$). ICH resulted in a decrease of 45% and 15% in the number of TH-immunoreactive cells in the ipsilateral SN at day 2 and 30, respectively ($p<0.05$). In contrast, the loss of total neuronal cells was less pronounced with a decrease of only 25% at day 2 ($p<0.05$) and no significant difference at day 30. Rats with ICH also exhibited higher numbers of BrdU-positive cells in the ipsilateral SVZ ($p<0.05$) and hippocampus ($p<0.05$). These observations indicate that ICH induces a transient downregulation of TH expression in a subpopulation of SN neurons and promotes endogenous stem cell proliferation.
Conclusions: Our results provide evidence that striatal ICH leads to behaviorally relevant dysfunction of the nigrostriatal dopaminergic pathway and stimulates endogenous stem cell proliferation. Neuroprotective strategies for dopaminergic neurons and/or dopamine substitution, as well as modulation of endogenous neurogenesis, might therefore be effective for improving the functional outcome after ICH.

DATABLITZ - SESSION 7: FRIDAY 30th November 15.40 – 16.20

7.1 Asuka Morizane

Immune or inflammatory responses by allo- vs. auto-transplantation with primate iPS cell-derived neurons

Authors: Asuka Morizane[a,b], Daisuke Doi[a,b], Tetsuhiro Kikuchi[a,b], Keisuke Okita[a], Jun Takahashi[a,b,c]
Affiliations: [a]Center for iPS Cell Research and Application, Kyoto University; [b]Institute for Frontier Medical Sciences, Kyoto University; [c]Department of Neurosurgery, Clinical Neuroscience, Kyoto University Graduate School of Medicine

Background: Pluripotent stem cells have promise for serving as a source of donor cells for cell transplantation. Especially induced pluripotent stem cell (iPSC) technology has potential to prepare the donor cells from a patient's own somatic cells that would cause minimal immune reaction after transplantation. On the other hand, brain is considered as immunologically privileged site and fetal mesencephalic grafts survive in allo-transplantation with or without immunosupression.
Materials & Methods: We generated several lines of iPSCs from skin fibroblasts or oral mucosa of cynomolgus monkeys. After differentiation into neural cells, we transplanted them back to the striatum of the original monkeys (auto) or to the other ones (allo).
Results: At three month after transplantation we sacrificed them and examined the immunoreaction and the graft survival histologically. The invasion of CD45 positive leukocytes were indentified more in the allo-grafts than the auto-grafts. The graft size and

the survival of DA neurons were dependent on the cell lines transplanted rather than the mode of transplantation.
Discussion: For the clinical application in the future, auto-graft is more preferable from the point of immunological response. However, allo-transplantation will also work if the appropriate cell line is selected and properly differentiated. Preparation of HLA-matched donor cells from a “cell bank” might be another option.

7.2 Meltem Özer

Electrophysiological comparison of in vitro differentiated dopaminergic neurons derived from transgenic TH-EGFP mice and intrastriatal transplanted rat embryo derived mesencephalic neurons in the rat model of Parkinson´s disease

Authors: Özer, M (1, 3), Rumpel, R (1), Fischer, M (2), Ratzka, A, (1) Wesemann, M (1), Fahlke, C (3, 4) Grothe, C (1, 3)
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Parkinson´s disease (PD) is a neurodegenerative disorder resulting from the loss of dopaminergic (DA) neurons in the substantia nigra (SN). Transplantation of embryonic ventral mesencephalic (VM) neurons was shown to substitute the missing DA input. However, little is known about the electrophysiological properties of DA neurons after intrastriatal grafting in the PD rat model.
For this purpose we combined our recently established protocol for transplantation of neural progenitor cells (Ratzka A et al, 2012 *Cell Transplantation, 21 479-762*) with whole-cell patch clamp studies in brain slices of the grafted striatum. Progenitor cells were transfected with a plasmid encoding the green fluorescent protein (EGFP) to identify intrastriatal grafts even 2 to 13 weeks after transplantation. Since DA neurons display similar features in both the substantia nigra in vivo and in organotypic cultures in vitro (Rohrbacher et al., 2000 *Neuroscience, 97, 703-714*), we additionally recorded from dissociated VM progenitor cells derived from transgenic TH-EGFP mice.
Using voltage and current clamp recordings we identified hyperpolarization-activated inward currents (I_h) and I_A potassium currents in the majority of DA neurons in TH-EGFP cultures. The same neurones displayed broad action potentials (AP-width: 2.4 ± 0, 2 ms, n = 5) with prominent afterhyperpolarizations (AHP-amplitude: 34 ± 9 mV, n =5). These properties correspond to the previously reported features that characterize DA neurons in vitro and in vivo (Richards et al., 1997 *Neuroscience, 80, 545-557*).
So far systematic determination of dopaminergic neurones by patch clamp recordings within intrastriatal grafts is not achievable. However, 29 investigated neurones exhibit

hyperpolarization activated Ih current, as well as similar prominent afterhyperpolarization amplitudes. Six out of six tested neurons exhibit also the characteristic IA potassium current. The action potential duration (1, 5 ±0,8ms) is indeed smaller then in vitro. Overall the transplanted neurons shared similar characteristic properties as cultured DA neurones. Our data could demonstrate the electrophysiological functionality of grafted DA neurons even 5-13 weeks after transplantation.

7.3 Pia Jensen

Influence of oxygen tension on dopaminergic differentiation of human fetal stem cells of midbrain and forebrain origin

Authors: Jensen P, Krabbe C, Bak ST, von Linstow CU and Meyer M
Affiliations: Department of Neurobiology Research, Institute of Molecular Medicine, University of Southern Denmark

Neural stem cells (NSCs) constitute a promising source of cells for transplantation in Parkinson's disease (PD), but a protocol for controlled dopaminergic differentiation is not yet available.
Here we investigated the influence of oxygen on dopaminergic differentiation of human fetal NSCs derived from midbrain and forebrain. Cells were differentiated for 10 days *in vitro* at low (3%) versus high (20%) oxygen tension.
Low oxygen increased the proportions of tyrosine hydroxylase-immunoreactive (TH-ir) cells in both types of cultures (midbrain: 9.1±0.5 and 17.1±0.4 ($P<0.001$); forebrain: 1.9±0.4 and 3.9±0.6 ($P<0.01$) percent of total cells). Regardless of oxygen (low or high), the content of TH-ir cells with mature neuronal morphologies was higher for midbrain as compared to forebrain cultures.
A substantial number of proliferative Ki67-ir cells were found in both types of cultures, but the relative proportion of these cells was significantly higher for forebrain NSCs cultured at low as compared to high oxygen tension. No such difference was detected for midbrain-derived cells.
Western blot analysis revealed that low oxygen enhanced β-tubulinIII and GFAP expression in both cultures, but upregulation of β-tubulinIII was most pronounced for midbrain cells, whereas GFAP expression was higher in forebrain as compared to midbrain cells. NSCs from both brain regions displayed less cell death when cultured at low oxygen tension.
Following mictrotransplantation into mouse striatal slice cultures (model of PD), midbrain NSCs were found to proliferate, migrate and differentiate into substantial numbers of TH-ir neurons with mature neuronal morphologies, particularly at low oxygen. In contrast, forebrain NSCs microtransplanted using identical conditions displayed little proliferation, almost no migration and contained very few TH-ir cells, all of which had an immature appearance.

Our data may reflect differences in dopaminergic differentiation capacity and region-specific requirements of NSCs, with the dopamine-depleted striatum cultured at low oxygen offering an attractive microenvironment for midbrain NSCs.

7.4 Jun Takahashi

Sorting and transplantation of dopaminergic progenitor cells derived from human pluripotent stem cells

Authors: Jun Takahashi[a,b,c], Daisuke Doi[a,b], Asuka Morizane[a,c], Asuka Morizane[a,b]
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Cell replacement therapy using embryonic stem cells (ESCs) or induced pluripotent stem cells (iPSCs) could be applied for Parkinson's disease in the near future. It is possible, however, that unwanted cells such as undifferentiated cells, non-neural cells, and other type of neurons, remain in the prepared donor cells. So, we tried to purify dopaminergic (DA) progenitor cells by using FACS.
We induced neural progenitors from human ES cells (KhES-1) and human iPS cells (404C2) by the SFEBq (serum-free embryoid body quick) method with dual BMP and Activin/Nodal inhibition, then analyzed the expression of a floor plate marker Corin. The expression of Corin arises from culture day 10 and about 10-20% of living cells were positive on day 21. After sorting, purity of Corin$^+$ cells was over 90%. Corin$^+$ cells also expressed Lmx1a. Corin$^+$ cells differentiated into TH$^+$ neurons after 2-3 weeks of culture, and the TH$^+$ cells were also immunoreactive for Nurr1 or Pitx3.
When grafted into non-lesioned NOD-SCID mice three days after cell sorting (differentiation totally for 24 days), grafts derived from Corin$^+$ cells were small, while graft overgrowth was observed in the grafts derived from Corin$^-$ or unsorted cells. Furthermore, more TH$^+$ neurons survived in Corin$^+$ cell-grafts.
After modification of the culture methods and the timing of sorting, we grafted Corin$^+$ cells into 6-OHDA-lesioned rats. Human TH$^+$ cells survived in the grafts for 8 weeks post-transplantation, and methamphetamine-induced rotation partially improved.
Sorting of DA progenitor cells using a surface marker reduced risk of graft overgrowth, and may lead to more efficient DA function of the grafted cells.

7.5 Olof Torper

Presentation title: Survival of induced human neuronal cells from fibroblasts and astrocytes, after transplantation into the striatum of the adult rat

Authors: O.Torper, A. Speidel, M. Parmar
Affiliations: Wallenberg Neuroscience Center, Lund University, BMC A11, S-221 84 Lund, Sweden

Recent studies have shown the possibility to convert one somatic cell type into another by forced expression of defined sets of transcription factors. In neuroscience, various subtype specific neurons have been obtained using this approach, interesting for their role in various neurodegenerative disorders like Alzheimers, ALS and Parkinsons disease.
Here we analyze neurons converted from human fibroblasts and astrocytes by the use of doxycycline regulated lentiviral vectors coding for Ascl1, Brn2 and Myt1L after transplantation into the rat striatum. When doxycycline was added in the drinking water, induced neurons (iNs) were detected in the grafts up to 12 weeks after transplantation. When doxycycline was removed 4 weeks after transplantation and animals left for an additional 8 weeks, a similar number of iNs could be detected indicating stable reprogramming. No cells with neuronal morphology or that stained positive for neuronal markers were ever detected in animals transplanted with untransduced fibroblasts on a doxycycline diet or in animals transplanted with control cells.
Similarly, when astrocytes were transplanted using the same strategy, grafts containing neurons were detected 5 weeks after transplantation.
These results opens up the possibility to use iN cells for cell replacement therapy and also to perform direct in vivo reprogramming where astrocytes would be an ideal target candidate for the direct conversion of astrocytes to neurons.

7.6 Daniella Rylander

Dopaminergic ventral mesencephalic neurons can restore activity-dependent synaptic plasticity in the host striatum

Authors: Daniella Rylander PhD[1,2], Vincenza Bagetta PhD[1], Valentina Pendolino[1], Barbara Picconi PhD[1], M. Angela Cenci, M.D[2], PhD and Paolo Calabresi MD, PhD[1].
Affiliations: 1) Basal Ganglia Pathophysiology Unit, BMC, Lund University, Lund, Sweden; 2) Neurophysiology group, Santa Lucia Foundation, Rome, Italy

Objective: Transplantation of ventral mesencephalic neurons to the striatum is a promising treatment for Parkinson´s disease (PD). Unfortunately, this treatment can cause severe dyskinesia (abnormal involuntary movements). We hypothesize that the occurrence of dyskinesia post-grafting depends on the abnormal synaptic wiring produced by the transplanted cells. Abnormal synaptic arrangements may be produced both by grafted dopaminergic neurons and by additional cell types within the donor tissue, in particular serotonergic neurons. We hypothesize that the grafted serotonergic cells produce pathological connections with the host striatal neurons, giving rise to abnormal morphology of host neuronal dendrites and spines and patterns of synaptic plasticity.
Materials and Methods: In order to test our hypotheses we investigated the functional alterations that occur in the host medium spiny neurons after transplantation. In a rat PD model, we compared grafts enriched in dopamine neurons ("DA-rich grafts") with those enriched in serotonin neurons ("5-HT-rich grafts"). Activity-dependent synaptic plasticity in the host medium-spiny neurons was examined in close proximity to the grafted core i.e. ventrolateral striatum as well as in the dorsolateral striatum.
Results: In the ventrolateral striatum medium-spiny neurons from intact control rats showed long-term potentiation (LTP) using the stimulating protocol that in the dorsolateral striatum induces long-term depression (LTD). The LTP in the ventral striatum was dependent on dopamine D1 receptor as well as NMDA receptor containing NR2A and NR2B subunit. The synaptic plasticity was lost in the dopamine-denervated striatum and could not be restored by "5-HT-rich grafts". Solely transplanted dopamine neurons were able to restore the LTP in the ventrolateral striatum.
Conclusions: Our data are the first to show distinct synaptic plasticity patterns in the host striatal neurons after grafting of DA-rich versus 5-HT-rich transplants.

CONGRESS INFORMATION

Previous NECTAR Meetings

Planning meeting	-	1990 Munich, Germany
Founding Meeting	-	1991 Le Vesinet, France
2nd Annual Meeting	-	1992 Milan, Italy
3rd Annual Meeting	-	1992 Sandbjerg Manor, Denmark
4th Annual Meeting	-	1993 Brussels, Belgium
5th Annual Meeting	-	1994 Amsterdam, The Netherlands
6th Annual Meeting	-	1995 Maastricht, The Netherlands
7th Annual Meeting	-	1996 Amsterdam, The Netherlands
8th Annual Meeting	-	1997 Brussels, Belgium
9th Annual Meeting	-	1998 Amsterdam, The Netherlands
10th Annual Meeting	-	1999 Odense, Denmark
11th Annual Meeting	-	2000 Hannover, Germany
12th Annual Meeting	-	2001 Brussels, Belgium
13th Annual Meeting	-	2002 Amsterdam, The Netherlands
14th Annual Meeting	-	2003 Amsterdam, The Netherlands
15th Annual Meeting	-	2004 Brussels, Belgium
16th Annual Meeting	-	2005 Amsterdam, The Netherlands
17th Annual Meeting	-	2006 Freiburg, Germany
18th Annual Meeting	-	2007 Lund, Sweden
19th Annual Meeting	-	2009 Cardiff, Wales
20th Annual Meeting	-	2010 Freiburg, Germany
21st Annual Meeting	-	2011 Cambridge, UK
22nd Annual Meeting	-	2012 Lund, Sweden

Preliminary venues (subject to change)

23rd Annual Meeting	-	2013 Cardiff, Wales
24th Annual Meeting	-	TBA

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