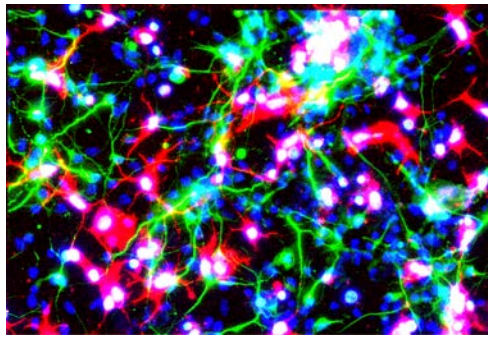


# Annual Report

2016

## Department of Neuroscience Uppsala University



*Cover Picture:*

*"Boundary cap cells differentiated to neurons (red) and astrocytes (green) in vitro"*

*Photo captured by Elena Kozlova, Regenerative Neurobiology*

## INTRODUCTION

Department of Neuroscience at Uppsala University Faculty of Medicine hosts a broad range of clinical and pre-clinical neuroscience research as well as a broad spectrum of education. During 2016 the Department consisted of 168 employees excluding PhD students, postdoctoral fellows and clinically active researchers. In total approximately 380 people were active at the department during 2016. More than a quarter of the staff is of overseas origin, giving the Department a strong international profile. The clinical research groups engage more than 100 clinicians, who are employed by the University Hospital, and they contribute both to teaching and research at the Neuroscience Department. The clinical research groups are distributed in different buildings in the main University Hospital campus including the House of Psychiatry, which also hosts Child and Adolescent Psychiatry. The pre-clinical research groups are mainly located at Uppsala University Biomedical Center.

During 2016 we started to formulate specific goals and strategies for the Department with the aim to strengthen the position as a leading national and international research institution as well as to maintain, the highest national and international quality within education. The goals were based on newly revised documents at both university and faculty level. The work was initiated with an open discussion during a two-day retreat in August with unit research group leaders, and was continued during the fall with discussions and information meetings. The importance of well consolidated conceptual foci on goals and strategies out-lined by several hands-on and pro-active measures within the Department was identified as being important. This is exemplified by an internal “friendly” peer-review of research group activities in order to support development of novel and high quality research activities. We will also share feedback on applications to increasing success rates in the competition for major national and international funding. A joint supervisor collegium (handledarkollegium) as well as enrolment seminars for new PhD students will also be included.

This strategy work also served as a start for the coming KoF17 evaluation, which is primarily expected to provide feedback on how the Department’s research environment may be developed and provide input how to further develop our systematic quality work and research renewal.

### **Research**

The Department of Neuroscience is one out of 12 Departments in the disciplinary domain of Medicine and Pharmacy. During the year 2016 we kept our position as one of the more productive departments within the Disciplinary Domain and the financial result within the research sector for fiscal year 2016 was in balance and followed at large the postulated budget.

The Department still faces challenges after the loss of three research groups during 2015, who were appointed positions at other departments. We acknowledge that the Department must be a dynamic arena and that the Department is a step stone for the continued careers of our researchers and students. However, loss of competent people will also lead to a decrease in both competence and the financial base of the Department. In this perspective we were very pleased that several PIs managed to get their project grants prolonged during 2016. The Department was behind almost a quarter of the granted projects from the Swedish Research Council, Health and Medicine. Our colleagues at the Department received a Consolidation grant and a grant for employment as a clinical researcher. Furthermore the Department was

invited to host a Professorship in Rehabilitation Medicine and a position as Associate Senior Lecturer in Molecular Psychiatry.

### **Information and department Retreats**

The annual Neuroscience Day with information and scientific presentations was held as usual in March. The theme was research at the department and special care was appointed to present both clinical and preclinical research. Newly recruited researchers presented themselves and their research and the event was finished with a banquet. The pedagogic award “*Neuroscience prize for better teaching*” was awarded to the second time.

In August the Department performed a two-day meeting for research group leaders with focus on goals and strategies. The meeting was held at Sigtuna höjden.

The annual Teaching conference “*Lärardag*” was also held in August. The half-day conference invited all staff involved in teaching, both teachers and course administrators, and focused on the importance of pedagogy relevant for mediating information from doctors to patients. This is important when detailed information about treatments and disease are fully available on the net. A second subject was the increasing cases of cheating during student examinations. A few current cases were discussed. The meeting was held in the main auditorium of the House of Psychiatry.

The media presence of the Department’s researchers has been high and daily updates regarding the Department’s activities in various areas have continued to be presented on the Department website during 2015. These updates are often based on internet searches, mainly in national and international media websites, of material published elsewhere on the activities of the Department’s scientists and teachers in the community. This news service has become popular for increasing in-house information on the external activities of the Department. The homepage has also been appreciated as a resource by the media and other institutions within the community as a source of expert advice from researchers within different areas of neuroscience.

### **Undergraduate and Graduate Education**

The Department of Neuroscience continued to receive one of the largest faculty grants for teaching within the Disciplinary Domain of Medicine and Pharmacy during 2016, amounting to 16 % of the total budget. Case oriented and student-activating teaching in groups of 8 to 10 students is introduced from the start of education in Neuroscience with emphasis on integrating basic and clinical sciences.

The Department has extensive responsibilities within the Physiotherapy and Speech Pathology and Therapy programmes. The Department has also considerable commitments within the Biomedicine, Nursing and Pharmacy programmes, and plays an active role in the efforts of the faculty to modernize the content and improve the teaching methods of these programmes. In addition, the Department hosts an international Masters Programme in Biomedicine.

In total we educate more than 611 full-year student equivalents at the department and 20 students received their doctoral degrees at the Department during 2016. Of these, 8 were

males and 12 females, 7 students were from the clinical research areas and 13 students were from the preclinical research area.

### **Conclusions**

The year 2016 has been successful thanks to the hard and dedicated work of staff and students at the Department. I would like that the creative spirit with increased mutual interactions between research groups and disciplines that were settled at the August group leader retreat, will flourish and contribute to the future activities at the Department. This would lead to both increased quality of research, cross-collaborations within the Department and contribute to teaching and administration in a positive and supportive departmental spirit.

Uppsala, February 22<sup>nd</sup> 2017

Finn Hallböök, PhD  
Professor  
Head of Department

## List of contents

<b>ORGANIZATION</b>	<b>- 7 -</b>
<b>ADDRESS LIST</b>	<b>- 9 -</b>
<b>DISSERTATIONS</b>	<b>- 17 -</b>
<b>FINANCE 2016</b>	<b>- 19 -</b>
<b>SCIENTIFIC REPORTS</b>	<b>- 21 -</b>
<b>Clinical Neurology &amp; Psychiatry</b>	<b>- 22 -</b>
Clinical Neurology	- 22 -
Epilepsy	- 22 -
Neurodegeneration/ Movement disorders	- 24 -
Neuroinflammation and Multiple sclerosis	- 25 -
Identification of biomarkers for patients with brain tumors and tumor-related seizures	- 26 -
Sleep medicine	- 27 -
Clinical Neurophysiology	- 41 -
Neuromuscular Synapse	- 41 -
Development of Advanced Electrophysiological Methods	- 44 -
Central and Somatosensory Nervous System	- 46 -
Psychiatry	- 51 -
Psychiatry	- 51 -
Personality and individual differences	- 52 -
Psychiatric Epidemiology	- 53 -
Emotional instability and impulsivity	- 54 -
Severe mental illness research	- 54 -
Health care research	- 55 -
Uppsala Psychiatric patient samples	- 56 -
Immunopsychiatry and the Biology of Severe Mental Illness	- 57 -
National Centre for Disaster Psychiatry (KcKP)	- 57 -
Child & Adolescent Psychiatry	- 67 -
Experience of stress, emotional regulation and physiological stress reactions	- 67 -
Outcomes of Adolescent Depression	- 68 -
Risk factors for the development of child psychiatric problems	- 68 -
Mental illness and antisocial behaviour: Causal factors, developmental trajectories, and treatment development	- 69 -
Children with traumatic experiences	- 69 -
<b>Experimental Neuroscience</b>	<b>- 75 -</b>
Developmental Genetics	- 75 -
Formation and Function of Neuronal Circuits	- 75 -
Neurodynamics	- 77 -
Sensory Circuits	- 79 -
<b>Ophthalmology &amp; Retina Biology</b>	<b>- 81 -</b>
Ophthalmology	- 81 -
Ophthalmic Biophysics	- 81 -
Paediatric Ophthalmology	- 88 -
Glaucoma	- 93 -
Retinal Stem and Progenitor Cell Development	- 96 -

<b>Physiology and Pharmacology</b>	<b>- 102 -</b>
Physiology	- 102 -
Gastrointestinal Physiology	- 102 -
Neurophysiology of Motion Vision	- 104 -
Molecular Physiology and Neuroscience	- 107 -
Behavioural Neuroendocrinology	- 111 -
Pharmacology	- 115 -
Pharmacology	- 115 -
Functional Pharmacology	- 120 -
Neuropsychopharmacology	- 133 -
<b>Neurotrauma &amp; Restorative Neuroscience</b>	<b>- 137 -</b>
Neurosurgery	- 137 -
Clinical Brain Injury Program	- 137 -
Experimental Brain Injury Programme	- 137 -
Regenerative Neurobiology	- 147 -
Physiotherapy	- 151 -
Speech and Language Pathology	- 159 -
<b>Uppsala University Behavioral Facility</b>	<b>- 166 -</b>
<b>UNDERGRADUATE STUDIES</b>	<b>- 167 -</b>
<b>Organization of Undergraduate studies at the Department</b>	<b>- 168 -</b>
<b>List of Courses given by the Dept of Neuroscience</b>	<b>- 170 -</b>
<b>Programmes at the Dept of Neuroscience</b>	<b>- 173 -</b>
Programme in Biomedicine	- 173 -
The Master Programme in Biomedicine	- 174 -
The Speech and Language Pathology Programme	- 176 -
The Medicine Programme	- 177 -
The Physiotherapy Programme	- 177 -
The Specialist Nursing Programme	- 180 -
The Nursing Programme	- 181 -
<b>Elective courses</b>	<b>- 182 -</b>
<b>Teaching by Units in the Department</b>	<b>- 182 -</b>
Developmental Genetics	- 182 -
Developmental Neuroscience	- 183 -
Functional Pharmacology	- 184 -
Medical History	- 184 -
Pharmacology	- 185 -
Physiology	- 185 -
Neuroanatomy	- 186 -
Clinical Neuroscience Units	- 187 -
Ophthalmology	- 188 -
Psychiatry	- 189 -

## **ORGANIZATION**

### **Head of Department**

Finn Hallböök

### **Deputy Head of Department**

Lisa Ekselius

### **Department board**

Lisa Ekselius teacher representative

Pernilla Åsenlöf, teacher representative

Helgi Schiöth, teacher representative

Bryndis Birnir, teacher representative

Cecilia Yates, representative for technical/administrative personnel

Sören Spörndly-Nees, graduate student representative (to 160930)

Arianna Cocco, graduate student representative (from 161001)

Frida Axén, student representative (to 160930)

Jan-Erik Borg, student representative (to 160930)

Anna Nylund, student representative (from 161001)

Carolina Perssin, student representative (from 161001)

Per Enblad, teacher representative, deputy

Robert Fredriksson, teacher representative, deputy (to 160930)

Malin Lagerström, teacher representative, deputy

Klas Kullander, teacher representative, deputy

Anki Gustafsson, representative for technical/administrative personnel, deputy (to 160701)

Neil Ormerod, representative for technical/administrative personnel, deputy, (from 160702)

Marina Senek, graduate student representative, deputy (to 160930)

Stefan Nasir, graduate student representative, deputy (from 161001)

Vacant, student representative, deputy (from 161001)

### **Assistant Head of Department for Undergraduate studies**

Anne-Marie Landtblom

### **Assistant Head of Department for Psychiatry**

Lisa Ekselius

### **Assistant Head of Department for Physiotherapy**

Cathrin Martin

### **Chief administrator**

Lena Karlsson

### **Director of graduate studies**

Helgi Schiöth

Lars Hillered

### **Director of undergraduate studies**

Anne-Marie Landtblom

Lena Zetterberg

Lisa Ekselius

Markus Sjöblom

Monica Blom Johansson

Mia Ramklint

Olof Nylander

Madeleine Le Grèves

**Administration**

A-C Fält  
Anders Nilsson  
Anki Gustafsson  
Berit Hård- Wallenqvist  
Cecilia Edling  
Cecilia Yates  
Eva-Lena Wahlberg  
Gunneli Ekberg  
Karin Nygren  
Lena Holm

Lena Karlsson  
Maria Brandt  
Mariana Hooli  
Mona Persson  
Neil Ormerod  
Pia Fredlund  
Sari Thunberg  
Sofie Hovberg  
Stefan Pettersson

**Undergraduate studies committee**

Anne-Marie Landtblom (Head of committee)  
Dan Larhammar  
Lena Zetterberg  
Mia Ramklint

Madeleine Le Grevès  
Monica Blom Johansson  
Neil Ormerod  
Olof Nylander

**Graduate studies committee**

Helgi Schiöth (Head of committee)  
Lars Hillered  
Anna Rostedt Punga  
Malin Lagerström

Neil Ormerod  
Niklas Marklund  
Susanna Tuvemo-Johnson

**Committe for Equal Opportunites**

Lena Karlsson (Head of committee Jan-July)  
Nadina Laurent (Head of committee Aug-Dec )  
Fotis Papadopoulos

Linn Mosten  
Madeleine le Grevès  
Petra Pichler  
Zhe Jin

**Health and Safety Committee**

Cecilia Edling (Head of committee)  
Camilla Ekwall  
Anders Nilsson  
Fredrik Clausen  
Maria Brandt

Karin Nygren  
Lena Karlsson  
Sari Thunberg  
Sofie Hovberg



## Persons with delegated responsibility for health and safety

Administration: Lena Karlsson  
Child & Adolescent Psychiatry: Mia Ramklint  
Clinical Neurology/ Rehab. medicine: Anja Smits/ Anne-Marie Landtblom  
Clinical Neurophysiology: Anna Rostedt Punga  
Clinical Psychiatry: Lisa Ekselius  
Developmental Neuroscience: Finn Hallböök  
Experimental Neuroscience: Klas Kullander  
Functional Pharmacology: Helgi Schiöth  
Neurosurgery: Per Enblad  
Ophthalmology: Per Söderberg  
Pharmacology/ Neuropsychopharmacology: Dan Larhammar  
Physiology: Bryndis Birnir  
Physiotherapy: Cathrin Martin  
Regenerative Neurobiology: Elena Kozlova  
Speech and Language Pathology: Monica Blom Johansson

## ADDRESS LIST DEPARTMENT OF NEUROSCIENCE

Abrahamsson, Ninnie	<a href="mailto:innie.abrahamsson@neuro.uu.se">innie.abrahamsson@neuro.uu.se</a>
Abu Hamdeh, Sami	<a href="mailto:sami.abu.hamdeh@akademiska.se">sami.abu.hamdeh@akademiska.se</a>
Aggarwal, Tanya	<a href="mailto:tanya.aggarwal@neuro.uu.se">tanya.aggarwal@neuro.uu.se</a>
Ahlsten, Eva	<a href="mailto:eva.ahlsten@neuro.uu.se">eva.ahlsten@neuro.uu.se</a>
Ahemaiti, Aikeremuy	<a href="mailto:aikeremu.ahemaiti@neuro.uu.se">aikeremu.ahemaiti@neuro.uu.se</a>
Alaie, Iman	<a href="mailto:iman.alaie@neuro.uu.se">iman.alaie@neuro.uu.se</a>
Aldskogius, Håkan	<a href="mailto:hakan.aldskogius@neuro.uu.se">hakan.aldskogius@neuro.uu.se</a>
Alm, Albert	<a href="mailto:albertalm@ymail.com">albertalm@ymail.com</a>
Alm, Per	<a href="mailto:per.alm@neuro.uu.se">per.alm@neuro.uu.se</a>
Amandusson, Åsa	<a href="mailto:asa.amandusson@akademiska.se">asa.amandusson@akademiska.se</a>
Andersen, Sören	<a href="mailto:soren.andersen@neuro.uu.se">soren.andersen@neuro.uu.se</a>
Anens, Elisabeth	<a href="mailto:elisabeth.anens@neuro.uu.se">elisabeth.anens@neuro.uu.se</a>
Aquilonius, Sten-Magnus	<a href="mailto:sten-magnus.aquilonius@neuro.uu.se">sten-magnus.aquilonius@neuro.uu.se</a>
Aresh, Bejan	<a href="mailto:bejan.ares@neuro.uu.se">bejan.ares@neuro.uu.se</a>
Arinell, Hans	<a href="mailto:Hans.Arinell@neuro.uu.se">Hans.Arinell@neuro.uu.se</a>
Arnberg, Filip	<a href="mailto:filip.arnberg@neuro.uu.se">filip.arnberg@neuro.uu.se</a>
Askmark, Håkan	<a href="mailto:hakan.askmark@neuro.uu.se">hakan.askmark@neuro.uu.se</a>
Aslani, Reza	<a href="mailto:reza.aslani@neuro.uu.se">reza.aslani@neuro.uu.se</a>
Attwood, Misty	<a href="mailto:misty.attwood@neuro.uu.se">misty.attwood@neuro.uu.se</a>
Axelsson, Hans	<a href="mailto:hans.axelsson@akademiska.se">hans.axelsson@akademiska.se</a>
Axfors, Cathrine Axling, Johanna	<a href="mailto:cathrine.axfors@neuro.uu.se">cathrine.axfors@neuro.uu.se</a>
Axling, Johanna	<a href="mailto:johanna.axling@neuro.uu.se">johanna.axling@neuro.uu.se</a>
Babateen, Omar	<a href="mailto:omar.babateen@neuro.uu.se">omar.babateen@neuro.uu.se</a>
Baghdassarian, Eva	<a href="mailto:eva.baghdassarian@neuro.uu.se">eva.baghdassarian@neuro.uu.se</a>
Bandstein, Marcus	<a href="mailto:marcus.bandstein@neuro.uu.se">marcus.bandstein@neuro.uu.se</a>
Babista Freitag, Fabio	<a href="mailto:Fabio fabio.freitag@neuro.uu.se">Fabio fabio.freitag@neuro.uu.se</a>
Benedict, Christian	<a href="mailto:christian.benedict@neuro.uu.se">christian.benedict@neuro.uu.se</a>
Bengtsson, Johan	<a href="mailto:johan.bengtsson@neuro.uu.se">johan.bengtsson@neuro.uu.se</a>
Bergdahl, Lena	<a href="mailto:lena.bergdahl@neuro.uu.se">lena.bergdahl@neuro.uu.se</a>
Berggren, Lennart	<a href="mailto:lennart.berggren@neuro.uu.se">lennart.berggren@neuro.uu.se</a>

Bergh Johannesson, Kerstin [Kerstin.bergh.johannesson@neuro.uu.se](mailto:Kerstin.bergh.johannesson@neuro.uu.se)  
Bergqvist, Christina [christina.bergqvist@neuro.uu.se](mailto:christina.bergqvist@neuro.uu.se)  
Berntsson, Shala [shala.berntsson@neuro.uu.se](mailto:shala.berntsson@neuro.uu.se)  
Bhandage, Amol [amol.bhandage@neuro.uu.se](mailto:amol.bhandage@neuro.uu.se)  
Birnir, Bryndis [bryndis.birnir@neuro.uu.se](mailto:bryndis.birnir@neuro.uu.se)  
Blixt, Maria [maria.blixt@neuro.uu.se](mailto:maria.blixt@neuro.uu.se)  
Blom Johansson, Monica [monica.blom.johansson@neuro.uu.se](mailto:monica.blom.johansson@neuro.uu.se)  
Boden, Robert [robert.boden@neuro.uu.se](mailto:robert.boden@neuro.uu.se)  
Bogatikov, Evgenii [evgenii.bogatikov@neuro.uu.se](mailto:evgenii.bogatikov@neuro.uu.se)  
Bohman, Hannes [hannes.bohman@neuro.uu.se](mailto:hannes.bohman@neuro.uu.se)  
Boije, Henrik [henrik.boije@neuro.uu.se](mailto:henrik.boije@neuro.uu.se)  
Boije, Maria [maria.boije@neuro.uu.se](mailto:maria.boije@neuro.uu.se)  
Bondjers, Kristina [kristina.bondjers@neuro.uu.se](mailto:kristina.bondjers@neuro.uu.se)  
Botling Taube, Amelie [amelie.taube@neuro.uu.se](mailto:amelie.taube@neuro.uu.se)  
Bouzarov, Dimitri [dimitri.bouzarov@akademiska.se](mailto:dimitri.bouzarov@akademiska.se)  
Brandt, Maria [maria.brandt@neuro.uu.se](mailto:maria.brandt@neuro.uu.se)  
Braun, Madelen Breedh, Julia [madelen.braun@neuro.uu.se](mailto:madelen.braun@neuro.uu.se)  
Breedh, Julia [julia.breedh@neuro.uu.se](mailto:julia.breedh@neuro.uu.se)  
Bring, Annika [annika.bring@neuro.uu.se](mailto:annika.bring@neuro.uu.se)  
Broman, Jan-Erik [Jan-Erik.Broman@neuro.uu.se](mailto:Jan-Erik.Broman@neuro.uu.se)  
Burman, Joachim [joachim.burman@neuro.uu.se](mailto:joachim.burman@neuro.uu.se)  
Bylund, Ann [ann.bylund@neuro.uu.se](mailto:ann.bylund@neuro.uu.se)  
Bäckström, Josefin [josefin.backstrom@neuro.uu.se](mailto:josefin.backstrom@neuro.uu.se)  
Cao, Hao [hao.cao@neuro.uu.se](mailto:hao.cao@neuro.uu.se)  
Ceder, Klaudia [klaudia.ceder@neuro.uu.se](mailto:klaudia.ceder@neuro.uu.se)  
Cedernaes, Jonathan [jonathan.cedernaes@neuro.uu.se](mailto:jonathan.cedernaes@neuro.uu.se)  
Cernvall, Martin [martin.cernvall@neuro.uu.se](mailto:martin.cernvall@neuro.uu.se)  
Cesarini, Kristina [kristina.cesarinni@neuro.uu.se](mailto:kristina.cesarinni@neuro.uu.se)  
Nehlin, Gordh, Christina [christina.nehlin.gordh@neuro.uu.se](mailto:christina.nehlin.gordh@neuro.uu.se)  
Ciuculete, Diana-Mari [diana-maria.ciuculete@neuro.uu.se](mailto:diana-maria.ciuculete@neuro.uu.se)  
Clapham, Eric [eric.clapham@neuro.uu.se](mailto:eric.clapham@neuro.uu.se),  
Clausen, Fredrik Cocco, Arianna [fredrik.clausen@neuro.uu.se](mailto:fredrik.clausen@neuro.uu.se)  
Cocco, Arianna [arianna.cocco@neuro.uu.se](mailto:arianna.cocco@neuro.uu.se)  
Comasco, Erika [erika.comasco@neuro.uu.se](mailto:erika.comasco@neuro.uu.se)  
Cunningham, Janet [janet.cunningham@neuro.uu.se](mailto:janet.cunningham@neuro.uu.se)  
Dahlbom, Josefin [josefin.dahlbom@neuro.uu.se](mailto:josefin.dahlbom@neuro.uu.se)  
Danielsson, Katarina [katarina.danielsson@neuro.uu.se](mailto:katarina.danielsson@neuro.uu.se)  
Daniilidou, Makrina [makrina.daniilidou@neuro.uu.se](mailto:makrina.daniilidou@neuro.uu.se)  
de Roos, Paul [paul.deroos@neuro.uu.se](mailto:paul.deroos@neuro.uu.se)  
Del Pozo, Ana Dyakova, Olga [ana.delpozo@neuro.uu.se](mailto:ana.delpozo@neuro.uu.se)  
Dyakova, Olga [olga.dyakova@neuro.uu.se](mailto:olga.dyakova@neuro.uu.se)  
Dyhrfort, Philip [philip.dyhrfort@neuro.uu.se](mailto:philip.dyhrfort@neuro.uu.se)  
Dyster-Aas, Johan [johan.dyster-aas@neuro.uu.se](mailto:johan.dyster-aas@neuro.uu.se)  
Ebendal, Ted [ted.ebendal@neuro.uu.se](mailto:ted.ebendal@neuro.uu.se)  
Edebol Eeg-Olofsson, Karin [karin.edebol.eeg-olofsson@akademiska.se](mailto:karin.edebol.eeg-olofsson@akademiska.se)  
Edling, Cecilia [cecilia.edling@neuro.uu.se](mailto:cecilia.edling@neuro.uu.se)  
Edvinsson, Dan [Dan.Edvinsson@neuro.uu.se](mailto:Dan.Edvinsson@neuro.uu.se)  
Ekberg, Gunneli [gunneli.ekberg@neuro.uu.se](mailto:gunneli.ekberg@neuro.uu.se)  
Ekselius, Lisa [Lisa.Ekselius@neuro.uu.se](mailto:Lisa.Ekselius@neuro.uu.se)

Ekström, Curt [curt.ekstrom@neuro.uu.se](mailto:curt.ekstrom@neuro.uu.se)  
Ekwall, Camilla [camilla.ekwall@neuro.uu.se](mailto:camilla.ekwall@neuro.uu.se)  
Elf, Kristin [kristin.elf@neuro.uu.se](mailto:kristin.elf@neuro.uu.se)  
Elmgren-Frykberg, Gunilla [gunilla.elmgren.frykberg@neuro.uu.se](mailto:gunilla.elmgren.frykberg@neuro.uu.se)  
Emilson, Christina [christina.emilson@neuro.uu.se](mailto:christina.emilson@neuro.uu.se)  
Emtner, Margareta [margareta.emtner@neuro.uu.se](mailto:margareta.emtner@neuro.uu.se)  
Enblad, Per [per.enblad@neuro.uu.se](mailto:per.enblad@neuro.uu.se)  
Ericson, Hans [hans.ericson@akademiska.se](mailto:hans.ericson@akademiska.se)  
Eriksson, Gunilla [gunilla.eriksson@neuro.uu.se](mailto:gunilla.eriksson@neuro.uu.se)  
Fagius, Jan [jan.fagius@neuro.uu.se](mailto:jan.fagius@neuro.uu.se)  
Fahlström, Andreas [andreas.fahlstrom@neuro.uu.se](mailto:andreas.fahlstrom@neuro.uu.se)  
Feresiadou, Amalia [amalia.fereseiadou@neuro.uu.se](mailto:amalia.fereseiadou@neuro.uu.se)  
Fernandez, Manuel [Manuel.Fernandez@neuro.uu.se](mailto:Manuel.Fernandez@neuro.uu.se)  
Firoz, Antoni [antoni.firoz@neuro.uu.se](mailto:antoni.firoz@neuro.uu.se)  
Flemström, Gunnar [gunnar.flemstrom@neuro.uu.se](mailto:gunnar.flemstrom@neuro.uu.se)  
Flink, Roland [roland.flink@akadmiska.se](mailto:roland.flink@akadmiska.se)  
Flood, Louise [louise.flood@neuro.uu.se](mailto:louise.flood@neuro.uu.se)  
Flygt, Johanna [johanna.flygt@neuro.uu.se](mailto:johanna.flygt@neuro.uu.se)  
Folke, Fredrik Franck, Marina [fredrik.folke@neuro.uu.se](mailto:fredrik.folke@neuro.uu.se)  
Franck, Marin Pia Fredlund [Franck, Marina marina.franck@neuro.uu.se](mailto:Franck, Marina marina.franck@neuro.uu.se)  
Pia Fredlund [pia.fredlund@neuro.uu.se](mailto:pia.fredlund@neuro.uu.se)  
Fredriksson, Anders [anders.fredriksson@neuro.uu.se](mailto:anders.fredriksson@neuro.uu.se)  
Fredriksson, Robert [robert.fredriksson@neuro.uu.se](mailto:robert.fredriksson@neuro.uu.se)  
Fällman Hedberg, Inger [inger.fallman.hedberg@neuro.uu.se](mailto:inger.fallman.hedberg@neuro.uu.se)  
Fält, AC [ann-charlotte.falt@neuro.uu.se](mailto:ann-charlotte.falt@neuro.uu.se)  
Färdig, Rickard [rickard.fardig@neuro.uu.se](mailto:rickard.fardig@neuro.uu.se)  
Galichanin, Konstantin [konstantin.galichanin@neuro.uu.se](mailto:konstantin.galichanin@neuro.uu.se)  
Galos, Peter Gao, Tianle [galos.peter@neuro.uu.se](mailto:galos.peter@neuro.uu.se)  
Gao, Tianle [tianle.gao@neuro.uu.se](mailto:tianle.gao@neuro.uu.se)  
Gauffin, Emelie [emelie.gauffin@neuro.uu.se](mailto:emelie.gauffin@neuro.uu.se)  
Gonzales Marrero, Humberto [humberto.gonzales.marrero@neuro.uu.se](mailto:humberto.gonzales.marrero@neuro.uu.se)  
Gonzalez Lindh, Margareta [margareta.gonzalez.lindh@neuro.uu.se](mailto:margareta.gonzalez.lindh@neuro.uu.se)  
Granstam, Elisabet [elisabet.granstam@akademiska.se](mailto:elisabet.granstam@akademiska.se)  
Grunér, Sofia [sofia.gruner@neuro.uu.se](mailto:sofia.gruner@neuro.uu.se)  
Grönbladh, Leif [leif.gronbladh@neuro.uu.se](mailto:leif.gronbladh@neuro.uu.se)  
Gudjonsson, Olafur [olafur.gudjonsson@neuro.uu.se](mailto:olafur.gudjonsson@neuro.uu.se)  
Gupta-Löfving, Sandra [sandra.gupta-lofving@neuro.uu.se](mailto:sandra.gupta-lofving@neuro.uu.se)  
Gustafsson, Ann-Catrine [anki.gustafsson@neuro.uu.se](mailto:anki.gustafsson@neuro.uu.se)  
Gustafsson, Isabelle [isabelle.gustafsson@neuro.uu.se](mailto:isabelle.gustafsson@neuro.uu.se)  
Gåve, Eva [eva.gave@neuro.uu.se](mailto:eva.gave@neuro.uu.se)  
Haglund, Kristina Haines, Helen [Kristina.Haglund@neuro.uu.se](mailto:Kristina.Haglund@neuro.uu.se)  
Haines, Helen [helen.haines@neuro.uu.se](mailto:helen.haines@neuro.uu.se)  
Halawa, Imad [imad.halawa@neuro.uu.se](mailto:imad.halawa@neuro.uu.se)  
Hallböök, Finn [finn.hallbook@neuro.uu.se](mailto:finn.hallbook@neuro.uu.se)  
Hallman, Jarmila [jarmila.hallman@neuro.uu.se](mailto:jarmila.hallman@neuro.uu.se)  
Hallnäs, Kerstin [kerstin.hallnas@neuro.uu.se](mailto:kerstin.hallnas@neuro.uu.se)  
Harun-Or-Rashid, Mohammad [mohammad.harun.or.rashid@neuro.uu.se](mailto:mohammad.harun.or.rashid@neuro.uu.se)  
Hedenius, Martina [martina.hedenius@neuro.uu.se](mailto:martina.hedenius@neuro.uu.se)  
Hedman, Martina [martina.hedman@neuro.uu.se](mailto:martina.hedman@neuro.uu.se)  
Hellsand, Minas [minas.hellsand@neuro.uu.se](mailto:minas.hellsand@neuro.uu.se)

Hellsten, Sofie [sofie.hellsten@neuro.uu.se](mailto:sofie.hellsten@neuro.uu.se)  
Hellström, Karin [karin.hellstrom@neuro.uu.se](mailto:karin.hellstrom@neuro.uu.se)  
Hesselager, Göran [goran.hesselager@neuro.uu.se](mailto:goran.hesselager@neuro.uu.se)  
Hillered, Lars [lars.hillered@neuro.uu.se](mailto:lars.hillered@neuro.uu.se)  
Hoerber, Jan [jan.hoerber@neuro.uu.se](mailto:jan.hoerber@neuro.uu.se)  
Hogenkamp, Pleunie Holm, Lena [pleunie.hogenkamp@neuro.uu.se](mailto:pleunie.hogenkamp@neuro.uu.se)  
Hoerber, Jan [lena.holm@neuro.uu.se](mailto:lana.holm@neuro.uu.se)  
Holm, Sara [sara.holm@neuro.uu.se](mailto:sara.holm@neuro.uu.se)  
Holmbäck, Johanna [johanna.holmback@neuro.uu.se](mailto:johanna.holmback@neuro.uu.se)  
Holmström, Gerd [gerd.holmstrom@neuro.uu.se](mailto:gerd.holmstrom@neuro.uu.se)  
Holmström, Ulrika [ulrika.holmstrom@neuro.uu.se](mailto:ulrika.holmstrom@neuro.uu.se)  
Holstad-Högberg, Maria [maria.holstad.hogberg@neuro.uu.se](mailto:maria.holstad.hogberg@neuro.uu.se)  
Holtz, Anders [anders.holtz@neuro.uu.se](mailto:anders.holtz@neuro.uu.se)  
Hooli, Mariana [mariana.hooli@neuro.uu.se](mailto:mariana.hooli@neuro.uu.se)  
Hovberg Sofie [sofie.hovberg@neuro.uu.se](mailto:sofie.hovberg@neuro.uu.se)  
Howells, Tim [tim.howells@neuro.uu.se](mailto:tim.howells@neuro.uu.se)  
Hreinsdottir, Jonina [jonina.hreinsdottir@neuro.uu.se](mailto:jonina.hreinsdottir@neuro.uu.se)  
Hulter Åsberg, Kerstin [kerstin.hulter.asberg@neuro.uu.se](mailto:kerstin.hulter.asberg@neuro.uu.se)  
Hynninen, Pirkko [pirkko.hynninen@akademiska.se](mailto:pirkko.hynninen@akademiska.se)  
Hård-Wallenqvist, Berit [berit.hard-wallenqvist@neuro.uu.se](mailto:berit.hard-wallenqvist@neuro.uu.se)  
Höglund, Anna-Stina [anna-stina.hoglund@neuro.uu.se](mailto:anna-stina.hoglund@neuro.uu.se)  
Hörberg, Niklas [niklas.horberg@neuro.uu.se](mailto:niklas.horberg@neuro.uu.se)  
Isaksson, Johan [johan.isaksson@neuro.uu.se](mailto:johan.isaksson@neuro.uu.se)  
Ivert, Patrik [Patrik.Ivert@neuro.uu.se](mailto:Patrik.Ivert@neuro.uu.se)  
Iyad Salah, Heba [heba.salah@neuro.uu.se](mailto:heba.salah@neuro.uu.se)  
Jackmann, Sven [sven.jackmann@akademiska.se](mailto:sven.jackmann@akademiska.se)  
Jakobsson Larsson, Birgitta [birgitta.jakobsson.larsson@neuro.uu.se](mailto:birgitta.jakobsson.larsson@neuro.uu.se)  
Jakobsson, Jon [jon.jakobsson@neuro.uu.se](mailto:jon.jakobsson@neuro.uu.se)  
Jennische, Margareta [margareta.jennische@neuro.uu.se](mailto:margareta.jennische@neuro.uu.se)  
Jin, Zhe [zhe.jin@neuro.uu.se](mailto:zhe.jin@neuro.uu.se)  
Johansson, Henrik [henrik.johansson@neuro.uu.se](mailto:henrik.johansson@neuro.uu.se)  
Johnson, Ulf [ulf.johnson@neuro.uu.se](mailto:ulf.johnson@neuro.uu.se)  
Jonsson, Jörgen [jorgen.jonsson@neuro.uu.se](mailto:jorgen.jonsson@neuro.uu.se)  
Jonsson, Ulf [ulf.jonsson@neuro.uu.se](mailto:ulf.jonsson@neuro.uu.se)  
Junemar, Silvermark, Annika [annika.silvemark@neuro.uu.se](mailto:annika.silvemark@neuro.uu.se)  
Jüris, Linda [linda.juris@neuro.uu.se](mailto:linda.juris@neuro.uu.se)  
Kabolis, Nikolaos [nikolaos.kabolis@neuro.uu.se](mailto:nikolaos.kabolis@neuro.uu.se)  
Kalnak, Nelli Kanders, Sofia [nelli.kalnak@neuro.uu.se](mailto:nelli.kalnak@neuro.uu.se)  
Kanders, Sofie [sofia.kanders@neuro.uu.se](mailto:sofia.kanders@neuro.uu.se)  
Karamanis, Georgios [Georgios.Karamanis@neuro.uu.se](mailto:Georgios.Karamanis@neuro.uu.se)  
Karlsson, Lena [lena.karlsson@neuro.uu.se](mailto:lana.karlsson@neuro.uu.se)  
Kask, Jan Konjusha, Dardan [jan.kask@neuro.uu.se](mailto:jan.kask@neuro.uu.se)  
Katsarogiannis, Evangelos [evangelos.katsarogiannis@neuro.uu.se](mailto:evangelos.katsarogiannis@neuro.uu.se)  
Knorring von, Lars [lars.von\\_knorring@neuro.uu.se](mailto:lars.von_knorring@neuro.uu.se),  
Konjusha, Dardan [dardan.konjusha@neuro.uu.se](mailto:dardan.konjusha@neuro.uu.se)  
Korol, Sergiy [sergiy.korol@neuro.uu.se](mailto:sergiy.korol@neuro.uu.se)  
Kouppis, Efthymios [efthymios.kouppis@neuro.uu.se](mailto:efthymios.kouppis@neuro.uu.se)  
Kouros, Ioannis [ioannis.kouros@neuro.uu.se](mailto:ioannis.kouros@neuro.uu.se)  
Kozlova-Aldskogius, Elena [elena.kozlova@neuro.uu.se](mailto:elena.kozlova@neuro.uu.se)  
Krüger-Vahlquist, Maria [maria.kruger.vahlquist@neuro.uu.se](mailto:maria.kruger.vahlquist@neuro.uu.se)

Kullander, Klas [klas.kullander@neuro.uu.se](mailto:klas.kullander@neuro.uu.se)  
Kumlien, Eva [eva.kumlien@neuro.uu.se](mailto:eva.kumlien@neuro.uu.se)  
König, Niclas [niclas.konig@neuro.uu.se](mailto:niclas.konig@neuro.uu.se)  
Lagerström, Malin [malin.lagerstrom@neuro.uu.se](mailto:malin.lagerstrom@neuro.uu.se)  
Landblom, Anne-Marie [anne-marie.landtblom@neuro.uu.se](mailto:anne-marie.landtblom@neuro.uu.se)  
Landgren, Eva [eva.landgren@akademiska.se](mailto:eva.landgren@akademiska.se)  
Lannsjö, Marianne [marianne.lannsjö@neuro.uu.se](mailto:marianne.lannsjö@neuro.uu.se)  
Larhammar, Dan [dan.larhammar@neuro.uu.se](mailto:dan.larhammar@neuro.uu.se)  
Larsson, Eva [eva.larsson@neuro.uu.se](mailto:eva.larsson@neuro.uu.se)  
Latini, Francesco [francesco.latini@neuro.uu.se](mailto:francesco.latini@neuro.uu.se)  
Laurent, Nadina [nadina.laurent@neuro.uu.se](mailto:nadina.laurent@neuro.uu.se)  
Le Greves, Madeleine [madeleine.legreves@neuro.uu.se](mailto:madeleine.legreves@neuro.uu.se)  
Leao, Richardson [richardson.leao@neuro.uu.se](mailto:richardson.leao@neuro.uu.se)  
Leijonmarck, Caroline [caroline.leijonmarck@akademiska.se](mailto:caroline.leijonmarck@akademiska.se)  
Lekholm, Emilia [emilia.lekholm@neuro.uu.se](mailto:emilia.lekholm@neuro.uu.se)  
Lenell, Samuel [samuel.lenell@neuro.uu.se](mailto:samuel.lenell@neuro.uu.se)  
Lewandowska, Marta [marta.lewandowska@neuro.uu.se](mailto:marta.lewandowska@neuro.uu.se)  
Lewén, Anders [anders.lewen@neuro.uu.se](mailto:anders.lewen@neuro.uu.se)  
Lindström Leif Loskog, Anna [Leif.Lindstrom@neuro.uu.se](mailto:Leif.Lindstrom@neuro.uu.se)  
Ljungvall, Hanna [hanna.ljungvall@neuro.uu.se](mailto:hanna.ljungvall@neuro.uu.se)  
Loskog, Anna [anna.loskog@neuro.uu.se](mailto:anna.loskog@neuro.uu.se)  
Lundberg, Per Olof [po.lundberg@neuro.uu.se](mailto:po.lundberg@neuro.uu.se)  
Lundin, Lars-Gustav [LG.Lundin@neuro.uu.se](mailto:LG.Lundin@neuro.uu.se)  
Lundin, Tom Magnúsdóttir Elin [Tom.Lundin@neuro.uu.se](mailto:Tom.Lundin@neuro.uu.se)  
Långström, Niklas [niklas.langstrom@neuro.uu.se](mailto:niklas.langstrom@neuro.uu.se)  
Magnúsdóttir Elin [elin.magnusdottir@neuro.uu.se](mailto:elin.magnusdottir@neuro.uu.se)  
Makris, Georgios [georgios.makris@neuro.uu.se](mailto:georgios.makris@neuro.uu.se)  
Malmqvist, Lars [lars.malmqvist@neuro.uu.se](mailto:lars.malmqvist@neuro.uu.se)  
Marklund, Niklas [niklas.marklund@neuro.uu.se](mailto:niklas.marklund@neuro.uu.se)  
Martin, Cathrin [cathrin.martin@neuro.uu.se](mailto:cathrin.martin@neuro.uu.se)  
Mattsson, Peter [peter.mattsson@neuro.uu.se](mailto:peter.mattsson@neuro.uu.se)  
Merkoudis, Nikolaos [nikolaos.merkoudis@akademiska.se](mailto:nikolaos.merkoudis@akademiska.se)  
Michel, Per-Olof [Per-Olof.Michel@neuro.uu.se](mailto:Per-Olof.Michel@neuro.uu.se)  
Mikulovic, Sanja [sanja.mikulovic@neuro.uu.se](mailto:sanja.mikulovic@neuro.uu.se)  
Milesson Fors, Björn [bjorn.milesson.fors@neuro.uu.se](mailto:bjorn.milesson.fors@neuro.uu.se)  
Molin, Carl Johan [carljohan.molin@neuro.uu.se](mailto:carljohan.molin@neuro.uu.se)  
Mollazadegan, Kaziwe [kaziwe.mollazadegan@akademiska.se](mailto:kaziwe.mollazadegan@akademiska.se)  
Molnar, Anna Mustafa, Arshi [anna.molnar@neuro.uu.se](mailto:anna.molnar@neuro.uu.se)  
Mustafa, Arshi [arshi.mustafa@neuro.uu.se](mailto:arshi.mustafa@neuro.uu.se)  
Mwinyi, Jessica [jessica.mwinyi@neuro.uu.se](mailto:jessica.mwinyi@neuro.uu.se)  
Mæpea, Olav [olav.maepea@neuro.uu.se](mailto:olav.maepea@neuro.uu.se)  
Nagaraja, Chetan [chetan.nagaraja@neuro.uu.se](mailto:chetan.nagaraja@neuro.uu.se)  
Nakeva Von Mentzer, Cecilia [cecilia.nakeva.vonMentzer@neuro.uu.se](mailto:cecilia.nakeva.vonMentzer@neuro.uu.se)  
Nandkumar Bendre, Megha [megha.bendre@neuro.uu.se](mailto:megha.bendre@neuro.uu.se)  
Nasir, Stefan [stefan.nasir@neuro.uu.se](mailto:stefan.nasir@neuro.uu.se)  
Niemelä, Valter [valter.niemela@neuro.uu.se](mailto:valter.niemela@neuro.uu.se)  
Nilsson, Anders [anders.nilsson@neuro.uu.se](mailto:anders.nilsson@neuro.uu.se)  
Nilsson, Björn [bjorn.nilsson@neuro.uu.se](mailto:bjorn.nilsson@neuro.uu.se)  
Nilsson, Pelle [pelle.nilsson@neuro.uu.se](mailto:pelle.nilsson@neuro.uu.se)

Nordström, Karin [karin.nordstrom@neuro.uu.se](mailto:karin.nordstrom@neuro.uu.se)  
Nuija, Eva [eva.nuija@neuro.uu.se](mailto:eva.nuija@neuro.uu.se)  
Nyberg, Christoffer [christoffer.nyberg@neuro.uu.se](mailto:christoffer.nyberg@neuro.uu.se)  
Nygren, Ingela [ingela.nygren@neuro.uu.se](mailto:ingela.nygren@neuro.uu.se)  
Nygren, Karin [karin.nygren@neuro.uu.se](mailto:karin.nygren@neuro.uu.se)  
Nyholm, Dag [dag.nyholm@neuro.uu.se](mailto:dag.nyholm@neuro.uu.se)  
Nyholm, Lena [lena.nyholm@neuro.uu.se](mailto:lena.nyholm@neuro.uu.se)  
Nylander, Olof [olof.nylander@neuro.uu.se](mailto:olof.nylander@neuro.uu.se)  
Odelius, Charlotta [charlotta.odelius@neuro.uu.se](mailto:charlotta.odelius@neuro.uu.se)  
Olivo, Gaia [gaia.olivo@neuro.uu.se](mailto:gaia.olivo@neuro.uu.se)  
Olsén Jonas [jonas.olsen@neuro.uu.se](mailto:jonas.olsen@neuro.uu.se)  
Oreland, Lars [lars.oreland@neuro.uu.se](mailto:lars.oreland@neuro.uu.se)  
Ormerod, Neil [neil.ormerod@neuro.uu.se](mailto:neil.ormerod@neuro.uu.se)  
Papadopoulos, Fotios [fotis.papadopoulos@neuro.uu.se](mailto:fotis.papadopoulos@neuro.uu.se)  
Pedersen, Julia [julia.pedersen@neuro.uu.se](mailto:julia.pedersen@neuro.uu.se)  
Perland, Emelie [emelie.perland@neuro.uu.se](mailto:emelie.perland@neuro.uu.se)  
Perry, Sharn [sharn.perry@neuro.uu.se](mailto:sharn.perry@neuro.uu.se)  
Persson, Jonas [jonas.persson@neuro.uu.se](mailto:jonas.persson@neuro.uu.se)  
Persson, Lennart [lennart.persson@neuro.uu.se](mailto:lennart.persson@neuro.uu.se)  
Persson, Mona [mona.persson@neuro.uu.se](mailto:mona.persson@neuro.uu.se)  
Pettersson, Kerstin [kerstin.pettersson@neuro.uu.se](mailto:kerstin.pettersson@neuro.uu.se)  
Pettersson, Stefan [stefan.pettersson@neuro.uu.se](mailto:stefan.pettersson@neuro.uu.se)  
Pétursdóttir, Dýrleif [dyrleif.petursdottir@neuro.uu.se](mailto:dyrleif.petursdottir@neuro.uu.se)  
Peuckert, Christiane [c.peuckert@neuro.uu.se](mailto:c.peuckert@neuro.uu.se)  
Piltan, Peggy [peggy.piltan@neuro.uu.se](mailto:peggy.piltan@neuro.uu.se)  
Pourakbar, Yousef [yousef.pourakbar@neuro.uu.se](mailto:yousef.pourakbar@neuro.uu.se)  
Pruner, Jasna [jasna.pruner@neuro.uu.se](mailto:jasna.pruner@neuro.uu.se)  
Ramirez, Adriana [adriana.ramirez@neuro.uu.se](mailto:adriana.ramirez@neuro.uu.se)  
Ramklint, Mia [Mia.Ramklint@neuro.uu.se](mailto:Mia.Ramklint@neuro.uu.se)  
Restrepo, Ernesto [ernesto.restrepo@neuro.uu.se](mailto:ernesto.restrepo@neuro.uu.se)  
Ring, Henrik [henrik.ring@neuro.uu.se](mailto:henrik.ring@neuro.uu.se)  
Ronne-Engström, Elisabeth [elisabeth.ronne.engstrom@neuro.uu.se](mailto:elisabeth.ronne.engstrom@neuro.uu.se)  
Roodakker, Kenney [kenney.roodakker@neuro.uu.se](mailto:kenney.roodakker@neuro.uu.se)  
Roshanbin, Sahar [sahar.roshanbin@neuro.uu.se](mailto:sahar.roshanbin@neuro.uu.se)  
Rosling Agneta [agneta.rosling@neuro.uu.se](mailto:agneta.rosling@neuro.uu.se)  
Rostami, Elham [elham.rostami@neuro.uu.se](mailto:elham.rostami@neuro.uu.se)  
Rostedt Punga, Anna [anna.rostedt.punga@neuro.uu.se](mailto:anna.rostedt.punga@neuro.uu.se)  
Rostedt, Margaretha [margaretha.rostedt@neuro.uu.se](mailto:margaretha.rostedt@neuro.uu.se)  
Rothkegel, Holger [holger.rothkegel@akademiska.se](mailto:holger.rothkegel@akademiska.se)  
Ruchkin, Vladislav [vladislav.ruchkin@neuro.uu.se](mailto:vladislav.ruchkin@neuro.uu.se)  
Ryttlefors, Mats [mats.ryttlefors@neuro.uu.se](mailto:mats.ryttlefors@neuro.uu.se)  
Rångtall Frida [frida.rangtall@neuro.uu.se](mailto:frida.rangtall@neuro.uu.se)  
Sabre, Liis [liis.sabre@neuro.uu.se](mailto:liis.sabre@neuro.uu.se)  
Salberg, Johanna [johanna.salberg@neuro.uu.se](mailto:johanna.salberg@neuro.uu.se)  
Salci, Konstantin [konstantin.salci@neuro.uu.se](mailto:konstantin.salci@neuro.uu.se)  
Sandberg Melin, Camilla [camilla.sandberg.melin@neuro.uu.se](mailto:camilla.sandberg.melin@neuro.uu.se)  
Sandberg, Arne [arne.sandberg@akademiska.se](mailto:arne.sandberg@akademiska.se)  
Sandström, Marie [marie.sandstrom@neuro.uu.se](mailto:marie.sandstrom@neuro.uu.se)  
Schiöth, Helgi [helgi.schioth@neuro.uu.se](mailto:helgi.schioth@neuro.uu.se)  
Schmidt, Roland [roland.schmidt@akademiska.se](mailto:roland.schmidt@akademiska.se)



Schweizer, Nadine [nadine.schweizer@neuro.uu.se](mailto:nadine.schweizer@neuro.uu.se)  
Senek, Marina Shebanits, Kateryna [marina.sanek@neuro.uu.se](mailto:marina.sanek@neuro.uu.se)  
Seyed Tafreshiha, Atieh [atieh.seyed.tafreshiha@neuro.uu.se](mailto:atieh.seyed.tafreshiha@neuro.uu.se)  
Shamoun, Simon [simon.shamoun@akademiska.se](mailto:simon.shamoun@akademiska.se)  
Shebanits, Kateryna [kateryna.shebanits@neuro.uu.se](mailto:kateryna.shebanits@neuro.uu.se)  
Siwani, Samer [samer.siwani@neuro.uu.se](mailto:samer.siwani@neuro.uu.se)  
Sjöblom, Markus [markus.sjoblom@neuro.uu.se](mailto:markus.sjoblom@neuro.uu.se)  
Sjölin, Karl [karl.sjolin@neuro.uu.se](mailto:karl.sjolin@neuro.uu.se)  
Sköld, Mattias [mattias.skold@neuro.uu.se](mailto:mattias.skold@neuro.uu.se)  
Smits, Anja [anja.smits@neuro.uu.se](mailto:anja.smits@neuro.uu.se)  
Spandau, Ulrich [ulrich.spandau@neuro.uu.se](mailto:ulrich.spandau@neuro.uu.se)  
Spangenberg, Hanna [hanna.spangenberg@neuro.uu.se](mailto:hanna.spangenberg@neuro.uu.se)  
Sperber, Göran [goran.sperber@neuro.uu.se](mailto:goran.sperber@neuro.uu.se)  
Spörndly-Nees, Sören [soren.sporndly-nees@neuro.uu.se](mailto:soren.sporndly-nees@neuro.uu.se)  
Stenfelt, Sonya [sonya.stenfelt@neuro.uu.se](mailto:sonya.stenfelt@neuro.uu.se)  
Stålberg, Erik [stalberg.erik@gmail.com](mailto:stalberg.erik@gmail.com)  
Stålberg, Gabriella [gabriella.stalberg@neuro.uu.se](mailto:gabriella.stalberg@neuro.uu.se)  
Sundberg, Isak [isak.sundberg@neuro.uu.se](mailto:isak.sundberg@neuro.uu.se)  
Sundblom, Jimmy [jimmy.sundblom@neuro.uu.se](mailto:jimmy.sundblom@neuro.uu.se)  
Sundbom, Ann Sundin, Josefin [ann.sundbom@neuro.uu.se](mailto:ann.sundbom@neuro.uu.se)  
Sundin, Josefin [josefin.sundin@neuro.uu.se](mailto:josefin.sundin@neuro.uu.se)  
Sveen, Josefin [josefin.sveen@neuro.uu.se](mailto:josefin.sveen@neuro.uu.se)  
Szalisznyo, Krisztina [krisztina.szalisznyo@neuro.uu.se](mailto:krisztina.szalisznyo@neuro.uu.se)  
Szmidt, Malgorzata [malgorzata.szmidt@neuro.uu.se](mailto:malgorzata.szmidt@neuro.uu.se)  
Söderberg, Per Sör, Ingrid [per.soderberg@neuro.uu.se](mailto:per.soderberg@neuro.uu.se)  
Sör, Ingrid [ingrid.sor@neuro.uu.se](mailto:ingrid.sor@neuro.uu.se)  
Talebizadeh, Nooshin [nooshin.talebizadeh@neuro.uu.se](mailto:nooshin.talebizadeh@neuro.uu.se)  
Tamador, Elsir [t\\_elsir@hotmail.com](mailto:t_elsir@hotmail.com)  
Thorvaldsson, Lina [lina.thorvaldson@mcb.uu.se](mailto:lina.thorvaldson@mcb.uu.se)  
Thunberg, Sari [sari.thunberg@neuro.uu.se](mailto:sari.thunberg@neuro.uu.se)  
Thyselius, Malin [malin.thyselius@neuro.uu.se](mailto:malin.thyselius@neuro.uu.se)  
Thörnqvist, Per-Ove [per-ove.thornqvist@neuro.uu.se](mailto:per-ove.thornqvist@neuro.uu.se)  
Tillman, Karin [karin.tillman@neuro.uu.se](mailto:karin.tillman@neuro.uu.se)  
Titova, Olga Tjäder, Solveig [olga.titova@neuro.uu.se](mailto:olga.titova@neuro.uu.se)  
Tjäder, Solveig  
Todkar, Aniruddha [aniruddha.todkar@neuro.uu.se](mailto:aniruddha.todkar@neuro.uu.se)  
Tolf, Andreas [andreas.tolf@neuro.uu.se](mailto:andreas.tolf@neuro.uu.se)  
Tomic, Lidija [lidija.tomic@neuro.uu.se](mailto:lidija.tomic@neuro.uu.se)  
Tomic, Zoran [zoran.tomic@neuro.uu.se](mailto:zoran.tomic@neuro.uu.se)  
Trolle, Carl [carl.trolle@neuro.uu.se](mailto:carl.trolle@neuro.uu.se)  
Tsitsopoulos, Parmenion [ptsitsopoulos@auth.gr](mailto:ptsitsopoulos@auth.gr)  
Tuvemo Johnson, Susanna [susanna.tuvemo.johnson@neuro.uu.se](mailto:susanna.tuvemo.johnson@neuro.uu.se)  
Törnquist, Per Uhlén, Staffan [per.tornquist@neuro.uu.se](mailto:per.tornquist@neuro.uu.se)  
Uhlén, Staffan [staffan.uhlen@neuro.uu.se](mailto:staffan.uhlen@neuro.uu.se)  
Urell, Charlotte [charlotte.urell@neuro.uu.se](mailto:charlotte.urell@neuro.uu.se)  
Wahlberg, Eva-Lena [eva-lena.wahlberg@neuro.uu.se](mailto:eva-lena.wahlberg@neuro.uu.se)  
Waldemarson, Anna  
Wallmark, Svante [svante.wallmark@neuro.uu.se](mailto:svante.wallmark@neuro.uu.se)  
Vasylovska, Svitlana [svitlana.vasylovska@neuro.uu.se](mailto:svitlana.vasylovska@neuro.uu.se)  
Vedung, Fredrik [fredrik.vedung@neuro.uu.se](mailto:fredrik.vedung@neuro.uu.se)

Velle, Fartein [fartein.velle@neuro.uu.se](mailto:fartein.velle@neuro.uu.se)  
Wenngren, Ewa [ewa.wenngren@neuro.uu.se](mailto:ewa.wenngren@neuro.uu.se)  
Wesslén, Nils [nils.wesslen@neuro.uu.se](mailto:nils.wesslen@neuro.uu.se)  
Westerberg, Elisabet [elisabet.westerberg@neuro.uu.se](mailto:elisabet.westerberg@neuro.uu.se)  
Widenfalk, Johan [johan.widenfalk@neuro.uu.se](mailto:johan.widenfalk@neuro.uu.se)  
Viegas Caixeta, Fabio [fabio.viegas.caixeta@neuro.uu.se](mailto:fabio.viegas.caixeta@neuro.uu.se)  
Vieillard, Jennifer [jennifer.vieillard@neuro.uu.se](mailto:jennifer.vieillard@neuro.uu.se)  
Wiemerslage, Lyle [lyle.wiemerslage@neuro.uu.se](mailto:lyle.wiemerslage@neuro.uu.se)  
Viereckel, Thomas [thomas.viereckel@neuro.uu.se](mailto:thomas.viereckel@neuro.uu.se)  
Wikberg Matsson, Anna [anna.wikberg-matsson@neuro.uu.se](mailto:anna.wikberg-matsson@neuro.uu.se)  
Willebrand, Mimmie [mimmie.willebrand@neuro.uu.se](mailto:mimmie.willebrand@neuro.uu.se)  
Williams, Michael [michael.williams@neuro.uu.se](mailto:michael.williams@neuro.uu.se)  
Winberg, Svante [svante.winberg@neuro.uu.se](mailto:svante.winberg@neuro.uu.se)  
Virhammar, Johan [johan.virhammar@neuro.uu.se](mailto:johan.virhammar@neuro.uu.se)  
Vlachogiannis, Pavlos [pavlos.vlachogiannis@neuro.uu.se](mailto:pavlos.vlachogiannis@neuro.uu.se)  
Voisin, Sarah [sarah.voisin@neuro.uu.se](mailto:sarah.voisin@neuro.uu.se)  
von Seth, Charlotta [charlotta.von\\_Seth@neuro.uu.se](mailto:charlotta.von_Seth@neuro.uu.se)  
Vossen, Laura [laura.vossen@neuro.uu.se](mailto:laura.vossen@neuro.uu.se)  
Vrettou, Maria [maria.vrettou@neuro.uu.se](mailto:maria.vrettou@neuro.uu.se)  
Xu, Bo [bo.xu@neuro.uu.se](mailto:bo.xu@neuro.uu.se)  
Yates, Cecilia [cecilia.yates@neuro.uu.se](mailto:cecilia.yates@neuro.uu.se)  
Yu, Zhaohua [zhaohua.yu@neuro.uu.se](mailto:zhaohua.yu@neuro.uu.se)  
Zelano, Johan [johan.zelano@neuro.uu.se](mailto:johan.zelano@neuro.uu.se)  
Zetterberg, Hedvig [hedvig.zetterberg@neuro.uu.se](mailto:hedvig.zetterberg@neuro.uu.se)  
Zetterberg, Lena [lena.zetterberg@neuro.uu.se](mailto:lena.zetterberg@neuro.uu.se)  
Zetterling, Maria [maria.zetterling@neuro.uu.se](mailto:maria.zetterling@neuro.uu.se)  
Zhang, Xiao [xiao.zhang@neuro.uu.se](mailto:xiao.zhang@neuro.uu.se)  
Zhou, Wei [wei.zhou@neuro.uu.se](mailto:wei.zhou@neuro.uu.se)  
Åkerblom, Hanna [hanna.akerblom@neuro.uu.se](mailto:hanna.akerblom@neuro.uu.se)  
Åkerblom, Ylva [ylva.akerblom@neuro.uu.se](mailto:ylva.akerblom@neuro.uu.se)  
Åsenlöf, Pernilla [pernilla.asenlof@neuro.uu.se](mailto:pernilla.asenlof@neuro.uu.se)  
Ögeföldt, Sofia [sofia.ogefeldt@neuro.uu.se](mailto:sofia.ogefeldt@neuro.uu.se)  
Öster, Caisa [Caisa.Oster@neuro.uu.se](mailto:Caisa.Oster@neuro.uu.se)



## DISSERTATIONS 2016

**Aresh, Bejan:** Developmental Genetics, "*Functional Aspects of Peripheral and Spinal Cord Neurons Involved in Itch and Pain*".

**Babateen, Omar:** Physiology, "*GABA signaling regulation by GLP-1 receptors agonists and GABA-A receptors modulator*".

**Bandstein, Marcus:** Functional Pharmacology, "*The role of genetics in regulations of weight loss and food intake*".

**Bhandage, Amol:** Physiology, "*Glutamate and GABA signalling components in the human brain and in immune cells*".

**Bauer Mikulovic Sanja:** Developmental Genetics, "*On the mechanisms behind hippocampal theta oscillations - The role of OLMalpha2 interneurons*".

**Danielsson, Katarina:** Psychiatry, "*Delayed Sleep Disorder: Prevalence, Diagnostic Aspects, Associated Factors, and Treatment Concepts*".

**Hagman, Carina:** Physiotherapy, "*Dysfunctional breathing - clinical characteristics and treatment*".

**Harun-or-Rashid, Mohammad:** Developmental Neuroscience, "*Modulation of the Progenitor Cell and Homeostatic Capacities of Müller Glia Cells in Retina. Focus on alpha2-Adrenergic and Endothelin Receptor Signaling Systems*".

**Hellsten, Sofie:** Functional Pharmacology, "*Characterization of amino acid transporters: Transporters expressed in the central nervous system belonging to the Solute Carrier family SLC38*".

**Jakobsson Larsson, Birgitta:** Neurology, "*Quality of Life, Coping and need for Support during the ALS disease trajectory*".

**Johansson, Ulf:** Neurosurgery, "*Pressure autoregulation of cerebral blood flow in traumatic brain injury and aneurysmal subarachnoid hemorrhage*".

**Perry, Sharn:** Developmental Genetics, "*Deciphering the locomotor network - The role of spinal cord interneurons*".

**Revenäs, Åsa:** Physiotherapy, "*Co-designing a mobile Internet service for self-management of physical activity in rheumatoid arthritis*".

**Roshanbin, Sahar:** Functional Pharmacology, "*Characterization of Centrally Expressed Solute Carriers - Histological and Functional Studies with Transgenic Mice*".

**Schweizer, Nadine:** Functional Neurobiology, "*Across Borders - A Histological and Physiological Study of the Subthalamic Nucleus in Reward and Movement*".

**Talebizadeh, Nooshin:** Ophthalmology, "*Caspase-3 in lens epithelium*".

**Todkar, Aniruddha:** Neuropsychopharmacology, *"Alcohol Consumption: A Study of Genetic and Environmental Correlates with Focus on the Stress System"*.

**Trolle, Carl:** Regenerative Neurobiology, *"Stem cell transplantation and regeneration after dorsal root avulsion"*.

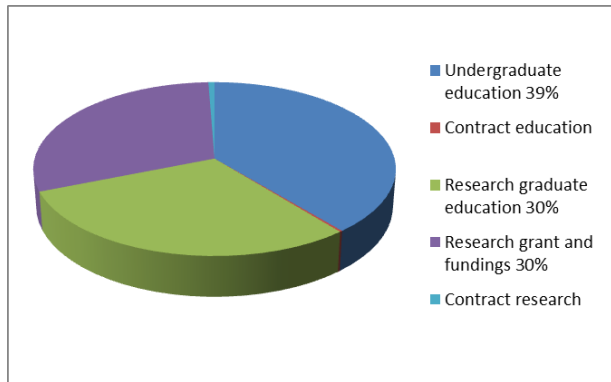
**Vadlin, Sofia:** CKF Västerås, *"Problematic Gaming and Gambling among Adolescents"*.

**Voisin, Sarah:** Functional Pharmacology, *"Bioinformatic and biostatistic analysis of epigenetic data from humans and mice in the context of obesity and its complications"*.

## Finance 2016

Total revenues 2016: 150 875 000 Swedish krona

Undergraduate education 39%	58 671
Contract education	331
Research graduate education 30%	45 078
Research grant and fundings 30%	45 865
Contract research	930



Total publication points 2016 at Dept of Neuroscience: 329,5011

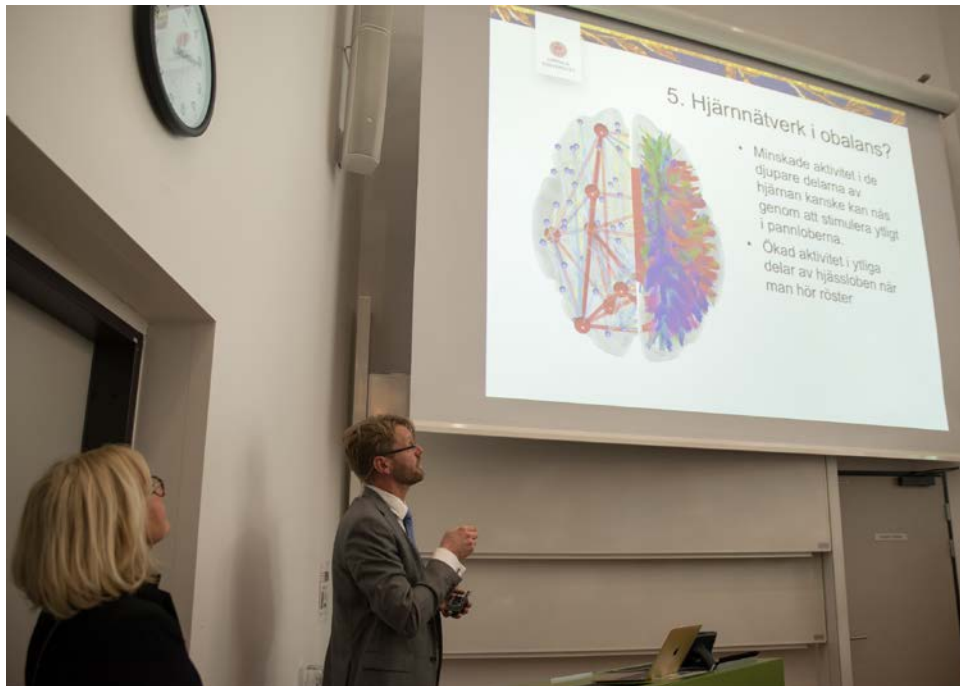
Top 20 researcher's publication points 2016 at Dept of Neuroscience:

Schiöth, Helgi B.	27,36344963
Benedict, Christian	10,91233213
Cedernaes, Jonathan	10,78059983
Brooks, Samantha J.	8,53144943
Wiemerslage, Lyle	7,347469106
Salah, Heba	6,505599976
Mwinyi, Jessica	6,040273324
Punga, Anna Rostedt	5,853500128
Sveen, Josefin	5,07370007
Smits, Anja	4,891675144
Comasco, Erika	4,814626545
Williams, Michael J.	4,345879987
Hallböök, Finn	4,15259999
Cunningham, Janet L.	4,010400057
Marklund, Niklas	3,875408337
Falkenström, Fredrik	3,855399877
Lindqvist, Johan	3,855199814
Holmström, Gerd	3,818483464
Danielsson, Katarina	3,616899922
Nordström, Karin	3,543200076

Research grants and funds: 47 023 000 Swedish krona

AFA Försäkring	2 501
AFOSR	772
Barncancerfonden	435
Beijerstiftelsen	838
Bissen Brainwalk	1 000
Carl Tryggers stiftelse	327
EU	1 807
FORMAS	2 062
Forte	1 300
Fredrik och Ingrid Thurings stiftelse	510
Hjärnfonden	4 121
Kungliga Vetenskapsakademin	400
Neuroförbundet	356
Novo Nordisk	1 283
Promobilia	200
Selanders stiftelse	570
SLS	1 154
Socialstyrelsen	2 213
SSMF	400
Stiftelsen Olle Engkvist Byggmästare	1 300
CAN Centralförbundet för alkohol och narkotikaupplysning	350
Stiftelsen Sävstaholm	250
Tore Nilssons stiftelse	210
Ulla-Carin Lindquists stiftelse	457
Uppsala Akademiförvaltning	4 207
Vetenskapsrådet	13 557
Vinnova	450
Åke Wibergs stiftelse	600
Ögonfonden	300

## SCIENTIFIC REPORTS



*Lisa Ekselius and Robert Boden, Psychiatry research group, present at Märta Naswell day 2016. Link to the research group:*  
<http://www.neuro.uu.se/forskning/Psykiatri/?languageId=3>

# ***Clinical Neurology & Psychiatry***

## **Clinical Neurology**

**Group leader: Anja Smits, Professor**

### **Members of the group during 2016**

Anja Smits, Professor	Johan Zelano, Assoc Prof
Anne-Marie Landtblom, Professor	Kenney Roodakker, PhD student
Dag Nyholm, Associate Professor	Madelen Braun, MD
Eva Kumlien, Associate Professor	Makrina Daniilidou, PhD
Ingela Nygren, MD PhD	Marina Senek, PhD student
Joachim Burman, MD, PhD	Paul de Roos, MD
Johan Virhammar, MD, PhD	Peter Mattsson, Associate Professor
Amalia Feresiadou, MD	Shala Berntsson, MD, PhD
Andreas Tolf, PhD student	Stergios Papadimitriou, MD
Birgitta Jakobsson-Larsson, PhD	Svante Wallmark, PhD student
Imad Halawa, MD PhD student	Tamador Elsir, PhD
Inger Boström, PhD	Valter Niemelä, PhD student

Research at Clinical Neurology is patient-oriented as well as translational. Common neurological disorders such as epilepsy, movement disorders, stroke and multiple sclerosis (MS) as well as rare diseases like hereditary neurological disorders, low-grade gliomas and sleep disorders are studied, often in tight collaborations with other clinical and preclinical centers. Biobanked material consisting of blood samples, CSF and tissues provides powerful resources for translational studies.

*Research groups:*

### ***Epilepsy***

Group leader: Eva Kumlien, associate professor

Members of the group: Torsten Danfors, MD, PhD, Imad Halawa, MD, PhD-student, Peter Mattsson, associate professor, Stergios Papadimitriou, MD.

Epilepsy is a common and serious disorder of the central nervous system, with a prevalence of approximately 0,5-1 % and accounts for 0.5% of the global burden of disease. Epilepsy can have congenital aetiologies, often presumed to affect the wiring of the brain with ensuing hyperexcitability of neuronal networks, but also arise after cerebral lesions, such as infections, trauma or stroke. Epilepsy is associated with serious consequences such as premature death, physical problems such as fractures and bruising, as well as higher rates of other diseases or psychosocial issues. Epilepsy has significant economic implications in terms of health-care needs and lost work productivity. Children of women with epilepsy have increased rates of malformations, lower mean IQ and school grades.

Ongoing Clinical and interventional projects in Epilepsy group:

***Role of exposure of antiepileptic drugs in utero in the prevention of later cognitive impairment in children to parents with epilepsy***

In this registry-based study we collect data on all children born 1973-2003 (N=2.000.000). We will compare school grades and later socioeconomic achievements of children exposed to anti-epileptic drugs (AEDs) in utero with children unexposed to such drugs.

***Role of pharmacological treatment in the prevention of sudden unexpected death in epilepsy (SUDEP)***

The study population comprises all persons living in Sweden at the end of 2006, who at some point during 1998-2005 were registered with the diagnosis code for epilepsy in the Swedish National Patient Register. Using death certificates we will identify cases of SUDEP. For these potential cases, medical records including autopsy protocols will be reviewed. For each case we will randomly select three epilepsy controls from the study population. The aim is to analyse the risk of SUDEP in relation to non-adherence to prescribed AEDs, type of prescribed AEDs and co-medication with SSRI-type antidepressants. In a separate study, cardiological problems in persons with epilepsy, as collaboration with the University of Linköping, are analysed.

***Focal epilepsy – clinical characteristics, prognosis, prevention and search for biomarkers.***

We are studying a cohort of patients with newly onset epilepsy Uppsala County. Data is been collected with the purpose to characterize the condition, and form the basis of future genetic and imaging studies. A prospective study of patients with newly diagnosed epilepsy is on going with the aim to identify biological and clinical biomarkers for epileptogenesis with a special focus on inflammation, neuronal antibodies and genetics.

***Cortical excitability in epilepsy – studies with Transcranial Magnet Stimulation (TMS)***

We are applying TMS to measure cortical excitability and risk of seizures in cohorts of patients with a primary cerebral insult, newly onset epilepsy, pharmacoresistant epilepsy and healthy control subjects. We also want to explore the effect of temporal lobe resection on neuronal networks for fear conditioning by means of TMS in relation to fMRI.

***Acute symptomatic seizures - a study in patients with dysmetabolic disorders and structural brain damage***

In the present study, we focus on seizures occurring in relation to an acute structural brain insult, i.e. subarachnoid haemorrhage and perform continuous measurements of amplitude integrated EEG (aEEG) and CSF biomarkers (neurofilament light (NFL) and tau).

***Quantitative assessment of synaptic density using the SV2A ligand <sup>11</sup>C-UCBA in humans***

Quantitative imaging of the synaptic vesicle glycoprotein 2A (SV2A) with PET can be used as a measure of synaptic density in the human brain. Changes of the density occur in many neurological diseases. <sup>11</sup>C-UCBA has previously been validated as an SV2A tracer in pigs. The aim of the present work was to evaluate tracer kinetic models and simplified methods for quantification of synaptic density using <sup>11</sup>C-UCBA in patients with focal epilepsy and healthy control subjects.

***Biomarkers in relation to acute epileptic seizures – a case-control study***

Are inflammatory factors and specific brain proteins up- or down regulated in connection to epileptic seizures? If they are, can they be used as biomarkers for diagnosis and prognosis? We are collecting blood samples from patients undergoing long-term EEG investigation with

video monitoring for diagnostic or epilepsy surgery work up. The study is performed in collaboration with Lund's University.

### ***Neurodegeneration/ Movement disorders***

Members of the group: Håkan Askmark, Adjunct Professor, Ingela Nygren, MD PhD, Dag Nyholm, Associate Professor, Birgitta Jakobsson Larsson, PhD, Valter Nimelä, PhD student, Paul de Roos, MD, Johan Virhammar, MD, PhD, Marina Senek , PhD student.

In collaboration with the PET-centre the role of PET with the new tracer <sup>11</sup>C-PE2I is studied in patients with different types of parkinsonism with the aim to improve the diagnostics. In collaboration with the Human Proteome Resource group at the Rudbeck laboratory and the Department of Physical and Analytical chemistry, Uppsala University screening for potential protein biomarkers is performed in plasma, CSF and muscle from patients with ALS, Parkinson's disease and atypical parkinsonism. Studies of biomarkers in CSF are also ongoing in patients with Huntington's disease. The quality of life and its relation to the disease progression as well as coping strategies in patients with ALS are investigated in a prospective study (Dissertation Birgitta Jakobsson Larsson, June 2016). Together with a research group at the unit for physiotherapy we are studying pain in ALS-patients. In collaboration with IMBIM, BMC, Uppsala University there is an ongoing genetic study on motorneuron diseases in humans and dogs.

Improved treatments for Parkinson's disease have been developed within the group, in collaboration with pharmaceutical industry. The latest developments are a dose dispenser for microtablets of levodopa/carbidopa and an intestinal gel with levodopa/entacapone/carbidopa. These were presented at Marina Senek's half-time seminar in 2016. Pharmacokinetic-dynamic modelling is ongoing. A new drug designed to prevent gastroparesis in Parkinson's disease has been tested in an international multicentre trial. Another national multicentre trial will soon be initiated to compare the efficacy of intestinal levodopa/carbidopa gel infusion versus deep brain stimulation in a register study. Ongoing projects are dealing with objective, computerized symptom evaluations in movement disorders and a review of outcome measures has been performed in an international collaboration. A project was initiated in 2014, funded by VINNOVA, in collaboration with Acreo Swedish Research Institute, Sahlgrenska University Hospital, Dalarna University, and Department of Information technology at Uppsala University. During 2016, a 3-year project was granted funding from Swedish Knowledge Foundation, for remote monitoring of health in Parkinson's disease, in collaboration with Örebro University.

Patients with chronic inflammatory demyelinating polyneuropathy (CIDP) and myasthenia gravis resistant to conventional treatment have been treated with hematopoietic stem cell transplantation (HSCT).

The Department participates in a national, prospective, placebo-controlled study, Rinomax. The purpose is to evaluate the efficacy and safety of a single-dose of rituximab to newly diagnosed myasthenia gravis patients.

Clinical and pharmacological studies to optimize the use of botulinum toxin in hyperhidrosis and in cervical dystonia, with direct clinical applications for these groups of patients, have been presented in a doctoral thesis (Alma Rystedt, 2012) and the Department participates in a multicenter clinical trial, "CD2", on botulinum toxin in cervical dystonia.



Normal pressure hydrocephalus (NPH) is an increasingly recognized condition among the elderly population and is associated with symptoms of gait impairment, cognitive decline, and urinary incontinence. The symptoms can be reduced by implantation of a shunt system. Our clinical studies focus on preoperative prognostic investigations used to diagnose and select patients for shunt surgery. In collaboration with the Department of Radiology at Uppsala University Hospital, advanced MRI methods are evaluated in NPH patients to investigate changes in cerebral perfusion, white matter function and volumetry after shunt surgery. In collaboration with several Nordic hospitals, the role of the CSF infusion test to predict an optimal shunt setting is being studied.

### ***Neuroinflammation and Multiple sclerosis***

Group leader Anne-Marie Landtblom, Professor

Members of the group: Joachim Burman, MD, PhD, Inger Boström, RN, PhD, Jan Fagius, associate professor, Andreas Tolf, PhD student, Evangelos Katsarogiannis, MD

#### ***Therapy***

The Neuro-inflammation group is a collaborative effort by the Departments of Neuroscience and Immunology, Genetics and Pathology. One focus of the group lies on studying clinical effects and mode of action of a novel therapy: hematopoietic stem cell transplantation (HSCT), which was introduced to Scandinavia as a treatment for MS by our group. The goal of this therapy is to achieve long-term remission through short-lasting ablation of the immune system. This procedure is potentially curative and in a follow up of Swedish MS patients, disease free survival was 68% at five years. The mode of action includes probably several mechanisms. HSCT causes a profound renewal of the immune system and not just long-lasting immune suppression. At least part of the effect is likely related to removal of auto-reactive cells, but some of these cells probably escape the treatment and remain after HSCT. If so, such auto-reactive cells must be kept in control to maintain remission, which could be due to restoration of tolerance to self-antigens. Further studies are being made to explore the mode of action.

During the last years there is an off label pharmacotherapy with rituximab that has become widely spread in Sweden, and now reaches number one. This has attracted attention internationally and some conflicts among the experts. We perform studies on side effects in an Uppsala material.

#### ***Epidemiology, radiology***

Our studies of MS epidemiology firstly include the multinational effort EnVIMS (Environmental factors in MS) using questionnaires in order to evaluate the risk contribution of known and suggested risk factors for MS. Results have already been published regarding the effect of body size, smoking, EBV, infectious mononucleosis at different latitudes and sun exposure. Analyses of occupational exposures and hormonal factors are now being performed at the international level.

The sex ratio of MS is now changing in the Western world with an increasing female morbidity, which we study in collaboration with the Swedish Multiple Sclerosis register. The frequency of patients with MS lacking oligoclonal bands, an interesting subtype, is studied in the Swedish Multiple Sclerosis register, with start in Uppsala. The scrutinizing of the register so far revealed the difficulty of correct diagnosing, and brought to light several patients with genetic degenerative disease mimicking MS. These efforts will be concluded

An imaging project evaluates the role of synthetic MRI in MS, including also a project with studies of unspecific white substance lesions in demyelination and ischemia. Our previous

contributions in this field include studies on Gd contrast in syMR, the characteristics of normal and dirty appearing white matter (NAWM, DAWM) in MS, now being further developed.

### ***Identification of biomarkers for patients with brain tumors and tumor-related seizures***

Group leader: Anja Smits.

Group members/collaborators: Madelen Braun, MD; Tamador Elsir, PhD; Shala Ghaderi Bertsson, MD, PhD; Anne-Marie Landtblom, professor; Kenney Roodakker, PhD student; Elisabeth Sandberg, project student; Krisztina Szalischnyo, MD, PhD; Maria Zetterling, MD, PhD.

Gliomas are the most common type of primary brain tumors and consist of low- and high-grade gliomas. Low-grade gliomas in adults are called diffuse low-grade gliomas (DLGG). DLGG are tumors with malignancy grade II that constitute an “interface” between benign and malignant tumors. DLGG have an annual incidence of 1.5-1.8 per 100 000 inhabitants. In spite of a relatively long survival, patients with DLGG will eventually develop malignant gliomas with fatal outcome. Treatment consists of a combination of surgery, radiotherapy and chemotherapy, but the most effective therapeutic modality as well as the optimal timing of treatment is still a matter of debate. This dilemma is strongly related to the variety in natural course of disease and response to therapy between individual patients.

Overview of research activity:

1) Our clinical studies on DLGG focus on the application of advanced MRI and <sup>11</sup>C-methionine PET for pre-operative evaluation, detection of early tumor progression and to monitor response to treatment. We are also interested in evaluating these results with respect to cognitive functions and epileptic seizures. We have recently developed a new method to visualize the extension of DLGG beyond radiological borders in en-bloc resected DLGG (Zetterling, Roodakker et al, 2016). This method is now used for histological studies of tumor invasion and tumor vascularization in relation to radiological parameters, in collaboration with the Dept of Neuroradiology, professor Elna-Marie Larsson and the Tumor Vascular Biology group at the Rudbeck laboratories, associate professor Anna Dimberg.

2) Translational studies consist of affinity-based proteomics on tissue samples of high-grade glioma in correlation to response to therapy and survival, with focus on the role PROX1 (Roodakker, Elsir et al, 2016) and PROX1-related factors. PROX1 is a transcription factor involved in cell cycle regulation and progenitor cell differentiation in the CNS. PROX1 has also been ascribed an oncogenic role in several human cancers including brain tumors. Our aim is to identify predictive and prognostic biomarkers that can guide clinical decisions and, in a longer perspective, provide a ground for new biological-based treatments. The Cancer Genome Atlas (TCGA) is a powerful resource for creating and validating hypotheses and is used for extracting expression data of candidate genes of interest for glioma development and tumor progression over time.

3) Von Hippel-Lindau (VHL) disease is an autosomal dominant hereditary disorder characterized by retinal and CNS hemangioblastoma, pheochromocytoma, and clear cell renal cell carcinoma. The VHL gene which is located on chromosome 3p25 and encodes for a 213 amino acid tumor suppressor protein, which is a key player in the regulation of the hypoxia response pathway and vital to tumor survival in low oxygen conditions. VEGF and other

proteins in the HIF-signaling pathway are easily available and non-invasive candidates for plasma biomarkers of VHL disease. No published reports so far have shown a correlation of these proteins to prognosis or treatment outcomes in VHL disease. A series of consecutive blood samples of approximately 30 patients with VHL disease at Uppsala University Hospital, together with clinical and radiological data, have been collected since 2012. The plasma measurements of relevant biomarkers are performed in collaboration with the Rudbeck laboratory.

### ***Sleep medicine***

Group leader: Anne-Marie Landtblom

Group members: Makrina Daniilidou, PhD, Inger Boström, PhD, Amalia Feresiadou MD, Simon Lidén, MD, Valter Niemelä PhD student

This group has internal collaborations with Dept of pediatrics. Dept of lung medicine and allergy and preclinical Dept of Neuroscience. We study diagnoses like narcolepsy, the Kleine-Levin syndrome (KLS) and idiopathic hypersomnia from a clinical, epidemiological and imaging perspective. We also study biomarkers in blood and CSF. The activities are performed in collaboration with Linköping University, also with input from Prof M Partinen, Helsinki University and the group of E Mignot, Stanford. Now, a synchronizing activity is planned regarding the national efforts (Stockholm, Gothenburg, Halland, Östersund), including the national register of narcolepsy, NARK REG, and focusing prevalence, pharmacotherapy and QoL. Collaboration with Dept of Economy in Gothenburg concerning the use of pharmacotherapy in narcolepsy, prof K Bolin. Our epidemiological studies so far concerned the occurrence of narcolepsy after Pandemrix vaccination and confirm an increased prevalence and further studies are ongoing. Imaging studies with fMRI show interesting differences in KLS, and narcolepsy. The differential diagnosing of teenagers with sleep disorders has been put in focus in speeches and articles. The sleep disturbance in Huntington's disease is also of interest for the future efforts of our group.

### **Publications 2014-2016**

Delgado AF, Nilsson M, Latini F, Mårtensson J, Zetterling M, Berntsson SG, Alafuzoff I, Lätt J, Larsson EM (2016) Preoperative Quantitative MR Tractography Compared with Visual Tract Evaluation in Patients with Neuropathologically Confirmed Gliomas Grades II and III: A Prospective Cohort Study. *Radiol Res Pract.* 2016;2016:7671854. doi: 10.1155/2016/7671854.

Berntsson SG, Katsarogiannis E, Lourenço F, Moraes-Fontes MF (2016) Progressive Multifocal Leukoencephalopathy and Systemic Lupus Erythematosus: Focus on Etiology. *Case Rep Neurol.* 2016 Mar 16;8(1):59-65. doi: 10.1159/000444874

Zetterling M, Roodakker K, Berntsson SG, Edqvist PH, Latini F, Landtblom AM, Pontén F, Alafuzoff I, Larsson EM, Smits A (2016) Extension of diffuse low-grade gliomas beyond radiological borders as shown by co-registration of histopathology with MRI. *J Neurosurg* 26:1-12.

Reijneveld JC, Taphoorn MJB, Coens C, van den Bent MJ, Mason WP, Hoang-Xuan, Brandes AA, Kantor G, Ben Hassel M, Ryan G, Thiessen B, Wick W, Klein M, Verger E,

Braun C, Hau P, Lamoury G, Smits A, Golfinopoulos V, Gorlia T, Bottomly A, Stupp R, Baumert BG (2016) Health-related quality of life in high-risk low-grade glioma; results of a randomized controlled trial. *Lancet Oncology* 17(11):1533-1542.

Kundu S, Xiong A, Spyrou A, Wicher G, Marinescu VD, Edqvist PD, Zhang L, Essand M, Dimberg A, Smits A, Ilan N, Vlodavsky I, Li JP, Forsberg-Nilsson K (2016) Heparanase promotes glioma progression and is inversely correlated with patient survival. *Mol Cancer Res* 14(12):1243-1253.

K Szalisznoy, D Silverstein, M Teichmann, H Duffau, A Smits (2016) Cortico-striatal language pathways dynamically adjust for syntactic complexity: a computational study . *Brain and Language* 25;164:53-62.

K Roodakker, T Elsir, PH Edqvist, D Hägerstrand, J Carlson, M Lysiak, R Henriksson, F Pontén, J Rosell, P Söderkvist, R Stupp, E Chugunova, M Nistér, A Malmström, A Smits (2016) PROX1 is a novel pathway-specific biomarker for high-grade astrocytomas; Results from independent glioblastoma cohorts stratified by age and IDH mutation status. *Oncotarget* doi: 10.18632/oncotarget.11957.

Sauro KM, Wiebe S, Dunkley C, Janszky J, Kumlien E, Moshé S, Nobukazu N Pedley TA, Perucca E, Senties H, Thomas S, Wang Y, Wilmschurst J, Jetté N. The current state of epilepsy guidelines: A systematic review. 2016 *Epilepsia* 57:13-23

Juran S, Lundström J, Geigant M, Åhs F, Kumlien E, Fredrikson M, Olsson M. Unilateral resection of the anterior medial temporal lobe impairs odor identification and valence perception. 2016 *Frontiers in Psychology*, Jan 8:6

Zelano J, Redfors P, Åsberg S, Kumlien E. Association between poststroke epilepsy and death: a nationwide cohort study. 2016 *Eur J of Stroke*, in press

Knight A, Pauksen K, Nordmark G, Kumlien E. Fatal outcome of tick borne encephalitis in two patients with rheumatic disease treated with rituximad. In press, *Rheumatology*

Drissi N, Szakacs A, Witt St, Wretman A, Ulander M, Ståhlbrandt H, Darin N, Hallböök T, Landtblom AM, Engström M. [Altered Brain Microstate Dynamics in Adolescents with Narcolepsy](#). *Front Hum Neurosci* 2016;10:369

Engström M, Landtblom AM, Karlsson T. New hypothesis on pontine-frontal eye field in Kleine Levin syndrome. *J Sleep res* 2016;25(6):716-19

Zetterling M, Roodakker K, Berntsson S, Edqvist PH, Latini F, Landtblom AM, Pontén F, Alafuzoff I, Larsson EM, Smits A. Extension of diffuse low-grade gliomas beyond radiological borders as shown by the coregistration of histopathological and magnetic resonance imaging data. *J Neurosurg* 2016;125(5):1155-66

Bjørnevik K, Riise T, Bostrom I, Casetta I, Cortese M, Granieri E, Holmøy T, Kampman MT, Landtblom AM, Magalhaes S, Pugliatti M, Wolfson C, Myhr KM. Negative interaction between smoking and EBV in the risk of MS: The EnviMS study. *Mult Scler*. 2016 Sep 23. pii: 1352458516671028. [Epub ahead of print]

Vågberg M, Axelsson M, Birgander R, Burman J, Cananau C, Forslin Y, Granberg T, Gunnarsson M, von Heijne A, Jönsson L, Karrenbauer VD, Larsson EM, Lindqvist T, Lycke J, Lönn L, Montesidou E, Müller S, Nilsson P, Piehl F, Svenningsson A, Vrethem M, Wikström J. Guidelines for the use of magnetic resonance imaging in diagnosing and monitoring the treatment of multiple sclerosis: recommendations of the Swedish Multiple Sclerosis Association and the Swedish Neuroradiological Society. *Acta Neurol Scand*. 2016 Aug 24.

Burman J, Raininko R, Blennow K, Zetterberg H, Axelsson M, Malmeström C. YKL-40 is a CSF biomarker of intrathecal inflammation in secondary progressive multiple sclerosis. *Journal of Neuroimmunology*, 2016 Mar;292:52-57.

Burman J, Svenningsson A. Cerebrospinal fluid concentration of Galectin-9 is increased in secondary progressive multiple sclerosis. *Journal of Neuroimmunology*, 2016 Mar;292:40-44.

van Laar T, Nyholm D, Nyman R. Transcutaneous port for levodopa/carbidopa intestinal gel administration in Parkinson's disease. *Acta Neurol Scand*. 2016 Mar;133(3):208-15

Pålhagen SE, Sydow O, Johansson A, Nyholm D, Holmberg B, Widner H, Dizdar N, Linder J, Hauge T, Jansson R, Bergmann L, Kjellander S, Marshall TS. Levodopa-carbidopa intestinal gel (LCIG) treatment in routine care of patients with advanced Parkinson's disease: An open-label prospective observational study of effectiveness, tolerability and healthcare costs. *Parkinsonism Relat Disord*. 2016 Aug;29:17-23

Senek M, Nielsen E, Nyholm D. Levodopa-Entacapone-Carbidopa Intestinal Gel in Parkinson Disease – a randomized, crossover study. *Mov Disord* 2016; in press.

Virhammar J, Nyholm D. Levodopa-carbidopa enteral suspension in advanced Parkinson's disease: clinical evidence and experience. *Ther Adv Neurol Disord* 2016; in press.

Senek M, Aquilonius SM, Askmark H, Bergquist F, Constantinescu R, Ericsson A, Lycke S, Medvedev A, Memedi M, Ohlsson F, Spira J, Westin J, Nyholm D. Levodopa/carbidopa microtablets in Parkinson's disease: A study of pharmacokinetics and blinded motor assessment. *Eur J Clin Pharmacol*. 2016; in press.

Halawa I, Zelano J, Kumlien E. Hypoglycemia and risk of seizures: A retrospective cross-sectional study. *Seizure* 2015, 25;147-149

Ferlisi M, Hocker S, Grade M, Trinka E, Shorvon S; International Steering Committee of the StEp Audit. [Preliminary results of the global audit of treatment of refractory status epilepticus](#). *Epilepsy Behav*. 2015, Aug;49:318-24

Zelano J, Gertz Lundberg, Baars, Hedegård E and Kumlien E. Clinical course of poststroke epilepsy: a retrospective nested case-control study. 2015 *Brain and Behaviour* Sept;5(9)

Ziemssen T, Bajenaru OA, Carrá A, de Klippel N, Correia de Sá J, Edland A, Frederiksen JL, Heinzlef O, Karageorgiou KE, Lander Delgado RH, Landtblom AM, Macías Islas MA, Tubridy N, Gilgun-Sherki Y. [A 2-year observational study of patients with relapsing-remitting multiple sclerosis converting to glatiramer acetate from other disease-modifying therapies: the COPTIMIZE trial](#). *J Neurol*. 2015 Jan;262(1):248. doi: 10.1007/s00415-014-7565-7.

Wesnes K, Riise T, Casetta I, Drulovic J, Granieri E, Holmøy T, Kampman MT, Landtblom AM, Lauer K, Lossius A, Magalhaes S, Pekmezovic T, Bjørnevik K, Wolfson C, Pugliatti M, Myhr KM. [Body size and the risk of multiple sclerosis in Norway and Italy: the EnvIMS study](#). *Mult Scler*. 2015 Apr;21(4):388-95. doi: 10.1177/1352458514546785.

Landtblom AM, Engström M. Brain Circuitries In Sleep Disorders. *Front Neurol* 2015 Apr 14;6:66

Gauffin H, Flensner G, Landtblom AM. [Being parents with epilepsy: thoughts on its consequences and difficulties affecting their children](#). *Neuropsychiatr Dis Treat*. 2015 May 27;11:1291-8. doi: 10.2147/NDT.S74222.

Bolin K, Berggren F, Landtblom AM. [Prevalence and cost of epilepsy in Sweden--a register-based approach](#). *Acta Neurol Scand*. 2015 Jan;131(1):37-44. doi: 10.1111/ane.12297.

Engström M, Karlsson T, Landtblom AM, Craig Ad. Evidence Of Conjoint Activation Of The Anterior Insular And Cingulate Cortices During Effortful Tasks. *Front Hum Neurosci* 2015;8:1071

Boström I, Landtblom AM. Does the changing sex ratio of multiple Sclerosis give opportunities for intervention? *Acta Neurol Scand* 2015;132:40-3

Landtblom AM, Engström. Brain circuitries in sleep disorders. *Front neurol* 2015;6:66

Magalhaes S, Pugliatti M, Casetta I, Drulovic J, Granieri E, Holmøy T, Kampman MT, Landtblom AM, Lauer K, Myhr KM, Parpinel M, Pekmezovic T, Riise T, Wolfson D, Zhu B, Wolfson C. [The EnvIMS Study: Design and Methodology of an International Case-Control Study of Environmental Risk Factors in Multiple Sclerosis](#). *Neuroepidemiology*.

2015;44(3):173-81. doi:

Rystedt A, Zetterberg L, Burman J, Nyholm D, Johansson A. A comparison of Botox® 100 U/ml and Dysport® 100 U/ml using dose conversion ratio 1:3 and 1:1.7 in the treatment of cervical dystonia - a double-blind, randomized, cross-over trial. *Clinical Neuropharmacology*. 2015 Sep-Oct;38(5):170-6.

Snarski E, Snowden J, Oliveira MC, Simoes B, Badoglio M, Carlson K, Burman J, Moore J, Rovira M, Clark R, Saiz A, Khelifa SH, Tan J, Crescimanno A, Musso M, Martin T, Farge D. Onset and outcome of pregnancy after autologous haematopoietic SCT (AHSCT) for autoimmune diseases: a retrospective study of the EBMT autoimmune diseases working party (ADWP). *Bone Marrow Transplant*. 2015 Feb;50(2):216-20.

Greco R, Bondanza A, Oliveira MC, Badoglio M, Burman J, Piehl F, Hagglund H, Krasulova E, Simões BP, Carlson K, Pohlreich D, Labopin M, Saccardi R, Comi G, Mancardi GL, Bacigalupo A, Ciceri F, Farge D. Autologous hematopoietic stem cell transplantation in neuromyelitis optica: A registry study of the EBMT Autoimmune Diseases Working Party. *Mult Scler*. 2015 Feb;21(2):189-97.

Burt RK, Balabanov R, Han X, Sharrack B, Morgan A, Quigley K, Yaung K, Helenowski IB, Jovanovic B, Spahovic D, Indira Arnautovic I, Lee D, Benefield B, Futterer S, Oliveira C, Burman J. Association of non-myeloablative hematopoietic stem cell transplantation with

survival and disease activity in patients with relapsing remitting multiple sclerosis. *JAMA*. 2015 Jan 20;313(3):275-84.

Sooman L, Freyhult E, Jaiswal A, Navani S, Edqvist PH, Pontén F, Tchougounova E, Smits A, Elsir T, Gullbo J, Lennartsson J, Bergqvist M, Ekman S (2015) FGF2 as a potential prognostic biomarker for proneural glioma patients. *Acta Oncol* 54(3):385-94.

Libard S, Popova SN, Amini RM, Kärjä V, Pietiläinen T, Hämäläinen KM, Sundström C, Hesselager G, Bergqvist M, Ekman S, Zetterling M, Smits A, Nilsson P, Pfeifer S, de Ståhl TD, Enblad G, Ponten F, Alafuzoff I (2014) Human cytomegalovirus tegument protein pp65 is detected in all intra- and extra-axial brain tumours independent of the tumour type or grade. *PLoS One* 9(9):e108861.

Babateen O, Jin Z, Bhandage A, Korol SV, Westermark B, Forsberg Nilsson K, Uhrbom L, Smits A, Birnir B. Etomidate, propofol and diazepam potentiate GABA-evoked GABAA currents in a cell line derived from human glioblastoma. *Eur J Pharmacol*. 2015 Feb 5;748:101-7.

Smits A, Zetterling M, Lundin M, Melin B, Fahlström M, Grabowska A, Larsson EM, Berntsson SG (2015) Neurological Impairment Linked with Cortico-Subcortical Infiltration of Diffuse Low-Grade Gliomas at Initial Diagnosis Supports Early Brain Plasticity. *Front Neurol*. 10;6:137.

Roy A, Coum A, Marinescu VD, Pölajeva J, Smits A, Nelander S, Uhrbom L, Westermark B, Forsberg-Nilsson K, Pontén F, Tchougounova E (2015) Glioma-derived plasminogen activator inhibitor-1 (PAI-1) regulates the recruitment of LRP1 positive mast cells. *Oncotarget* 15;6(27):23647-61.

Langenkamp E, Zhang L, Lugano R, Huang H, Elhassan T Elsir, Georganaki M, Bazzar W, Lööf J, Trendelenburg G, Essand M, Pontén F, Smits A, Dimberg A (2015) Elevated Expression of the C-Type Lectin CD93 in the Glioblastoma Vasculature Regulates Cytoskeletal Rearrangements That Enhance Vessel Function and Reduce Host Survival. *Cancer Research* 1;75(21):4504-16.

Zhang L, Kundu S, Feenstra T, Li X, Jin C, Laaniste L, El Hassan TE, Ohlin KE, Yu D, Olofsson T, Olsson AK, Pontén F, Magnusson PU, Nilsson KF, Essand M, Smits A, Dieterich LC, Dimberg A (2015) Pleiotrophin promotes vascular abnormalization in gliomas and correlates with poor survival in patients with astrocytomas. *Science Signaling* 8;8(406):ra125.

Landtblom AM, Engström M. Brain circuitries in sleep disorders. *Front Neurol* 2015 Apr 14;6:66

Gauffin H, Landtblom AM. Epilepsy and violence: case series concerning physical trauma in children of persons with epilepsy. *Neuropsych dis treat* 2014;10:2183-9

Elf, K., Askmark, H., Nygren, I., Punga, A. Vitamin D deficiency in patients with primary immune-mediated peripheral neuropathies. *Journal of the Neurological Sciences*, 2014;345:184-188

Engström M, Karlsson T, Landtblom AM, Craig AD. Evidence of conjoint activation of the anterior insular and cingulate cortices during effortful tasks. *Front Hum Neurosci* 2015;8:1071 doi:10.3389/fnhum.2014.01071

Engström M, Warntjes M, Tisell A, Landtblom AM, Lundberg P. Multiparametric representation of voxel based quantitative magnetic resonance imaging. *PLoS One* 2014 Nov 13;9:e111688

Sooman L, Freyhult E, Jaiswal A, Navani S, Edqvist PH, Pontén F, Tchougounova E, Smits A, Elsir T, Gullbo J, Lennartsson J, Bergqvist M, Ekman S (2015) FGF2 as a potential prognostic biomarker for proneural glioma patients. *Acta Oncol* 54(3):385-94.

Zelano J, Möller F, Dobesberger J, Trinka E, Kumlien E. [Infections in status epilepticus: a retrospective 5-year cohort study](#). *Seizure*, 2014, Sep;23(8):603-6.

Halawa I, Zelano J, Kumlien E. Hypoglycemia and risk of seizures: A retrospective cross-sectional study. *Seizure* 2015, 25;147-149.

Ferlisi M, Hocker S, Grade M, Trinka E, Shorvon S; International Steering Committee of the StEp Audit. [Preliminary results of the global audit of treatment of refractory status epilepticus](#). 2015 *Epilepsy Behav* Aug;49:318-24.

Zelano J, Gertz Lundberg, Baars, Hedegård E and Kumlien E. Clinical course of poststroke epilepsy: a retrospective nested case–control study. 2015 *Brain and Behav* Sept;5(9).

Jakobsson Larsson B, Fröjd C, Nordin K, Nygren I. Relatives to patients with amyotrophic lateral sclerosis- their experience of care and support. *Palliat Support Care*. 2015;16:1-8

Jansson D, Medvedev A, Axelson H, Nyholm D. Stochastic anomaly detection in eye-tracking data for quantification of motor symptoms in Parkinson's disease. *Adv Exp Med Biol*. 2015;823:63-82.

Appel L, Jonasson M, Danfors T, Nyholm D, Askmark H, Lubberink M, Sörensen J. Use of 11C-PE2I PET in Differential Diagnosis of Parkinsonian Disorders. *J Nucl Med*. 2015 Feb;56(2):234-42.

Memedi M, Nyholm D, Johansson A, Palhagen S, Willows T, Widner H, Linder J, Westin J. Validity and responsiveness of at-home touch-screen assessments in advanced Parkinson's disease. *IEEE J Biomed Health Inform*. 2015 Nov;19(6):1829-34

Rystedt A, Zetterberg L, Burman J, Nyholm D, Johansson A. A Comparison of Botox 100 U/mL and Dysport 100 U/mL Using Dose Conversion Ratio 1: 3 and 1: 1.7 in the Treatment of Cervical Dystonia: A Double-Blind, Randomized, Crossover Trial. *Clin Neuropharmacol*. 2015 Sep-Oct;38(5):170-6.

Memedi M, Sadikov A, Groznik V, Žabkar J, Možina M, Bergquist F, Johansson A, Haubenberger D, Nyholm D. Automatic Spiral Analysis for Objective Assessment of Motor Symptoms in Parkinson's Disease. *Sensors (Basel)*. 2015 Sep 17;15(9):23727-44.

Jakobsson Larsson, B., Nordin, K., Nygren, I. Coping with amyotrophic lateral sclerosis: from diagnosis and during disease progression. *J of Neurol Sciences* 2016 (361) 235-42.



Virhammar J, Warntjes M, Laurell K, Larsson EM. "Quantitative MRI for Rapid and User-independent Monitoring of Intracranial CSF Volume in Hydrocephalus". *AJRN Am J Neuroradiol*. 2015 Dec 24. [Epub ahead of print]

Babateen O, Jin Z, Bhandage A, Korol SV, Westermark B, Forsberg Nilsson K, Uhrbom L, Smits A, Birnir B. Etomidate, propofol and diazepam potentiate GABA-evoked GABAA currents in a cell line derived from human glioblastoma. *Eur J Pharmacol*. 2015 Feb 5;748:101-7.

Smits A, Zetterling M, Lundin M, Melin B, Fahlström M, Grabowska A, Larsson EM, Berntsson SG (2015) Neurological Impairment Linked with Cortico-Subcortical Infiltration of Diffuse Low-Grade Gliomas at Initial Diagnosis Supports Early Brain Plasticity. *Front Neurol*. 10;6:137.

Roy A, Coum A, Marinescu VD, Pölajeva J, Smits A, Nelander S, Uhrbom L, Westermark B, Forsberg-Nilsson K, Pontén F, Tchougounova E (2015) Glioma-derived plasminogen activator inhibitor-1 (PAI-1) regulates the recruitment of LRP1 positive mast cells. *Oncotarget* 15;6(27):23647-61.

Rystedt A, Zetterberg L, Burman J, Nyholm D, Johansson A. A comparison of Botox® 100 U/ml and Dysport® 100 U/ml using dose conversion ratio 1:3 and 1:1.7 in the treatment of cervical dystonia - a double-blind, randomized, cross-over trial. *Clinical Neuropharmacology*. 2015 Sep-Oct;38(5):170-6.

Snarski E, Snowden J, Oliveira MC, Simoes B, Badoglio M, Carlson K, Burman J, Moore J, Rovira M, Clark R, Saiz A, Khelifa SH, Tan J, Crescimanno A, Musso M, Martin T, Farge D. Onset and outcome of pregnancy after autologous haematopoietic SCT (AHSCT) for autoimmune diseases: a retrospective study of the EBMT autoimmune diseases working party (ADWP). *Bone Marrow Transplant*. 2015 Feb;50(2):216-20.

Greco R, Bondanza A, Oliveira MC, Badoglio M, Burman J, Piehl F, Hagglund H, Krasulova E, Simões BP, Carlson K, Pohlreich D, Labopin M, Saccardi R, Comi G, Mancardi GL, Bacigalupo A, Ciceri F, Farge D. Autologous hematopoietic stem cell transplantation in neuromyelitis optica: A registry study of the EBMT Autoimmune Diseases Working Party. *Mult Scler*. 2015 Feb;21(2):189-97.

Burt RK, Balabanov R, Han X, Sharrack B, Morgan A, Quigley K, Yaung K, Helenowski IB, Jovanovic B, Spahovic D, Indira Arnautovic I, Lee D, Benefield B, Futterer S, Oliveira C, Burman J. Association of non-myeloablative hematopoietic stem cell transplantation with survival and disease activity in patients with relapsing remitting multiple sclerosis. *JAMA*. 2015 Jan 20;313(3):275-84.

Langenkamp E, Zhang L, Lugano R, Huang H, Elhassan TE, Georganaki M, Bazzar W, Lööf J, Trendelenburg G, Essand M, Pontén F, Smits A, Dimberg A (2015) Elevated Expression of the C-Type Lectin CD93 in the Glioblastoma Vasculature Regulates Cytoskeletal Rearrangements That Enhance Vessel Function and Reduce Host Survival. *Cancer Res* 1;75(21):4504-16.

Zhang L, Kundu S, Feenstra T, Li X, Jin C, Laaniste L, El Hassan TE, Ohlin KE, Yu D, Olofsson T, Olsson AK, Pontén F, Magnusson PU, Nilsson KF, Essand M, Smits A, Dieterich LC, Dimberg A (2015) Pleiotrophin promotes vascular abnormalization in gliomas and correlates with poor survival in patients with astrocytomas. *Science Signaling* 8;8(406):ra125.

Magalhaes S, Pugliatti M, Casetta I, Drulovic J, Granieri E, Holmoy T, Kampman M, Landtblom AM, Lauer K, Myhr KM, Parpinel M, Pekzemovic T, Riise T, Wolfson D, Zhu B, Wolfson C. The EnviMS study: Design and Methodology of an international case-control study of environmental risk factors in Multiple sclerosis. *Neuroepidemiology* 2015;44:173-81

Boström I, Landtblom AM. Does the changing sex ratio of multiple sclerosis give opportunities for intervention? *Acta Neurol Scand Suppl* 2015;132:42-5

Gauffin H, Flensner G, Landtblom AM. Being parents with epilepsy: thoughts on its consequences and difficulties affecting their children. *Neuropsych Dis Treat* 2015;11:1291-8

Bolin K, Berggren F, Landtblom AM. Prevalence and cost of epilepsy in Sweden – a register based approach. *Acta Neurol Scand* 2015;1:37-44

Wesnes K, Riise T, Casetta I, Drulovic J, Granieri E, Holmoy T, Kampman M, Landtblom AM, Lauer K, Lossius A, Magalhaes S, Pekzemovic T, Bjørnevik, Wolfson C. Body size and the risk of multiple sclerosis in Norway and Italy; the EnviMS study. *Multiple Sclerosis Jnl* 2015;21:388-95

Åhs F, Engman J, Persson J, Larsson EM, Wikström J, Kumlien E, Fredrikson M. Medial temporal lobe resections eliminate modulation of superior temporal sulcus activity evoked by facial stimuli. *Neuropsychologia*. 2014 Aug; 61:291-8

Zelano J, Möller F, Dobesberger J, Trinka E, Kumlien E. [Infections in status epilepticus: a retrospective 5-year cohort study](#). *Seizure*, 2014, Sep;23(8):603-6

Boström I, Stawiarz L, Landtblom AM. Age-specific sex ratio of multiple sclerosis in the national Swedish MS register (SMSreg). *Mult scler* 2014;20(4): 513-4

Lossius A, Riise T, Pugliatti M, Bjørnevik K, Casetta I, Drulovic , Granieri E, Kampman M, Landtblom AM, Lauer K, Magalhaes S, Myhr KM, Pekmezovic T, Wesnes K, Wolfson C, Holmøy T. Season of infectious mononucleosis and risk of multiple sclerosis at different latitudes; the Envims study. *Mult scler* 2014;20(6) 669-74

Bjørnevik K, Riise T, Casetta I, Drulovic J, Granieri E, Holmøy T, Kampman M, Landtblom AM, Lauer K, Lossius A, Magalhaes S, Myhr KM, Pekmezovic T, Wesnes K, Wolfson C, Pugliatti M. Sun exposure and multiple sclerosis risk in Norway and Italy; The Envims study. *Mult Scler* 2014;20(8):1042-49.

Engström M, Karlsson T, Landtblom AM. Thalamic activation in the Kleine Levin syndrome. *Sleep* 2014;37(2):379-86.

Sarkanen T, Niemelä V, Landtblom AM, Partinen M. Psychosis in patients with narcolepsy as an adverse effect of sodium oxybate. *Front Neurol* 2014 Aug 20;5:136.

West J, Aalto A, Tisell A, Dahlqvist Leinhard O, Landtblom AM, Smedby Ö, Lundberg P. Normal and Diffusely Abnormal White Matter in Patients with Multiple Sclerosis, Assessed with Quantitative MR. *PLOS one* 2014 Apr 18;9(4):e95161.

Warntjes M, Tisell A, Landtblom AM, Lundberg P. Effects Of Gadolinium Contrast Administration On Automatic Brain Tissue Segmentation Of Multiple Sclerosis Patients. *Am J Neurorad* 2014;35(7):1330-6

Westerlind H, Boström I, Stawiarz L, Landtblom AM, Almqvist C, Hillert J. New Data Identify An Increasing Sex Ratio Of Multiple Sclerosis In Sweden. *Mult Scler J*. 2014 20;1578-83

Engström M, Karlsson T, Landtblom AM. Reduced thalamic and pontine connectivity in Kleine-Levin syndrome during sleep episode. *Front Neurol* 2014 Apr 2;5:42.

Landtblom AM, Engström M. The Sleepy Teenager – Diagnostic Challenges. *Front Neurol* 2014 Aug 4;5:140.

Engström M, Hallböök T, Szakacs A, Karlsson T, Landtblom AM. Functional Magnetic Resonance Imaging In Narcolepsy And The Kleine-Levin Syndrome. *Front Neurol* 2014 June 25;5:105.

Engström M, Warntjes M, Tisell A, Landtblom AM, Lundberg P. Multiparametric Representation Of Voxel Based Quantitative Magnetic Resonance Imaging. *Plos One* 2014 Nov 13;9:E111688.

Vigren P, Engström M, Landtblom AM. SPECT In The Kleine-Levin Syndrome. *Front Neurol* 2014 Sep 23;5:178

Hallböök,T, Malmgren K, Feltelius N, Szakasc A, Landtblom AM. Narkolepsi - En sällsynt sjukdom med ökande betydelse. *Läkartidningen* 2014;111:1770-3

Landtblom AM. Neuroimaging In Sleep Disorders. *Front Neurol* 2014 Sep 23

Burman J, Svensson E, Fransson M, Loskog ASI, Zetterberg H, Raininko R, Svenningsson A, Fagius J, Mangsbo, SM. The cerebrospinal fluid cytokine signature of multiple sclerosis: a homogenous response that does not conform to the Th1/Th2/Th17 convention. *J Neuroimmunol*. 2014 Oct 18;277(1-2):153-159.

Burman J, Fagius J. Blodstamcellstransplantation effektiv behandling för MS. *Läkartidningen* 2014:111.

Burman J, Iacobaeus E, Svenningsson A, Lycke J, Gunnarsson M, Nilsson P, Vrethem M, Fredrikson S, Martin C, Sandstedt A, Ugglä B, Lenhoff S, Johansson JE, Isaksson C, Hägglund H, Carlson K, Fagius J. Autologous hematopoietic stem cell transplantation for aggressive multiple sclerosis: the Swedish experience. *J Neurol Neurosurg Psychiatry*. 2014 Oct;85(10):1116-21.

Fransson M, Piras E, Hao W, Burman J, Rasmusson Duprez I, Harris RA, LeBlanc K, Brittebo E, and Loskog ASI. Human mesenchymal stromal cells expressing a CNS-targeting receptor can be administrated intranasally and cure experimental autoimmune encephalomyelitis. *Immunology*. 2014 Jul;142(3):431-41.

Burman J, Zetterberg H, Fransson M, Loskog ASI, Raininko R, Fagius J. Assessing tissue damage in multiple sclerosis: a biomarker approach. *Acta Neurol Scand.* 2014 Aug;130(2):81-9.

Fagius J, Burman J. Normal outcome of pregnancy with ongoing treatment with natalizumab. *Acta Neurologica Scandinavica. Acta Neurol Scand.* 2014 Jun;129(6):e27-9.

Boström I, Stawiarz L, Landtblom AM. Age-specific sex ratio of multiple sclerosis in the national Swedish MS register (SMSreg). *Mult scler* 2014;20(4): 513-4

Lossius A, Riise T, Pugliatti M, Bjørnevik K, Casetta I, Drulovic , Granieri E, Kampman M, Landtblom AM, Lauer K, Magalhaes S, Myhr KM, Pekmezovic T, Wesnes K, Wolfson C, Holmøy T. Season of infectious mononucleosis and risk of multiple sclerosis at different latitudes; the Envims study. *Mult scler* 2014;20(6) 669-74

Bjørnevik K, Riise T, Casetta I, Drulovic J, Granieri E, Holmøy T, Kampman M, Landtblom AM, Lauer K, Lossius A, Magalhaes S, Myhr KM, Pekmezovic T, Wesnes K, Wolfson C, Pugliatti M. Sun exposure and multiple sclerosis risk in Norway and Italy; The Envims study. *Mult Scler* 2014;20(8):1042-49.

Engström M, Karlsson T, Landtblom AM. Thalamic activation in the Kleine Levin syndrome. *Sleep* 2014;37(2):379-86.

Engström M, Flensner G, Landtblom AM, Ek AC, Karlsson T. Thalamo-striato-cortical determinants to fatigue in multiple sclerosis. *Brain & Behaviour* 2013 Nov;3(6):715-28

Burman J, Fransson M, Tötterman TH, Fagius J, Mangsbo SM, Loskog ASI. T cell responses after hematopoietic stem cell transplantation for aggressive relapsing-remitting multiple sclerosis. *Immunology.* 2013 Oct;140(2):211-9.

Elsir T, Edqvist PH, Carlson J, Ribom D, Bergqvist M, Ekman S, Popova S, Alafuzoff I, Ponten F, Nister M, Smits A (2014) A study of embryonic stem cell-related proteins in human astrocytomas: identification of Nanog as a predictor of survival. *International Journal of Cancer* 134, 1123-1141

Pöläjeva J, Bergström T, Edqvist PH, Lundequist A, Nilsson G, Smits A, Bergqvist M, Pontén F, Westermarck B, Pejler G, Forsberg Nilsson K, Tchougounova E (2014) Glioma-derived macrophage migration inhibitory factor (MIF) promotes mast cell recruitment in a STAT5-dependent manner. *Molecular Oncology* 8, 50-58

Popova SN, Bergqvist M, Dimberg A, Edqvist PH, Ekman S, Hesselager G, Ponten F, Smits A, Sooman L, Alafuzoff I (2014) Subtyping of gliomas of various WHO grades applying immunohistochemistry. *Histopathology* 64, 365-79

Falk A, Fahlström M, Rostrup E, Berntsson S, Zetterling M, Morell A, Larsson HB, Smits A, Larsson EM. Discrimination between glioma grades II and III in suspected low-grade gliomas using dynamic contrast-enhanced and dynamic susceptibility contrast perfusion MR imaging: a histogram analysis approach (2014) *Neuroradiology* 56(12):1031-8.

Libard S, Popova SN, Amini RM, Kärjä V, Pietiläinen T, Hämäläinen KM, Sundström C, Hesselager G, Bergqvist M, Ekman S, Zetterling M, Smits A, Nilsson P, Pfeifer S, de Ståhl

TD, Enblad G, Ponten F, Alafuzoff I (2014) Human cytomegalovirus tegument protein pp65 is detected in all intra- and extra-axial brain tumours independent of the tumour type or grade. *PLoS One* 9(9):e108861.

Åhs F, Engman J, Persson J, Larsson EM, Wikström J, Kumlien E, Fredrikson M. Medial temporal lobe resections eliminate modulation of superior temporal sulcus activity evoked by facial stimuli. *Neuropsychologia*. 2014 Aug; 61:291-8.

Feresiadou A, Eriksson U, Larsen HC, Raininko R, Nygren I, Melberg A. Recurrence of Susac syndrome following remission of 23 years. *Case Rep Neurol* 2014 May 21;6(2):171-5. doi: 10.1159/000362868.

Press R, Askmark H, Svenningsson A, Anderson O, Axelson HW, Strömberg U, Wahlin A, Isaksson C, Johansson JE, Hägglund H. Autologous haematopoietic stem cell transplantation: a viable treatment option for CIDP. *J Neurol Neurosurg Psychiatry*. 2014 Jun;85(6):618-24.

Virhammar J, Laurell K, Cesarini KG, Larsson EM. The callosal angle measured on MRI as a predictor of outcome in idiopathic normal-pressure hydrocephalus. *J Neurosurg* 2014; 120(1): 178-84.

Virhammar J, Laurell K, Ahlgren A, Cesarini KG, Larsson EM. Idiopathic normal pressure hydrocephalus: cerebral perfusion measured with pCASL before and repeatedly after CSF removal. *J Cereb Blood Flow Metab* 2014; 34(11): 1771-8.

Virhammar J, Laurell K, Cesarini KG, Larsson EM. Preoperative prognostic value of MRI findings in 108 patients with idiopathic normal pressure hydrocephalus. *AJNR Am J Neuroradiol* 2014; 35(12): 2311-8.

Nyholm D; Stepien V. Levodopa fractionation in Parkinson's disease. *J Parkinson's Dis*. 2014;4(1):89-96.

Jakobsson Larsson B, Nordin K, Askmark H, Nygren I. Coping strategies among newly diagnosed ALS patients. *J Clin Nursing* 2014 Nov;23 (21-22): 3148-55.

West J, Aalto A, Tisell A, Dahlqvist Leinhard O, Landtblom AM, Smedby Ö, Lundberg P. Normal and Diffusely Abnormal White Matter in Patients with Multiple Sclerosis, Assessed with Quantitative MR. *PLOS one* 2014 Apr 18;9(4):e95161. Doi:10.1371/journal.pone.0095161. eCollection 2014.

Warntjes M, Tisell A, Landtblom AM, Lundberg P. Effects of gadolinium contrast administration on automatic brain tissue segmentation of multiple sclerosis patients. *Am J Neurorad* 2014;35(7):1330-6

Westerlind H, Boström I, Stawiarz L, Landtblom AM, Almqvist C, Hillert J. New data identify an increasing sex ratio of multiple sclerosis in Sweden. *In press Mult Scler J*. 2014 20;1578-83

Engström M, Karlsson T, Landtblom AM. Reduced thalamic and pontine connectivity in Kleine-Levin syndrome during sleep episode. *Front Neurol* 2014 Apr 2;5:42. doi: 10.3389/fneur.2014.00042. eCollection 2014

Bolin K, Berggren F, Landtblom AM. Prevalence and cost of epilepsy in Sweden – a register-based approach. *Acta Neurol Scand* 2015;131:37-44 doi 10.1111/ane.12297.

Sarkanen T, Nimelä V, Landtblom AM, Partinen M. Psychosis in patients with narcolepsy as an adverse effect of sodium oxybate. *Front Neurol* 2014 Aug 20;5:136. Doi: 10.3389/fneur.2014.00136. eCollection 2014

Burman J, Svensson E, Fransson M, Loskog ASI, Zetterberg H, Raininko R, Svenningsson A, Fagius J, Mangsbo, SM. The cerebrospinal fluid cytokine signature of multiple sclerosis: a homogenous response that does not conform to the Th1/Th2/Th17 convention. *J Neuroimmunol*. 2014 Oct 18;277(1-2):153-159.

Burman J, Fagius J. Blodstamcellstransplantation effektiv behandling för MS. *Läkartidningen* 2014:111.

Burman J, Iacobaeus E, Svenningsson A, Lycke J, Gunnarsson M, Nilsson P, Vrethem M, Fredrikson S, Martin C, Sandstedt A, Uggla B, Lenhoff S, Johansson JE, Isaksson C, Hägglund H, Carlson K, Fagius J. Autologous hematopoietic stem cell transplantation for aggressive multiple sclerosis: the Swedish experience. *J Neurol Neurosurg Psychiatry*. 2014 Oct;85(10):1116-21.

Fransson M, Piras E, Hao W, Burman J, Rasmusson Duprez I, Harris RA, LeBlanc K, Brittebo E, and Loskog ASI. Human mesenchymal stromal cells expressing a CNS-targeting receptor can be administrated intranasally and cure experimental autoimmune encephalomyelitis. *Immunology*. 2014 Jul;142(3):431-41.

Burman J, Zetterberg H, Fransson M, Loskog ASI, Raininko R, Fagius J. Assessing tissue damage in multiple sclerosis: a biomarker approach. *Acta Neurol Scand*. 2014 Aug;130(2):81-9.

Fagius J, Burman J. Normal outcome of pregnancy with ongoing treatment with natalizumab. *Acta Neurologica Scandinavica*. *Acta Neurol Scand*. 2014 Jun;129(6):e27-9.

Landtblom AM, Engström M. The sleepy teenager – diagnostic challenges. *Front Neurol* 2014 Aug 4;5:140. Doi: 10.3389/fneur.2014.00140. eCollection 2014 Review

Ziemssen T, Bajenaru OA, Carra A, de Klippel N, de Sa JC, Edland A, Frederiksen JL, Heinzlef O, Karageorgiou KE, Lander Delgado RH, Landtblom AM, Maclas Islas MA, Tubridy N, Gilgun Shanki Y. A 2-year observational study of patients with relapsing-remitting multiple sclerosis converting to glatiramer acetate from other disease-modifying therapies: the COPTIMIZE trial. *J Neurol* 2014 Aug 14, e-pub ahead of print.

Bolin K, Berggren F, Landtblom AM. Regional variation in prevalence and health care utilization due to epilepsy in Sweden. *Acta Neurol Scand* 2014;130:354-9 Doi: 10.1111/ane.12274

Engström M, Hallböök T, Szakacs A, Karlsson T, Landtblom AM. Functional magnetic resonance imaging in narcolepsy and the Kleine-Levin syndrome. *Front Neurol* 2014 June 25;5:105. Doi:10.3389/fneur.2014.00105 eCollection 2014. Review.

Vigren P, Engström M, Landtblom AM. SPECT in the Kleine-Levin syndrome. *Front Neurol* 2014 Sep 23;5:178

Hallböök T, Malmgren K, Feltelius N, Szakasc A, Landtblom AM. Narkolepsi - en sällsynt sjukdom med ökande betydelse. *Läkartidningen* 2014;111:1770-3

Landtblom AM. Neuroimaging in sleep disorders. Book review, *Front Neurol* 2014 Sep 23

Elsir T, Edqvist PH, Carlson J, Ribom D, Bergqvist M, Ekman S, Popova S, Alafuzoff I, Ponten F, Nister M, Smits A (2014) A study of embryonic stem cell-related proteins in human astrocytomas: identification of Nanog as a predictor of survival. *International Journal of Cancer* 134, 1123-1141

Pölajeva J, Bergström T, Edqvist PH, Lundequist A, Nilsson G, Smits A, Bergqvist M, Pontén F, Westermarck B, Pejler G, Forsberg Nilsson K, Tchougounova E (2014) Glioma-derived macrophage migration inhibitory factor (MIF) promotes mast cell recruitment in a STAT5-dependent manner. *Molecular Oncology* 8, 50-58

Popova SN, Bergqvist M, Dimberg A, Edqvist PH, Ekman S, Hesselager G, Ponten F, Smits A, Sooman L, Alafuzoff I (2014) Subtyping of gliomas of various WHO grades applying immunohistochemistry. *Histopathology* 64, 365-79

Falk A, Fahlström M, Rostrup E, Berntsson S, Zetterling M, Morell A, Larsson HB, Smits A, Larsson EM (2014) Discrimination between glioma grades II and III in suspected low-grade gliomas using dynamic contrast-enhanced and dynamic susceptibility contrast perfusion MR imaging: a histogram analysis approach. *Neuroradiology* 56(12):1031-8

## Reviews

Nyholm D; Senek M, Continuous drug delivery in Parkinson's disease. *CNS Drugs* 2014;28(1):19-27.

Shunt vid hydrocefalus – Behandlingsöversikt på [www.internetmedicin.se](http://www.internetmedicin.se), 2015-04-14 (Virhammar J, Fahlström A, Cesarini K)

Hydrocefalus, kommuniserande - Behandlingsöversikt på [www.internetmedicin.se](http://www.internetmedicin.se), 2015-08-06 (Cesarini K, Virhammar J)

Wieloch T et al. A healthy aging brain promotes Swedish growth – a strategic innovation agenda to combat diseases of the aging brain. 2015. [Nyholm D listed among collaborators]

Odin P, Ray Chaudhuri K, Slevin JT, Volkmann J, Dietrichs E, Martinez-Martin P, Krauss JK, Henriksen T, Katzenschlager R, Antonini A, Rascol O, Poewe W; National Steering Committees. Collective physician perspectives on non-oral medication approaches for the management of clinically relevant unresolved issues in Parkinson's disease: Consensus from an international survey and discussion program. *Parkinsonism Relat Disord.* 2015 Oct;21(10):1133-44. [Nyholm D listed among 74 collaborators].

Wirdefeldt K, Odin P, Nyholm D. Levodopa-Carbidopa Intestinal Gel in Patients with Parkinson's Disease: A Systematic Review. *CNS Drugs.* 2016 May;30(5):381-404

Wirdefeldt K, Odin P, Nyholm D. Authors' Reply to Lambarth: "Levodopa-Carbidopa Intestinal Gel in Patients with Parkinson's Disease: A Systematic Review". CNS Drugs. 2016; 30(10), 1009-1010

A Smits & AS Jakola (in press). Clinical presentation of diffuse low-grade gliomas. In: "Diffuse Low-Grade Gliomas in Adults", 2<sup>nd</sup> edition. Ed H Duffau. Springer London Ltd.

### **Others**

Anja Smits (2016) "Tumörmarkörer kan bidra till val av behandling vid lågmaligna gliom". Läkartidningen 44-45/2016.

Moraes-Fontes MF, Berntsson SG (2016) Comment on: PML in patients with systemic lupus erythematosus: a systematic literature review. Lupus. 2016 Jun 16. pii: 0961203316655216.

### **Agencies that support the work/ Funding**

ALF

BiogenIDEC unrestricted research grant

Erik, Karin och Gösta Selanders Stiftelse

Hanna Eklunds Foundation

Lion's hjälpfond

Lions Cancer Fond

MÅH Ländell foundation

Major Gösta Linds minnesfond

Margaretahemmet Foundation

NorrBacka-Eugeniastiftelsen

Parkinsonfonden

Regional Research Council Uppsala/Örebro

Selander Foundation

SSMF postdocstipendium

Svenska Läkaresällskapet (SLS-593521) 183 600

Swedish Knowledge Foundation (KK-stiftelsen)

Swedish Research Council (Vetenskapsrådet)

Thurenius Foundation

Ulla-Carin Lindquist stipendium

Uppsala County Council (ALF)

Vinnova



# Clinical Neurophysiology

## *Neuromuscular Synapse*

### **Group leaders:**

**Anna Rostedt Punga, MD, PhD, Associate Professor**

### **Members of the group during 2016:**

Anna Rostedt Punga, Associate Professor  
Marta Lewandowska, Postdoctoral fellow  
Liis Sabre, Postdoctoral fellow  
Elisabet Westerberg, PhD student  
Carl Johan Molin, PhD student  
Evgenii Bogatkov, PhD student  
Johan Widenfalk, Associate Professor  
Margaretha Rostedt, Research assistant

### **Collaborators:**

The group of Prof Sonia Berrih-Aknin, INSERM, Paris, France is working together with “Neuromuscular synapse” in finding new biomarkers in MG.

Prof Amelia Evoli, Catholic University, Rome, is working together with the group on finding biomarkers in MuSK+ MG and on the preclinical model of MuSK+ MG.

Prof Markus Rüegg, Basel, Switzerland (pathophysiology of the neuromuscular synapse)

Prof Elisabeth Chroni, Patras, Greece

Dr Mohammad Alimohammadi, Medical Sciences, Uppsala University

Dr Tanel Punga, IMBIM; Uppsala University

Dr Henry Kaminski, USA, George Washington University, USA

Klas Kullander, Dept of Neuroscience, Uppsala University

### **The general aims of the research group are:**

1. Elucidation of the pathogenic mechanisms underlying neuromuscular disorders, and establishment of biomarkers, with focus on myasthenia gravis (MG).
2. Development of an in-vitro neuromuscular junction (NMJ) on an electronic chip device.

### ***Neuromuscular synapse and myasthenia gravis:***

Disorders of disturbed neuromuscular transmission include the autoimmune disorder Myasthenia Gravis (MG), in which antibodies attack the receptors of the neuromuscular synapse. The symptoms manifest as fatigable weakness of skeletal muscles in the face, in the neck, arms and legs and often cause droopy eyelids, difficulty in swallowing and chewing etc. In many patients, there is also a subsequent muscle wasting, in particular in patients with antibodies against the receptor muscle specific tyrosine kinase (MuSK). Our main research interest is to elucidate the pathogenesis of MG and, ultimately, to find new therapeutic interventions against the muscle wasting following chronic neuromuscular disorders. Additionally, we aim to discover novel biomarkers for improved diagnostics, prognosis and treatment in conditions of disturbed neuromuscular transmission. We work both with the

preclinical model of experimental autoimmune myasthenia gravis (EAMG), in the clinical setting with MG patients and on establishing an “NMJ on a chip” system.

### ***Biomarkers***

During the past year we have continued our expansion of data on circulating microRNAs in the sera of MG patients as biomarkers. The levels of the most sensitive biomarker, miR150-5p, were reduced in patients with immunosuppressive treatment. We also established the novel biomarker let7-family of miRNAs in MG patients with MuSK antibodies, which support the etiological differences between AChR antibody and MuSK antibody seropositive MG. These potential biomarkers in the sera of MG patients are important, since no biomarkers have been available to date. We will now continue to elucidate the role of these immuno-miRNAs in the processes of the autoimmune response more specifically and in the neuromuscular transmission, both in-vivo and in-vitro. Also, we will examine the effects in a longitudinal MG patient cohort before and after thymectomy and introduction of corticosteroids through collaboration with Dr Henry Kaminski, USA.

As a complement to circulating miRNAs, we have recently confirmed novel protein biomarkers in MG. The three most significantly elevated protein markers in MG compared to healthy controls were: matrix metalloproteinase 10 (MMP-10), transforming growth factor alpha (TGF- $\alpha$ ) and extracellular newly identified receptor for advanced glycation end-products binding protein (EN-RAGE) (also known as protein S100-A12). Further, levels of MMP-10, C-X-C motif ligand 1 (CXCL1) and brain derived neurotrophic factor (BDNF) differed between early and late onset MG. These novel targets provide valuable additional insight into the systemic inflammatory response in MG (*Molin CJ et al, Sci Rep, 2017*).

Further, we have established neurophysiological parameters to assess the effects upon physical training that will be used in future studies of physical exercise in MG patients. The next step will be to evaluate the examination of neuromuscular ultrasound in trained and untrained healthy individuals to see whether muscle mass and nerve diameter are affected by high-resistance strength training. We have also used these neurophysiological biomarkers (CMAP) in a recently performed pilot study of supervised physical exercise in MG patients, where we concluded that the clinical course does not worsen due to moderate physical exercise. This study has recently been repeated in another cohort of MG patients to be able to draw more extensive conclusions.

### ***Novel cutting-edge model systems to study diseases at the NMJ***

We have been able to record postsynaptic spikes from generated muscle cells (myocytes) on a high-density electrode chip. The chip contains an array of 26.400 platinum electrodes at a density of 3265 electrodes per mm<sup>2</sup>. A subset of 1024 electrodes can be read out simultaneously and can be stimulated through the 32 on-chip stimulation buffers. Recently, this model system was able to record large spikes along many axonal sites (Lewandowska et al, 2015). We are now expanding on this model to include motor neuron recordings, to finally develop an NMJ on a chip.

### **Publications 2014-2016**

1. Westerberg E, Molin CJ, Lindblad I, Emtner M, Punga AR. Physical exercise in Myasthenia Gravis is safe and improves neuromuscular parameters and physical

- performance-based measures: A pilot study. *Muscle Nerve*. 2016 Dec 9. doi: 10.1002/mus.25493. [Epub ahead of print] PubMed PMID: 27935072.
2. Liik M, Punga AR. Repetitive nerve stimulation often fails to detect abnormal decrement in acute severe generalized Myasthenia Gravis. *Clin Neurophysiol*. 2016;127(11):3480-3484. Punga AR, Alimohammadi M, Fagrell D, Nyberg F, Rees D, Wong C. A Randomized, Comparative Study to Evaluate Efficacy and Safety of Two Injection Volumes of AbobotulinumtoxinA in Treatment of Glabellar Lines. *Dermatol Surg*. 2016;42(8):967-976.
  3. Punga T, Bartoccioni E, Lewandowska M, Damato V, Evoli A, Punga AR. Disease specific enrichment of circulating let-7 family microRNA in MuSK+ myasthenia gravis. *J Neuroimmunol*. 2016;292:21-26.
  4. Molin CJ, Punga AR. Compound Motor Action Potential: Electrophysiological Marker for Muscle Training. *J Clin Neurophysiol*. 2016;33(4):340-345.
  5. Chroni E, Dimisianos N, Punga AR. Low vitamin D levels in healthy controls and patients with autoimmune neuromuscular disorders in Greece. *Acta Neurol Belg*. 2016;116(1):57-63.
  6. Punga AR, Andersson M, Alimohammadi M, Punga T. Disease specific signature of circulating miR-150-5p and miR-21-5p in myasthenia gravis patients. *J Neurol Sci*. 2015;356(1-2):90-96.
  7. Punga AR, Eriksson A, Alimohammadi M. Regional Diffusion of Botulinum Toxin in Facial Muscles: A Randomised Double-blind Study and a Consideration for Clinical Studies with Split-face Design. *Acta Derm Venereol*. 2015;95(8):948-951.
  8. Punga AR, Kaminski HJ, Richman DP, Benatar M. How clinical trials of myasthenia gravis can inform pre-clinical drug development. *Exp Neurol*. 2015;270:78-81
  9. Phillips WD, Christadoss P, Losen M, Punga AR, Shigemoto K, Verschuuren J, Vincent A. Guidelines for pre-clinical animal and cellular models of MuSK-myasthenia gravis. *Exp neurol*, 2015; 270:29-40.
  10. Elf K, Askmark H, Nygren I, Punga AR. Vitamin D deficiency in patients with primary immune-mediated peripheral neuropathies. *J Neurol Sci*. 2014; 345 (1-2): 184-188.
  11. Punga T, Le Panse R, Andersson M, Truffault F, Berrih-Aknin S, Punga AR. Circulating miRNAs in myasthenia gravis: miR-150-5p as a new potential biomarker. *Ann Clin Trans Neurol*, 2014; 1 (1): 49-58.
  12. Alimohammadi M, Andersson M, Punga AR. Correlation of botulinum toxin dose with neurophysiological parameters of efficacy and safety in the glabellar muscles: a double-blind placebo-controlled, randomized study. *Acta Derm Venerol*, 2014; 94 (1):32-37.

## **Agents that support the work/ Funding**

Vetenskapsrådet  
Neuroförbundet  
Uppsala Läns Landsting  
Uppsala University  
Svenska Läkarsällskapet  
Erik, Karin och Gösta Selanders Stiftelse

## **Awards**

”Eberhardt Pfeleiderer Preis” from the German Myasthenia Gravis foundation (ARP)  
Honorary member of IFCN (ES).

## ***Development of Advanced Electrophysiological Methods***

**Group leaders: Erik Stålberg, Professor em.**

### **Members of the group during 2016:**

Erik Stålberg  
Arne Sandberg

### **Collaborators:**

S Nandedkar, USA  
L Puuksa, Estonia  
DB Sanders USA  
J Kouyoumdjian Brazil  
M Sonoo, Japan  
Dr S Löseth, Norway

**AIM:** Improvement of diagnostic methods/markers in neuromuscular disorders, including loss of motor neurons (ALS, post-polio, SMA) as well as disorders with disturbed neuromuscular transmission.

Development of electrophysiological methods for the study of neuromuscular disorders continues. In the past year, our focus has been on new electrodes for jitter analysis. Results have been published, and a multicenter study has been undertaken. There is also a need to replace conventional reusable and expensive macro-EMG needle with a disposable electrode. The macro EMG technique has a proven value to study and follow reinnervation processes, and is superior to the conventional needle-EMG in these respects.

A study regarding a reusable needle is running and reference values are published. Also, a needle manufacturer has shown interest in this project.

Over the last few years, criteria and methodological details for the MUNIX method for axonal counting have been developed; and a European and US multicenter study has confirmed its reproducibility. Further, MUNIX has been applied in the follow-up of patients with ALS, providing a good quantitative measure of the dynamic changes in this disease.

The method for direct muscle stimulation is being evaluated in critical illness (together with Prof Larssons group, at Karolinska Institute). Data have been collected from a large group of critically ill patients to be published as a PhD thesis, Humberto Skott, Karolinska Hospital. Surface EMG is being evaluated as an alternative to invasive needle EMG examinations.

New algorithms for analysis of surface EMG particularly in pediatric praxis are being established, for example in children with spinal muscle atrophy (SMA). Surface EMG (neurography) from many muscles has also been tested for monitoring of ALS. This should be an easier technique than the so called MUNE methods.

A new way to obtain "normal" reference material from a large mixed group of patients, some of whom were found normal is under development. Comparison between this mathematical way and actual recordings will be made.

Abnormalities in the neurographic parameters F-waves are studied in relation to various diseases. Detailed studies of the sensitivity in carpal tunnel syndrome of different methods are in progress (with doc G Ahlsén, Örebro),

Prof em Erik Stålberg is involved in collaborations with J Navallas, Spain, S Nandedkar, USA and M Sonoo, Japan in developing new motor unit analysis techniques.

He is also involved in projects with Prof DB Sanders USA and J Kouyoumdjian Brazil to improve the method of single-fiber EMG.

#### **Publications 2014-2016**

1. **Sandberg A.** The standard concentric needle cannula cannot replace the Macro EMG electrode. *Clin Neurophysiol.* 2014 Feb;125(2):406-10.
2. **Sandberg A.** Single fiber EMG Fiber density and its relationship to Macro EMG 3. amplitude in reinnervation. *J Electromyogr Kinesiol.* 2014 Dec;24(6):941-6.
4. Caliendo P, Padua L, Rossi A, Rossini PM, **Stålberg E**, Feurra M, Ulivelli M, Bartalini S, Giannini F, Rossi S. Jitter of corticospinal neurons during repetitive transcranial magnetic stimulation. Method and possible clinical implications. *Brain Stimul* 2014;7:580-586.
5. Nicole S, Chaouch A, Torbergsen T, Bauche S, de BE, Fontenille MJ, Horn MA, van GM, Loseth S, Issop Y, Cox D, Muller JS, Evangelista T, **Stålberg E**, Ioos C, Barois A, Brochier G, Sternberg D, Fournier E, Hantai D, Abicht A, Dusl M, Laval SH, Griffin H, Eymard B, Lochmuller H. Agrin mutations lead to a congenital myasthenic syndrome with distal muscle weakness and atrophy. *Brain* 2014;137:2429-2443.
6. Neuwirth C, Barkhaus PE, Burkhardt C, Castro J, Czell D, de CM, Nandedkar S, **Stålberg E**, Weber M. Tracking motor neuron loss in a set of six muscles in amyotrophic lateral sclerosis using the Motor Unit Number Index (MUNIX): a 15-month longitudinal multicentre trial. *J Neurol Neurosurg Psychiatry* 2015;86:1172-1179.
7. **Stålberg E**, Sanders DB, Ali S, Cooray G, Leonardis L, Loseth S, Machado F, Maldonado A, Martinez-Aparicio C, Sandberg A, Smith B, Widenfalk J, Kouyoumdjian JA. Reference values for jitter recorded by concentric needle electrodes in healthy controls: A multicenter study. *Muscle Nerve* 53: 351–362, 2016
8. **Stålberg E.** Between genetics and biology. Is ENEMG useful in peripheral neuropathy diagnosis and management? *Revue Neurologique* 2016;172.
9. Marrero HG, **Stalberg EV.** Optimizing testing methods and collection of reference data for differentiating critical illness polyneuropathy from critical illness myopathy. *Muscle Nerve* 2015.

10. Torbergsen T, Jurkat-Rott K, **Stalberg EV**, Loseth S, Hodneo A, Lehmann-Horn F. Painful cramps and giant myotonic discharges in a family with the Nav1.4-G1306A mutation. *Muscle Nerve* 2015;1.

### **Book chapters**

**Stålberg E.** Quantifying needle EMG. In: Adatepe T, editor. *Comprehensive Guide and Muscle Atlas for Needle Electromyography*. Istanbul: Sep Medikal; 2014. p 15-25

**Stålberg E** Electromyography. In K. Mills, editor. *Oxford Textbook of Clinical Neurophysiology*. DOI: 10.1093/med/9780199688395.003.0007

## ***Central and Somatosensory Nervous System***

### **Members of the group during 2016**

Roland Flink, Karin Edebol Eeg-Olofsson, Hans Axelson, Åsa Amandusson, Kristin Elf, Holger Rothkegel, Dmitri Bouzarov, Roland Schmidt

#### ***Project 1: Focal epilepsy and epilepsy surgery***

Project leader: Roland Flink

The aim of the project is to improve the localization of epileptic foci with dipole analysis methods in patients undergoing preoperative evaluation for epilepsy surgery. A new system for dipole analysis and reconstruction of 3D MR scans in order to superimpose dipole location with anatomical structures, Curry 8®, has been implemented.

#### ***Project 2: Transcranial magnetic stimulation in the evaluation of patients with epilepsy and brain tumors***

**Project leaders:** Åsa Amandusson, Hans Axelson

Transcranial magnetic stimulation (TMS) is a well-tolerated technique by which cortical neurons can be activated non-invasively. By using neuronavigation in conjunction with TMS, cortical function can be studied in relation to anatomical structures. Paired-pulse TMS (ppTMS) is a further development of TMS by which it is possible to obtain measurement values of cortical excitability. Recent studies have shown that these values may predict the therapeutic response to antiepileptic drugs and the outcome of epilepsy surgery. We have initiated studies focusing primarily on different aspects of cortical excitability in healthy subjects and patients with seizures, epilepsy and brain tumors. We have developed a standardized semi-automatic method for ppTMS measurement and recently completed a methodological study comparing different ways of performing ppTMS.

#### ***Project 3: Neurophysiologic methods in intraoperative monitoring (IOM)***

**Project leader:** Hans Axelson, Dmitri Bouzarov

Intraoperative neurophysiology (ION) provides the surgeons with information regarding the location and function of nervous tissues such as sensor, motor and speech cortical areas and pathways. Work in progress is divided into three main topics

- 1) Analysis of retrospective data from motor threshold measurements during asleep supratentorial glioma surgery and determining to what extent non-surgical factors (technical and physiological) influence the motor threshold that may produce false “warning” alerts during surgery.
- 2) Implementation of automatic motor threshold assessment during supratentorial glioma surgery for more time efficient and reliable motor threshold determination for both cortical and subcortical stimulation.
- 3) Development and implementation of additional tests of higher order cerebral functions during awake craniotomy such as memory, facial recognition and vision.

This project main aim is to provide neurosurgeons with more reliable intraoperative information on the integrity and location of “eloquent” nervous structure in the operating field in a time efficient manner.

#### ***Project 4: Continuous EEG during intensive care***

**Project leader:** Kristin Elf, Åsa Amandusson

Continuous EEG has been carried out increasingly in intensive care units for last few years. It has then become evident that subclinical seizures and even status epilepticus are fairly common, especially in patients with a primary brain injury, but also in patients with, for example, metabolic and infectious diseases.

The interpretation of continuous EEG is very time consuming. The burden of interpretation increases with time recorded and number of electrodes. Therefore trend analysis of few electrodes is often used. The most common trend is amplitude integrated EEG, aEEG. It is not known how many electrodes are necessary for acceptable sensitivity therefore we currently perform a study on this.

Data collection on a prospective study regarding stimulus induces rhythmic, periodic and ictal discharges, SIRPIDs is soon complete. SIRPIDs are pathologic EEG patterns and seizures elicited by all kinds of sensory stimuli. Patients with SIRPIDs have an increased risk of seizures and SIRPIDs may cause neuronal injury. We aim at discovering patients with SIRPIDs and to map what nursing and other medical processes that elicit SIRPIDs, with the goal of minimizing secondary brain injury.

During 2016 a prospective study on postoperative seizure occurrence in patients with brain tumors started. Another study in the pipeline is a prospective study on seizure occurrence and sleep patterns in critically ill patients without a primary brain injury. Seizures and sleep disturbances may be involved in the development of delirium, a common problem in the general ICU which may lead to cognitive decline.

#### ***Project 5: Pain and Itch in Human Disease***

**Project leader:** Roland Schmidt

*Background:* About 1.5 % of the Swedish population suffers from neuropathic pain. The mechanisms are largely unknown. No mechanism-based classification system is available.

More effective and better tolerated treatments are needed (Swedish Medical Products Agency 2007, Sheets et al. 2008).

*Questions, methods and goals:* The technique of microneurography was initiated in Uppsala by Vallbo and Hagbarth in 1968. For many years we have performed recordings of action potentials from individual nociceptive (pain) C-fibre axons (microneurography) in awake humans who can simultaneously report their sensations. This kind of single fibre recording is technically complex and it is mainly performed only by 2 groups internationally (Norway – Uppsala Sweden – Germany).

Pain and central sensitisation in man in experimental conditions is mainly mediated by specific mechanoinensitive C-nociceptors (CMi) first described by our group (Schmidt et al. 1995). Parts of the sensation of itch is mediated by specific CMi fibres also first described by our group (Schmelz et al 1997).

*Pain mechanisms:* We aim at understanding the contribution of the different ion channels to pathologic axon membrane excitability. (Mutations of NaV1.7 sodium channels can result in pain). Since different classes of human C-nociceptive axons have separate specific and tightly coupled receptive, axonal, central and ion channel properties, it is possible to develop drugs specifically targeting one class of peripheral nociceptive neurons, decreasing high frequency discharges without influencing acute pain and defensive reflexes, and avoiding side effects from the CNS (sedation etc.). Several pharmaceutical companies are now developing drugs targeting voltage gated sodium channels for treatment of neuropathic pain. (Sheets et al 2008, Dib-Hajj et al 2009) We have the capacity to test such drugs and drug candidates injected in minute amounts near the peripheral axons during microneurography.

*Future:* We continue to unveil the mechanisms of hyperexcitability in patients with neuropathic pain. Recordings include patients with mutations of NaV1.7, NaV1.8 and NaV1.9. As a result of our work a new method to diagnose thin fiber neuropathy by objective laser doppler measurement of the axon reflex is now being implemented in Uppsala.

### **International collaboration**

Hermann Handwerker (1) T. Helås (2), E. Jørum (2), IP Kleggetveit (2), B. Namer(1), O. Obreja (1), K. Ørstavik (2), M. Schmelz (1), B. Turnquist (3), SG Waxman (4), C. Weidner (1).

1: Germany, Erlangen and Mannheim universities

2: Norway, Rikshospitalet and Trondheim University

3: USA, Univ. Minnesota

4: USA, Yale University

### **Publications 2014-2016**

1. Namer B, Schick M, Kleggetveit IP, Orstavik K, Schmidt R, Jorum E, Torebjörk E, Handwerker H, Schmelz M. Differential sensitization of silent nociceptors to low pH stimulation by prostaglandin E2 in human volunteers. *Eur J Pain.* 2014 May 30. Original article.
2. Namer B, Ørstavik K, Schmidt R, Kleggetveit IP, Weidner C, Mørk C, Kvernebo MS, Kvernebo K, Salter H, Carr TH, Segerdahl M, Quiding H, Waxman SG, Handwerker HO, Torebjörk HE, Jørum E, Schmelz M.



Specific changes in conduction velocity recovery cycles of single nociceptors in a patient with erythromelalgia with the I848T gain-of-function mutation of Nav1.7. *Pain*. 2015 Sep;156(9):1637-46

3. Bjellvi J, Flink R, Rydenhag B, Malmgren K 1: Complications of Epilepsy Surgery in Sweden 1996-2010: A Prospective, Population-based Study. *J Neurosurg*, 2014 (in print online)
4. Axelson HW, Isberg M, Flink R, Amandusson Å. Trigeminal nerve stimulation does not acutely affect cortical excitability in healthy subjects. *Brain Stimul*. 2014 Jul-Aug;7(4):613-7
5. Hameed MQ, Goodrich GS, Dhamne SC, Amandusson Å, Hsieh TH, Mou D, Wang Y, Rotenberg A. A rapid lateral fluid percussion injury rodent model of traumatic brain injury and post-traumatic epilepsy. *Neuroreport*. 2014 May;25(7):532-6
6. Franck-Larsson K, Eeg-Olofsson KE, Axelsson HW, Rönnblom A. Physiological and structural anorectal abnormalities in patients with systemic sclerosis and fecal incontinence. *Scand J Gastroenterol*, 2014, Sept; 49(9): 1076-83.
7. Elf, K., Shevchenko, G., Nygren, I., Larsson, L., Bergquist, J. et al. (2014). Alterations in muscle proteome of patients diagnosed with amyotrophic lateral sclerosis. *Journal of Proteomics*, vol. 108, ss. 55-64 2014
8. Elf, K., Askmark, H., Nygren, I., Punga, A. (2014). Vitamin D deficiency in patients with primary immune-mediated peripheral neuropathies. *Journal of the Neurological Sciences*, vol. 345, ss. 184-188, 2014
9. Press R, Askmark H, Svenningsson A, Andersen O, Axelson HW, Strömberg U, Wahlin A, Isaksson C, Johansson JE, Hägglund H. Autologous haematopoietic stem cell transplantation: a viable treatment option for CIDP. *J Neurol Neurosurg Psychiatry*. 2014 Jun;85(6):618-24. doi: 10.1136/jnnp-2013-306014. Epub 2013 Nov 21. PubMed PMID: 24262917.
10. Edelvik A, Flink R, Malmgren K: Prospective and longitudinal long-term employment outcomes after resective epilepsy surgery. *Neurology*, 2015 on line publication 10.1212/WNL.0000000000002069
11. Nilsson DT, Rydenhag B, Flink R, Malmgren K: Outcomes of multilobar resections for focal epilepsy in Sweden 1990-2013 - a national population-based study. *Acta Neurochirurgica*, DOI 10.1007/s++701-016-2807-3, 2016.
12. Ambrus GG, Chaieb L, Stilling R, Rothkegel H, Antal A, Paulus W. Monitoring transcranial direct current stimulation induced changes in cortical excitability during the serial reaction time task. *Neurosci Lett*. 2016 Mar 11;616:98-104. doi: 10.1016/j.neulet.2016.01.039.

#### **Agencies that support the work/ Funding**

The Swedish Brain Foundation  
ALF  
Margarethahemmet  
Wallenbergstiftelsen  
Utvecklingsfonden Akademiska sjukhuset  
Svenska Läkarsällskapet  
Swedish Chapter of ILAE (Svenska Epilepsisällskapet)  
Stiftelsen Epilepsifonden

# Psychiatry

## *Psychiatry*

**Group leader: Lisa Ekselius, Professor**

### **Members of the group during 2016**

Adriana Ramirez, PhD	Jonas Persson, PhD
Anders Fredriksson, Associate Professor	Josefin Bäckström, PhD
Björn Nilsson, PhD	Josefin Sveen, PhD
Björn Milesson-Fors, PhD student	Karin Tillman, PhD student
Caisa Öster, Associate Professor	Katarina Danielsson, PhD
Cathrine Axfors, PhD student	Kerstin Bergh Johannesson, PhD
Charlotte Odelius, PhD student	Kristina Bondjers, PhD student
Christina Nehlin Gordh, PhD	Kristina Haglund, Associate Professor
Dan Edvinsson, PhD student	Krisztina Szalisznoy, PhD
Eric Clapham, PhD student	Lars von Knorring, Professor Emeritus
Efthymios Kouppis, PhD student	Leif Grönbladh, PhD
Elin Thörnblom, PhD student	Leif Lindström, Professor Emeritus
Eva Baghdassarian, PhD student	Lena Bergdahl, PhD student
Eva Lindström, Associate Professor	Lennart Jansson, PhD
Filip Arnberg, Associate Professor	Linda Jüris, PhD
Fanny Söderquist, PhD student	Lisa Ekselius, Professor
Fotios Papadopoulos, Associate Professor	Malgorzata Szmido, PhD student
Fredrik Folke, PhD student	Manuel Fernandez, PhD student
Georgios Makris, PhD student	Maria Holstad Högberg, PhD
Georgios Karamanis, Consultant	Martin Cernvall, PhD
Hans Arinell, statistician	Martina Hedman, PhD student
Hanna Ljungvall, PhD student	Mia Ramklint, Associate Professor
Hanna Spangenberg, PhD student	Mikaela Syk, PhD student
Ioannis Kouros, PhD student	Mimmie Willebrand, Professor
Isak Sundberg, PhD student	Niklas Hörberg, PhD student
Jan Kask, PhD student	Robert Bodén, Associate Professor
Jan-Erik Broman, Associate Professor	Stefan Nasir, PhD student
Janet Cunningham, Associate Professor	Tom Lundin, Professor Emeritus
Johan Bengtsson, PhD student	Tommy Lewander, Associate Professor
Johanna Salberg, PhD student	

Within the Department of Neuroscience, research related to psychiatry focuses on investigating factors relevant to psychiatric morbidity. The research group boasts a wide variety of competences, and most members have substantial clinical experience. There is broad expertise in research methods, from pre-clinical and experimental methods to methods used in clinical studies. These include, but are not limited to, methods for evaluation of psychiatric symptomatology and methods used in genetic and proteomic research.

This wide knowledge base facilitates clinically relevant research on many levels. The ultimate goal of our research is to improve psychiatric health. This requires optimal definitions of psychiatric states, optimal diagnostic procedures and subsequently best available, evidence-

based care and treatments. All of this must be based on up-to-date knowledge of the enigmas of the nervous system. Major individual projects are described below.

### ***Personality and individual differences***

#### ***1) Vulnerability and resilience; medical, psychological and social adaptation after severe injury***

Participants within the Department: Lisa Ekselius (PI), Mimmie Willebrand, Caisa Öster, Josefin Sveen, Josefin Bäckström.

Collaborators: Professor Elna Marie Larsson, Department of Radiology, Uppsala University (UU), Malin Gingnell, MD, PhD, Dept of Psychology, UU, Professor Folke Sjöberg and Emelie Gauffin, MD, PhD student, Dept of Clinical and Experimental Medicine, Linköping University, Professor Gerhard Andersson, Dept of Behavioural Sciences and Learning, Linköping University.

Our overall aim is to investigate factors that influence outcomes after a severe life threatening physical trauma or stressor, in this case a severe burn injury. According to the working hypothesis, several factors act, and interact, to shape the adaptation process and outcome (see Figure 1 below). Individual factors such as genotype, gender, psychiatric history, cognitive function, personality traits and coping strategies will be related to acute and long-term outcome. Also, physiological stress responses during treatment for the burn injury, with focus on the hypothalamo-pituitary-adrenocortical-axis, are studied in relation to individual factors and to outcome. Another objective is to study signs of neurobiological alterations using neuroimaging techniques. Outcome is broadly defined in medical, psychological and social terms. Some specific outcomes, to which we devote much interest, are cognitive function, e.g. attention and memory, and psychiatric morbidity e.g. delirium, posttraumatic stress disorder and depression.

Patients treated for severe burn injuries and associated family members are assessed prospectively during care and several years after discharge from hospital. Burn injury provides an excellent model for severe trauma with a protracted recovery. Therefore, the results can be generalized and facilitate the development of new treatment strategies that can improve outcome also after other severe conditions with an increased risk for psychiatric morbidity. Specifically, the situation of parents of children with burns has been studied. As parent health is of vital importance for children's health, an Internet-based information and self-help programme is developed and evaluated for parents of children with burns.

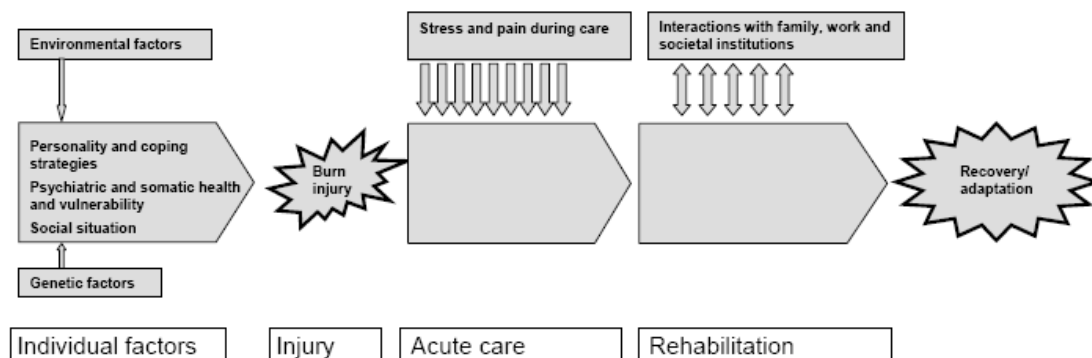


Figure 1. A model of trauma outcome.

## ***II) Ongoing PhD projects within the “Personality and Individual Differences group”***

*Long-term outcome after pharmacological treatment in adult ADHD* (Dan Edvinsson, PhD student);

*Effect of behavioural activation in hospital treated patients with depressive or anxiety disorders* (Fredrik Folke, PhD student, med dr Per Söderberg and med dr Stefan Tungström, the General Psychiatric Clinic, Landstinget Dalarna, associate professor Timo Hursti, Dept of Psychology, UU).

*Epidemiological studies of patients with personality disorders* (Efthymios Kouppis, PhD student, professor emeritus Bengt Gerdin, Surgical Sciences, UU, med dr Emma Björkenstam and med dr Charlotte Björkenstam, University of California Los Angeles, Los Angeles, California, USA).

*Chronic opioid treatment in chronic pain conditions: benefits and work ability versus addiction and abuse* (MSc Hanna Ljungvall, professor Pernilla Åsenlöf, Dept of Neuroscience, UU, med dr Rolf Karlsten, Dept of Surgery, UU, professor Markus Heilig, Dept. of Clinical and Experimental Medicine, Linköping University).

*GABA and depressive states* (professor Bryndis Birnir and Amol Bhandage, PhD, Dept of Neuroscience, UU, associate professor Janet Cunningham, associate professor Robert Bodén).

### ***Psychiatric Epidemiology***

**Participants:** Fotios Papadopoulos (PI), Georgios Makris, Jan Kask, Karin Tillman, Georgios Karamanis, Costas Adamidis, Mia Ramklint, Lisa Ekselius

**Collaborators:** Johan Reutfors, PhD and Professor Anders Ekblom, Clinical Epidemiology Unit, Department of Medicine Solna, Karolinska University Hospital, Karolinska Institutet; Ass. Professor, Alkistis Skalkidou, Department of Women’s and Children’s Health, Uppsala University; Richard White, PhD, Norwegian Institute of Public Health, Oslo, Norway; Professor Eleni Petridou, Department of Hygiene, Epidemiology and Medical Statistics, Athens University Medical School, Athens, Greece; Professor Dimosthenis Panagiotakos, Department of Nutrition and Dietetics, Harokopio University, Athens, Greece

Our research focuses on epidemiological aspects of suicide, affective disorders, anorexia nervosa and gender dysphoria. We investigate predictors of both psychiatric and somatic outcomes.

Various aspects of suicide are studied using descriptive and analytical methods. Seasonality in suicides and perinatal depression is studied in particular with focus on the theoretical framework and possible clinical implications.

Retrospective register cohorts in anorexia nervosa, craniofacial disorders and gender dysphoria are utilized to study risk factors, mortality, comorbidity patterns and somatic outcomes. Anorexia nervosa serves as a model of severe caloric restriction in humans, while craniofacial disorders may provide neurodevelopmental insights for several psychiatric outcomes. Gender dysphoria which presents an unprecedented prevalence increase internationally may moreover serve as a model to increase our understanding on the interplay between sex hormones and personality, cognition as well as inflammation.

## ***Emotional instability and impulsivity***

**Participants:** Mia Ramklint (PI), Lisa Ekselius, Adriana Ramirez, Janet Cunningham, Maria Holstad Högberg, Martina Wolf, Dan Edvinsson, Ioannis Kouros, Niklas Hörberg, Charlotta Odelius, Martina Hedman, Cathrine Axfors, Stefan Nasir, Hanna Spangenberg.

**Collaborators:** Professor Kent W Nilsson, Center for Clinical Research Västerås, Professor Ulf Högberg, Dept of Women's and Children's health, Assoc. professor Alkistis Skalkidou, Dept of Women's and Children's health, Professor Anna-Karin Wikström, Dept of Women's and Children's health, Assoc. professor Daniel Nowinski, Dept of Surgical Sciences, Professor Ata Ghaderi, Dept of Clinical Neuroscience, KI.

Emotions control our behaviors. Difficulty regulating emotions and impulses, therefore, affects our behaviors. Difficulty regulating emotions and impulses is common in various mental disorders. Strong negative emotions can lead to behaviors that are intended to deal with the feeling. However, it may be self-destructive behaviors such as substance abuse, self-starvation, binge-eating, self-harm or suicidal acts.

Difficulty with emotion regulation concerns the ability to handle strong emotions such as being sad or angry, and it is common in patients with psychiatric diagnoses such as borderline personality disorder. The difficulty also concerns the ability to regulate mood states that characterize individual experiences of the world over longer time periods. This difficulty is seen, for example, in bipolar disorder and depression where the patient suffers from longer periods of depression or mania.

The ability to regulate emotions also requires cognitive abilities. Self-control functions such as impulse control are located in the brain's frontal lobes. Patient with neuropsychiatric disabilities such as ADHD and autism spectrum disorders have altered function in their frontal lobes. These patients often have difficulties regulating emotions.

Our research work is based on the stress-vulnerability model. This is an interactive model in which genes and environment interact in the development of mental illness. We study difficulties with emotional and impulse control in psychiatric patients. Is there a common vulnerability in patients with similar symptoms? How do life events affect which symptoms develop? We also work with developing methods in psychiatry, both methods for treatment and assessment. How are problems identified, diagnosed, treated, and how are the treatments evaluated?

## ***Severe mental illness research***

**Participants:** Bodén Robert (PI), Jonas Persson, Martin Cernvall, Johan Bengtsson, Elin Thörnblom, Eric Clapham, Janet Cunningham, Lisa Ekselius, Eva Baghdassarian, Eva Lindström, Leif Lindström, Björn Milesson-Fors, Björn Nilsson.

**Collaborators:** Hans Axelson, Åsa Amandusson, Bryndis Birnir, Dept Neuroscience, UU, Erik Olsson, Department of Public Health and Caring Sciences, Elna-Marie Larsson, (Radiology), Dr Jakob Hedberg, and associate professor Magnus Sundbom, Surgical Sciences, UU, Gunnar Antoni, Dpt of Medicinal Chemistry, Division of Molecular Imaging; Caroline Wass, dpt of pharmacology, GU, Hatice Zora, SU, Associate professor Helle Kieler, biostatistician Lena Brandt, Dr Johan Reutfors, and professor Morten Andersen at the Centre for Pharmacoepidemiology, Dept of Medicine, KI. Professor Jari Tiihonen, dpt Neuroscience,

KI. Dr Urban Ösby and Professor Claes-Göran Östenson Dept of Molecular Medicine and Surgery, KI; Prof Jeff Daskalakis, CAMH, Toronto.

Our research projects encompass clinical studies as well as national register-based studies. Our projects focus on severe mental illness such as schizophrenia, bipolar disorder, melancholic depression and catatonia. In our clinical studies we investigate effect and mechanisms of different brain stimulation treatments for severe mental illness (ECT and rTMS). The assessments covers cognition assessments, brain imaging with MRI, PET as well as different neurophysiology assessment (ppTMS, NIRS, EEG with ERP, startle response, and HRV). Further, an ongoing project evaluates brainstem evoked response audiometry as a diagnostic tool in schizophrenia and ADHD.

Severe mental illness, metabolic syndrome and mortality is another research track. We investigate differences in the care of metabolic syndrome related morbidity in patients with and without schizophrenia or bipolar disorder, from myocardial infarction care to bariatric surgery.

We also have several pharmacoepidemiology projects using the Swedish Prescribed Drugs Register, along with other registers such as health care quality registers. In these cohorts we study adherence to drug treatment and outcome in severe mental illness and the safety and effectiveness of psychotropic drug use.

### ***Health care research***

**Participants:** Lena Bergdahl, Jan-Erik Broman, Josefin Bäckström, Johan Dyster-Aas, Kristina Haglund, Lars von Knorring, Agneta Markström, Christina Nehlin Gordh, Mia Ramklint, Caisa Öster.

**Collaborators:** Anne Berman, Department of Clinical neuroscience, Karolinska Institutet.

#### ***I) A randomized controlled trial comparing auricular acupuncture versus CBT in persons suffering from insomnia***

In this study we have used actigraphy, sleep-diary and evaluated surveys to measure insomnia, depression/anxiety, daytime sleepiness and quality of life to evaluate improvement in insomnia symptoms during acupuncture- or CBT treatment.

#### ***II) Caring research in psychiatric care and mental health***

**Participants:** Lena Bergdahl, Josefin Bäckström, Kristina Haglund, Christina Nehlin Gordh, Mia Ramklint, Caisa Öster.

**Collaborators:** Marit Silén, Department of Public Health and Caring Sciences, Centre for Research Ethics & Bioethics, Uppsala University; Mats G Hansson, Department of Public Health and Caring Sciences, Centre for Research Ethics & Bioethics, Uppsala University.

The over all aim is to explore factors of importance for patient care, with respect to patient and close relations unique situation and their wishes. In addition, research aiming to improve education in care.

Ongoing projects investigate:

- experience/perception of psychiatric and mental health
- experience of receiving/giving care and receive support in care

- interaction between personnel, patient, and close persons
- factors of importance for individual quality of life
- factors that improve learning; clinical exams; quality in students' degree projects; and patients' perception of student participation in care.

### ***III) Substance use and psychiatric care***

**Participants:** Christina Nehlin Gordh, Caisa Öster, Johan Dyster-Aas

**Collaborators:** Fred Nyberg, Department of Pharmaceutical Biosciences, Biological Research on Drug Dependence, Uppsala University, Anders Hammarberg, Department of Clinical neuroscience, Karolinska Institute, Kari Jess, Department of Sociology, Uppsala University

The overall aim is to explore the connection between mental health and substance use, in order to develop psychiatric care to better meet the needs of patients with co-occurring problems.

#### ***Uppsala Psychiatric patient samples***

**Participants:** Janet Cunningham, Mia Ramklint, Lisa Ekselius

**Collaborators:** Uppsala Biobank

Current clinical practice in psychiatry is conducted through subjective evaluation of phenotypes. Diagnostic instruments, such as structured interviews and questionnaires, greatly improve the sorting of patients into valid diagnostic groups where generalizations about etiology and appropriate treatment can be made reliably. Biological markers are, however, absent and an important dimension of diagnostics is missing.

Our major aim is to create an infrastructure for the collection of biological material from patients with well-characterized psychiatric symptoms. The infrastructure would enable systematic collection of material from patients before treatment start and regularly during treatment. This step is essential to:

- identify diagnostic biological markers (including genetic, hormonal, inflammatory markers) for disease
- identify differences between diagnosis groups
- follow biological changes induced by treatment
- conduct case studies on selected patients-validate new diagnostic instruments

“Uppsala Psychiatric Patient samples” (UPP) was initiated in October 2012 and is a longitudinal biobank with material and data from well over 800 individuals. The collection has three patient subgroups: i) a small scale level where individuals with extreme and atypical phenotypes are included and using exploratory methods and examined on a case-report basis ii) a large scale population based level which is important for determining the generalizability of theories developed in the small scale work and proposed by others and finally iii) collections in conjunction with specific treatment studies. This material is unique in Sweden, is extremely rare internationally and is expanding.



## ***Immunopsychiatry and the Biology of Severe Mental Illness***

**Participants:** Janet L. Cunningham (PI), Isak Sundberg, Fanny Söderqvist, Mikaela Syk, Mia Ramklint, Robert Bodén, Lisa Ekselius, Björn Nilsson, Joachim Burman

Other collaborators include: Prof. P Hellström at Sect. for Hepatology and Gastroenterology, UAS, Prof. B. Birnir (BB), Prof. H Schiöth and Assoc Prof. R Fredriksson at the BMC, Uppsala University. Assoc. prof. A Karlsson-Parra (AP) Sect. of Clin. Immunology, Uppsala University hospital, Uppsala, Prof. O Kämpe and Prof. M Schalling, at the CMM and Assoc. prof. S Erhardt Dept. of Physiology & Pharmacology at KI.

The overall aim is to identify and validate objective methods to diagnose the subgroup of patients with psychiatric symptoms and immune system involvement. In cases with immune system involvement we aim to first describe and follow the clinical symptoms and treatment response and then implement new treatment strategies.

*Project 1: Proinflammatory biomarkers in relation to Major depressive disorder, symptom severity, treatment response and prognosis.*

A bidirectional communication between the immune system and the brain is essential for normal brain functions such as initiating and regulating stress responses. Peripheral and central immunological signaling can induce changes in neuronal transmission that influence cognition, emotions and behavior both short term and long term. Pro-inflammatory cytokines induce “sickness behavior”, which includes lethargy, depression, anxiety, loss of appetite, sleepiness, hyperalgesia, reduction in grooming and failure to concentrate. It is estimated that 20% of the clinical population with depression has disturbances in their immusystem that contribute to disease development. Biomarkers to identify this subgroup of patients have not been established and it is still unclear how the inflammatory process is initiated; if it is in itself sufficient to cause depression and if current treatment is effective for this group. Both known and novel biomarkers are being evaluated using large scale screening platforms.

*Project 2: Autoimmunity and Severe Mental Illness*

“The Autoimmune Psychiatry Clinic” established in 2015 provides a multi disciplinary evaluation of atypical cases with suspected immune system involvement and when indicated, treatment. Myself and a neurologist perform consultations and clinical collaborations with rheumatology and gastroenterology are also established. Cases of autoimmune encephalitis are identified at the Section for Clinical Immunology at UAS and in collaboration with other international labs. Serum and cerebral spinal fluid is also examined for novel autoimmune targets. Potential targets and clinical significance are then validated using broader patient and cohorts from “Uppsala Psychiatric Patient samples” and controls.

## ***National Centre for Disaster Psychiatry (KcKP)***

**Participants** Kerstin Bergh Johannesson (PI to March 1<sup>st</sup> 2016), Filip Arnberg (PI from March 1st 2016), Kristina Bondjers, Martin Cernvall, Josefin Sveen, Mimmie Willebrand, Caisa Öster. Project assistants: Julia Heinsoo, Erik Johansson, Tobias Tenglin, Axelia Ahlund.

The National Centre for Disaster Psychiatry (Kunskapscentrum för Katastrofpsykiatri, KcKP) is established and supported by the National Board of Health and Welfare, and is located at the Department of Neuroscience at Uppsala University in close collaboration with the division of psychiatry at the Uppsala University Hospital. The main objective of the centre is to conduct and disseminate research on the psychological and psychiatric effects of disasters and psychological trauma. KcKP also is tasked with an advisory role towards the National Board of Health and Welfare and improving preparedness in health care and society to meet the psychosocial needs of those affected by severe accidents and disasters. The centre conducts research into various areas of psychotraumatology, including epidemiology, assessment, and interventions. Specific projects are listed briefly below.

***The long-term psychosocial consequences of a natural disaster***

Project leaders and researchers: Kerstin Bergh Johannesson, Filip Arnberg, Martin Cernvall, Josefin Sveen.

Collaborators: Professors Christina Hultman and Unnur Valdimarsdottir, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet.

This project concerns a longitudinal follow-up of a large cohort of Swedish survivors and home-staying relatives after the tsunami in Southeast Asia in 2004. The large group of afflicted individuals have created a unique opportunity to study the effects of exposure to a natural disaster, patterns of recovery, and risk factors for chronic symptoms. Potentially contributing factors such as traumatic bereavement, social support, personality traits and socio-demographic characteristics are studied with respect to the risk for maintenance of symptoms. Currently, active work within this project involves survey studies of the long-term trajectories of recovery and register-based studies on psychiatric morbidity. During 2016, preparations have taken place for a study of the genetics of posttraumatic stress disorder in this population.

***TRACES: Traumatic events in a longitudinal survey***

Project leader: Filip Arnberg. Researcher: Mimmie Willebrand. PhD student: Kristina Bondjers. Project assistant: Julia Heinsoo, Erik Johansson, Tobias Tenglin.

There is a lack of consensus about how PTSD should be conceptualized and diagnosed, as well as a scarcity of prospective studies on the impact of PTSD on functional impairment and health costs. This project aims to advance our understanding of posttraumatic stress by investigating the prevalence, course, and associations among stress reactions and related psychopathology, functional disability, and health-economic aspects. It also examines patterns of distress related to core symptoms and more peripheral symptoms, and their predictive validity for the course and severity of the disorder. To accomplish this task, a longitudinal study is in progress in which a cohort of adults with a recent experience of a traumatic event is recruited among patients in primary and outpatient psychiatric care as well as among individuals not seeking out healthcare services. A second aim of the project is to evaluate current and novel methods of assessing PTSD. This project thus provides valuable data on psychometric properties of several assessment methods commonly used in research and clinical settings.

***PTSD Coach: A smartphone app for posttraumatic stress after potentially traumatic events***

Project leader: Kerstin Bergh Johannesson. Researchers: Filip Arnberg, Martin Cernvall, Josefin Sveen, Kristina Bondjers. Project assistants: Julia Heinsoo, Axelia Ahlund.

There is scarce empirical evidence for early and effective interventions after traumatic events. PTSD Coach is a smartphone application which includes information about posttraumatic stress reactions, basic support for symptom management, and resources for finding care and support. The app was developed by the National Center for PTSD in collaboration with the Department of Defense's National Center for Telehealth and Technology in the United States. In this project, the PTSD Coach app is adapted to Swedish and its efficacy will be evaluated. A pilot study of the acceptability of the app and preliminary data on symptom change is underway. Aiming to increase the access to interventions for individuals who have been exposed to traumatic incidents, we examine whether the app can alleviate symptoms of posttraumatic stress among people with recent experiences of a potentially traumatic event in a randomized controlled trial. We also investigate the interplay between the components of the app and changes in posttraumatic stress symptoms.

### ***Variations in PTSD prevalence after disasters***

Project leader: Filip Arnberg.

Collaborator: Hugo Pedder, National Institute of Clinical Excellence, National Health Services, United Kingdom

This project aims to investigate to what extent the large variation in the prevalence rates of posttraumatic stress disorder among survivors from disasters can be explained by variation in disaster settings, study methods, or population characteristics. The study focuses on disasters worldwide during the period 1980 to 2013. Differences in the rates of PTSD in survivors from these large-scale traumatic events are assessed by multi-level meta-regression analytic strategies, in order to quantify the impact of various predictors. This project is underway and will potentially provide quantitative data that will inform future research as well as preparation and implementation of psychosocial services after disasters.

### ***Validation and standardization of a Swedish version of the Trauma Symptom Inventory 2 (TSI-2), a self-evaluation scale for adults for symptoms of complex traumatic experiences.***

Project leader: Kerstin Bergh Johannesson.

Collaborators: Associate professor Doris Nilsson, associate professor Marie Wadsby, Örjan Dahlström, Department of Psychology, University of Linköping.

Complex psychological trauma includes posttraumatic stress disorder (PTSD) as well as symptoms that highlight self-regulatory disturbances like dissociation, somatic distress, relational alienation and impulsiveness. Commonly used assessment instruments may be insufficient to properly assess this group of clients. There is a need for the development of reliable and valid assessment methods that can discriminate between PTSD and complex presentations of PTSD. The aim of the present study is to examine, in a Swedish setting, the psychometric properties such as reliability and validity of the TSI-2, a self-evaluation scale for symptoms related to complex traumatic experiences in four samples recruited from Linköping University, Akademiska sjukhuset, Tranås outpatient clinic, and homecoming Swedish soldiers.

### **Publications 2014-2016**

In press

1. Makris GD, Reutfors J, Andersen M, White RA, Ekselius L, Papadopoulos FC. Season of treatment initiation with antidepressants and suicidal behavior: A population-based cohort study in Sweden. *Journal of Affective Disorders*, on press.

2. Bodén R, MD, Persson J, Wall A, Lubberink M, Ekselius L, Larsson EM, Antoni G. Striatal Phosphodiesterase 10A and Medial Prefrontal Cortical Thickness in Patients with Schizophrenia - a PET and MRI study. *Translational Psychiatry*, in press.
3. Condén P, Wagner P, Leppert J, Ekselius L, Åslund C. Type D personality as an independent risk factor for recurrent myocardial infarction and all-cause mortality in addition to the Framingham risk score – A prospective cohort-study. *European Journal of Preventive Cardiology*, in press.
4. Folke F, Hursti T, Kanter J, Arinell H, Tungström S, Söderberg P, Ekselius L. Exploring the relation between activities and emotional experience with a diary in a mental health inpatient setting. *International Journal of Mental Health Nursing*, in press.
5. Kask J, Ramklint M, Kolia N, Panagiotakos D, Ekblom A, Ekselius L, Papadopoulos FC. Anorexia nervosa in males: Excess mortality and psychiatric comorbidity in 609 Swedish inpatients. *Psychological Medicine*, in press.
6. Edvinsson A, Brann E, Hellgren C, Freyhult E, White R, Kamali-Moghaddam M, et al. Lower inflammatory markers in women with antenatal depression brings the M1/M2 balance into focus from a new direction. *Psychoneuroendocrinology*, in press.
7. Cunningham JL, Zanzi M, Willebrand M, Ekselius L, Ramklint M. No regrets: Young adult patients in psychiatry report positive reactions to biobank participation. *BMC Psychiatry*, in press.
8. Sveen J, Willebrand M. Feelings of guilt and embitterment in parents of children with burns and its associations with depression. *Journal of Burn Care and Research*, in press.

2016

9. Gauffin E, Öster C, Sjöberg F, Gerdin B, Ekselius L. Health-related quality of life (EQ-5D) early after burn injury predicts long-term post-burn pain. *Burns* **2016**;42:1781-1788.
10. Soderquist F, Janson ET, Rasmusson AJ, Ali A, Stridsberg M, Cunningham JL. Melatonin Immunoreactivity in Malignant Small Intestinal Neuroendocrine Tumours. *PLoS One*. **2016**;11(10):e0164354.
11. Pisanu C, Preisig M, Castela E, Glaus J, Cunningham JL, Del Zompo M, et al. High leptin levels are associated with migraine with aura. *Cephalalgia*. **2016**.
12. Kask J, Ekselius L, Brandt L, Kolia N, Ekblom A, Papadopoulos FC. Mortality in Women With Anorexia Nervosa: The Role of Comorbid Psychiatric Disorders. *Psychosom Med*. **2016** Oct;78(8):910-919.
13. Georgakis MK, Papadopoulos FC, Protogerou AD, Pagonari I, Sarigianni F, Biniaris-Georgallis SI, Kalogirou EI, Thomopoulos TP, Kapaki E, Papageorgiou C, Papageorgiou SG, Tousoulis D, Petridou ET. Comorbidity of Cognitive Impairment and Late-Life Depression Increase Mortality: Results From a Cohort of Community-Dwelling Elderly Individuals in Rural Greece. *J Geriatr Psychiatry Neurol*. **2016** Jul;29(4):195-204.
14. Esscher A, Essén B, Innala E, Papadopoulos FC, Skalkidou A, Sundström-Poromaa I, Högberg U. Suicides during pregnancy and 1 year postpartum in Sweden, 1980-2007. *Br J Psychiatry*. **2016** May;208(5):462-9.
15. Petridou ET, Kousoulis AA, Michelakos T, Papatoma P, Dessypris N, Papadopoulos FC, Stefanadis C. Folate and B12 serum levels in association with depression in the aged: a systematic review and meta-analysis. *Aging Ment Health*. **2016** Sep;20(9):965-73.

16. Arnberg FK, Lekander M, Morey JN, Segerstrom SC. Self-rated health and interleukin 6: Longitudinal relationships in older adults. *Brain Behav Immun.* **2016**;54:226-32.
17. Bergdahl L, Broman JE, Berman AH, Haglund K, von Knorring L, Markström A. Auricular Acupuncture and Cognitive Behavioural Therapy for Insomnia: A Randomised Controlled Study. *Sleep Disord.* **2016**:70.
18. Björkenstam C, Gerdin B, Berlin M, Ekselius L, Björkenstam E. Suicide Risk and Suicide Method in Patients with Personality Disorders. *Journal of Psychiatric Research* **2016**:83:29-36.
19. Danielsson K, Jansson-Fröjmark M, Broman J-E, Markström A, Cognitive behavioral therapy as an adjunct treatment to light therapy for delayed sleep phase disorder in young adults: A randomized controlled feasibility study. *Behavioral Sleep Medicine* 2016;14(2):212-232.
20. Danielsson K, Jansson-Fröjmark M, Broman J-E, Markström A. Light therapy with scheduled risetimes in young adults with delayed sleep phase disorder Therapeutic outcomes and possible predictors. *Behavioral Sleep Medicine* 2016 Aug 11:1-15.
21. Danielsson K, Markström A, Broman J-E, von Knorring L, Jansson-Fröjmark M. Delayed sleep phase disorder in a Swedish cohort of young adults and adolescents: Prevalence and associated factors. *Chronobiology International* 2016;33(10):1331-1339.
22. Frick A, Åhs F, Palmquist ÅM, Pissioti A, Wallenquist U, Fernandez M, Jonasson M, Appel L, Frans Ö, Lubberink M, Furmark T, von Knorring L, Fredrikson M. Overlapping expression of serotonin transporters and neurokinin-1 receptors in posttraumatic stress disorder: a multi-tracer PET study. *Molecular Psychiatry* **2016**:21:1323. doi: 10.1038/mp.2016.159.
23. Hörberg N, Kouros I, Ekselius L, Ramklint M. The Swedish version of the Sheehan Disability Scale – a valid and brief measure of functioning. *European Journal of Person Centered Health Care* **2016** Vol 4 Issue 1 PP1-7
24. Larsson K, Nehlin C: Screening accuracy of brief alcohol screening instruments in a general hospital setting. *Scandinavian Journal of Public Health*, **2016**; 44: 599–603.
25. Makris G, Reutfors J, Larsson R, Isacson G, Ösby U, Ekblom A, Ekselius L, Papadopoulos F. Serotonergic medication enhances the association between suicide and sunshine. *Journal of Affective Disorders* **2016**:189:276-281
26. Jansson-Fröjmark M, Danielsson K, Markström A, Broman J-E. Developing a cognitive behavioral therapy manual for delayed sleep phase syndrome. *Cognitive Behavioral Therapy* 2016:45 (6):518-532.
27. Malmström E, Hörberg N, Kouros I, Haglund K, Ramklint M Young patients' views about provided psychiatric care.. *Nord J Psychiatry.* **2016** Oct;70(7):521-7
28. Nehlin C, Nyberg F, Jess K: Brief intervention in primary care for at-risk gambling: A pilot study. *Journal of Gambling Studies.* **2016**.
29. Nilsson G, Hilgard J, Lekander M, Arnberg FK. Effects of bias on the association between post-traumatic stress disorder and interleukin-6 [letter]. *Lancet Psychiatry*, **2016**:3(3);200-1.
30. Nilsson B, Holm H, Ekselius L. Karolinska Scales of Personality, cognition and psychotic symptoms in patients with schizophrenia and healthy controls. *Nordic Journal of Psychiatry*, **2016**:70:53-61.
31. Parling T, Cernvall M, Ramklint M, Holmgren S, Ghaderi A. A randomised trial of Acceptance and Commitment Therapy for Anorexia Nervosa after daycare treatment, including five-year follow-up. *BMC Psychiatry.* **2016** Jul 29; 16:272.

32. Sundberg I, Ramklint M, Stridsberg M, Papadopoulos FC, Ekselius L, Cunningham JL. Salivary Melatonin in Relation to Depressive Symptom Severity in Young Adults. *PLoS One*. **2016** Apr 4;11(4).
33. Sveen J, Andersson G, Buhrman B, Sjöberg F, Willebrand M. Internet-based information and support program for parents of children with burns: A randomized controlled trial. *Burns*. **2016**. Epub ahead of print.
34. Sveen J, Arnberg FK, Arinell H, Johannesson KB. The role of personality traits in trajectories of long-term posttraumatic stress and general distress six years after the tsunami in Southeast Asia. *Pers Individ Dif*. **2016**:97, 134-139.
35. Sveen J, Bondjers K, Willebrand M. Psychometric properties of the PTSD Checklist for DSM-5: a pilot study. *Eur J Psychotraumatol*. **2016**:7. doi: 10.3402/ejpt.v7.30165
36. Sveen J, Pohlkamp L, Öhlén J, Sandberg J, Brandänge K, Gustavsson P. Posttraumatic Stress among Not-Exposed Traumatically Bereaved Relatives after the MS Estonia Disaster. *PLoS One*. **2016**:11:e0166441
37. Syk M, Ramklint M, Fredriksson R, Ekselius L, Cunningham J. Elevated total plasma-adiponectin is stable over time in young women with bulimia nervosa. *European Psychiatry* **2016**:41:30-36.
38. Wahlberg Å, Sachs MA, Johannesson KB, Hallberg G, Jonsson M, Svanberg AS, Högberg U. Self-reported exposure to severe events on the labour ward among Swedish midwives and obstetricians: A cross-sectional retrospective study. *Int J Nurs Stud*. **2016**. Epub ahead of print.
39. Westling S, Ramklint M. Självskadebeteende vanligt även utan personlighetssyndrom - Felaktig koppling trolig orsak till överdiagnostik av borderline-personlighetssyndrom. *Lakartidningen*. **2016** Dec 6;113.
40. Willebrand M, Sveen J. Injury-related fear-avoidance and symptoms of posttraumatic stress in parents of children with burns. *Burns*. **2016**:42:414-20
41. Willebrand M, Sveen J. Perceived support in parents of children with burns. *Gen Hosp Psychiatry* **2016**;38:105-8.
42. Öster C, Arinell H, Nehlin C: The Drinking Motives Questionnaire among Swedish psychiatric patients: An exploration of the four-factor structure. *Drug and Alcohol Review*. **2016**.

#### 2015

43. Arnberg FK, Bondjers K, Sveen J. Panel discussion: early interventions after traumatic events. *Eur J Psychotraumatol*, **2015**:6:28636.
44. Arnberg FK, Gudmundsdottir R, Butwicka A, Fang F, Lichtenstein P, Hultman CM, Valdimarsdottir UA. Psychiatric disorders and suicide attempts in Swedish tsunami survivors: A 5-year matched cohort study. *Lancet Psychiatry*, **2015**:2, 817-24.
45. Arnberg FK, Hultman CM, Michel PO, Lundin T. Posttraumatic stress in survivors 1 month to 19 years after an airliner emergency landing. *PLoS ONE*, **2015**:10(3): e0119732
46. Arnberg FK, Hultman CM, Valdimarsdottir UA. Cohort study on Swedish survivors of 2004 southeast Asia tsunami - issues related to registration and definitions of mental disorders: Authors' reply [letter]. *Lancet Psychiatry*, **2015**:2, 962-3.
47. Björkenstam E, Björkenstam C, Holm H, Gerdin B, Ekselius L. Excess cause-specific mortality in inpatient-treated individuals with a diagnosis of personality disorder: a 25-year nationwide population-based study in Sweden. *British Journal of Psychiatry*, **2015**:207:339-345.

48. Björkenstam E, Björkenstam C, Holm H, Gerdin B, Ekselius L. Excess cause-specific mortality in out-patients with personality disorder. *British Journal of Psychiatry Open* **2015**;1:54-55.
49. Bodén R, Molin E, Jernberg T, Kieler H, Lindahl B, Sundström J. Myocardial infarction survival in patients with and without severe mental illness - a nationwide cohort study, *J Intern Med*, **2015** June; 277(6):727-736
50. Folke F, Hursti T, Söderberg P, Tungström S, Ekselius L, Kanter JW. Behavioral activation between acute inpatient and outpatient psychiatry: description of a protocol and a pilot feasibility study. *Cognitive and Behavioral Practice*, in press.
51. Folke F, Hursti T, Tungström S, Söderberg P, Kuutmann K, Kanter JW, Ekselius L. Behavioral activation in acute inpatient psychiatry: a multiple baseline evaluation. *Journal of Behavior Therapy and Experimental Psychiatry* **2015**;46:170-81.
52. Gauffin E, Öster C, Gerdin B, Ekselius L. Prevalence and prediction of prolonged pruritus after severe burns. *Burn Care Res.* **2015**;36:405-13.
53. Hallgren, S., Fredriksson, A., and Viberg, H. More signs of neurotoxicity of surfactants and flame retardants - Neonatal PFOS and PBDE 99 cause transcriptional alterations in cholinergic genes in the mouse CNS. *Environmental toxicology and pharmacology* **2015**;40, 409-416.
54. Hasan AI, Falkai P, Wobrock T, Lieberman J, Glenthøj B, Gattaz WF, Thibaut F, Möller HJ, Altamura A, Andreasen N, Barnes TR, Ceylan M, Ollivier JC, Crow T, Danaci AE, David A, Davidson M, Deakin B, Elkis H, Farde L, Gaebel W, Gallhofer B, Gerlach J, Hirsch SR, Hojajj CR, Hwang M, Hwo HG, Jablensky AV, Jarema M, Kane J, Kojima T, Larach V, Lieberman J, Meltzer H, Mosolov S, Moussaoui D, Olié JP, Palha AP, Sarandöl A, Sato M, Sauer H, Schooler N, Taneli B, von Knorring L, Weinberger D, Yamawaki S. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia. Part 3: Update 2015 Management of special circumstances: Depression, Suicidality, substance use disorders and pregnancy and lactation. *World J Biol Psychiatry.* **2015** Apr;16:142-70.
55. Iliadis SI, Koulouris P, Gingnell M, Sylvén SM, Sundström-Poromaa I, Ekselius L, Papadopoulou FC, Skalkidou A. Personality and risk for postpartum depressive 1 symptoms. *Archives of Women's Mental Health*, **2015**;18:539-46.
56. Johannesson KB, Arinell H & Arnberg FK. Trajectories of long-term posttraumatic stress in a cohort of survivors from a natural disaster in comparison with a non-exposed sample. *J Anxiety Disord*, **2015**;36, 15-24.
57. Lee, I., Eriksson, P., Fredriksson, A., Buratovic, S., and Viberg, H. Developmental neurotoxic effects of two pesticides: Behavior and neuroprotein studies on endosulfan and cypermethrin. *Toxicology* **2015**;335, 1-10.
58. Lee, I., Eriksson, P., Fredriksson, A., Buratovic, S., and Viberg, H. Developmental neurotoxic effects of two pesticides: Behavior and biomolecular studies on chlorpyrifos and carbaryl. *Toxicology and applied pharmacology* **2015**;288, 429-438.
59. Lekander M, Arnberg FK, Segerstrom S. Longitudinal relationship between inflammation and poor self-rated health in elderly. *Brain Behav Immun*, **2015**;49S: e37
60. Mellekjaer L, Papadopoulou FC, Pukkala E, Ekblom A, Gissler M, Christensen J, Olsen JH. Cancer Incidence among Patients with Anorexia Nervosa from Sweden, Denmark and Finland. *PLoS One.* **2015** May 22;10(5):e0128018.
61. Mårtensson B, Pettersson A, Berglund L, Ekselius L. Bright White Light Therapy in Depression: A Critical Review of the Evidence. *Journal of Affective Disorders*, **2015**;182:1-7.

62. Nehlin C, Nyberg F, Öster C: The patient's perspective on the link between ADHD and substance use: A qualitative interview study. *Journal of Attention Disorders* **2015**; 19(4), 344-351
63. Nilsson BM, Hultman CM, Ekselius L. Cognition and autonomic function in schizophrenia: Inferior cognitive test performance in electrodermal and niacin skin flush non-responders. *European Psychiatry*, **2015**;30:8-13.
64. Nordanskog P, Hulten M, Landen M, Lundberg J, von Knorring L, Nordenskjöld A. Electroconvulsive therapy in Sweden 2013. Data from the National Quality Register for ECT. *Journal of ECT* **2015** Dec;31(4):263-73.
65. Olsson E, Westman J, Sudic Hukic D, Eriksson SV, Edman G, Bodén R, Jedenius E, Reutfors J, Berntsson A, Hilding A, Schalling M, Östenson CG, Ösby U. Diabetes and glucose disturbances in patients with psychosis in Sweden. *BMJ Open Diab Res Care* **2015**;3:1.
66. Petterson A, Bengtsson Boström K, Gustavsson JP, Ekselius L. Which instruments to support diagnosis of depression have sufficient accuracy? - a systematic review. *Nordic Journal of Psychiatry* **2015**;69:497-508.
67. Ramirez A, Ekselius L, Ramklint M. Depression in young adult psychiatric outpatients: delimiting early onset. *Early Intervention in Psychiatry*, **2015**;9:108-17.
68. Schalling M, Engberg, O. Andreassen, S. Erhardt, J. Cunningham, I. Agartz, H. Fatouros Bergman. Nya rön om schizofreni kan ge ny diagnostik och behandling. *Läkartidningen* **2015**.
69. Silén M, Haglund K, Hansson MG, Ramklint M. (2015) Ethics rounds do not improve the handling of ethical issues by psychiatric staff. *Nord J Psychiatry*. Jan 16:1-8.
70. Sonby K, Skordas K, Olofsdotter S, Vadlin S, Nilsson KW, Ramklint M. Validation of the World Health Organization Adult ADHD Self-Report Scale for adolescents. *Nord J Psychiatry*. **2015**;69(3): 216-223.
71. Sveen J, Andersson G, Ekselius L, Sjöberg F, Buhrman B, Willebrand M. Internet-based information and self-help program for parents of children with burns: Study protocol for a randomized controlled trial. *Internet Interventions* **2015**;2(4):367-371.
72. Sveen J. & Öster C. Alcohol Consumption After Severe Burn: A Prospective Study. *Psychosomatics*, **2015**;56:390-6.
73. Söderquist F, Hellström PM, Cunningham J. Human gastroenteropancreatic expression of melatonin and its receptors MT1 and MT2. *Plos One* Mar 30;10(3):e0120195. doi: 10.1371/journal.pone.0120195. eCollection **2015**.
74. White RA, Azrael D, Papadopoulos FC, Lambert GW, Miller M. Does suicide have a stronger association with seasonality than sunlight? *BMJ Open*. **2015** Jun 3;5(6):e007403.
75. Öster C, Bäckström S, Lantz I, Ramklint M. Psychiatric patients perspectives of student involvement in their care. *BMC Medical Education*. **2015**;15:69, doi: 10.1186/s12909-015-0352-z.
76. Öster C. & Sveen J. Is sexuality a problem? A follow-up of severe burn patients 6 months to seven years post injury. *Burns*. **2015** Nov;41(7):1572-8

2014

77. Archer T, Garcia D, Fredriksson A. Restoration of MPTP-induced deficits by exercise and Milmed(R) co-treatment. *Peer J* **2014**;2, e531.
78. Arnberg FK, Linton SJ, Hultcrantz M, Heintz E, Jonsson U. Internet-delivered psychological treatments for mood and anxiety disorders: a systematic review of their efficacy, safety, and cost-effectiveness. *PLoS One* **2014**; 9: e98118.



79. Arnberg FK, Michel PO, Johannesson KB. Properties of Swedish posttraumatic stress measures after a disaster. *Journal of Anxiety Disorders* **2014**; 28: 402-409.
80. Bergdahl L, Berman A.H, Haglund K. Patients' experience of auricular acupuncture during protracted withdrawal. *J Psychiatr Ment Health Nurs*. **2014**, 21(2): 163-169
81. Björkenstam C, Björkenstam E, Hjern A, Bodén R, Reutfors J. Suicide in first episode psychosis: a nationwide cohort study, *Schiz Res*. **2014**:157:1-7.
82. Bodén R, Wettermark B, Brandt L, Kieler H. Factors associated with pregabalin dispensing at higher than the approved maximum dose. *Eur J Clin Pharm*, **2014**:70:197-204.
83. Brain C, Sameby B, Allerby K, Quinlan P, Joas E, Lindström E, Burns T, Waern M. Stigma, discrimination and medication adherence in schizophrenia: Results from the Swedish COAST study. *Psychiatry Res*. **2014**:Oct 23;220(3):811-817.
84. Buratovic S, Stenerlow B, Fredriksson A, Sundell-Bergman S, Viberg H, Eriksson P. Neonatal exposure to a moderate dose of ionizing radiation causes behavioural defects and altered levels of tau protein in mice. *Neurotoxicology* **2014**;45, 48-55.
85. Buratovic S, Viberg H, Fredriksson A, Eriksson P. Developmental exposure to the polybrominated diphenyl ether PBDE 209: Neurobehavioural and neuroprotein analysis in adult male and female mice. *Environmental toxicology and pharmacology* **2014**:38, 570-585.
86. Bäckström J, Öster C, Ekselius L, Gerdin B, Willebrand M. Health related quality of life in family members of patients with burns. *J Burn Care Res*. **2014**:35:3.
87. Condén E, Rosenblad A, Ekselius L, Åslund C. Prevalence of Type D Personality and factorial and temporal stability of the DS14 after myocardial infarction in a Swedish Population. *Scandinavian Journal of Psychology*, **2014**:55:601-10.
88. Ekeblad F, Gerdin B, Öster C. Impact of personality disorders on health-related quality of life one year after burn injury. *Disability & Rehabilitation*. **2014**: 25:1-7
89. Eriksson H, Haglund K, Leo-Swenne C, Arakelian E. Patients' experience of post operative health related to cytoreductive surgery and hyperthermic intraoperative chemotherapy. *J Clin Nurs*. **2014**:23: 201-210.
90. Johannesson KB. Erfarenheter från svenska katastrofer: vad har varit viktigt för drabbade? *Omsorg: Nordisk tidskrift för palliativ medicin*, **2014**:1:22 – 25.
91. Jonsson U, Alaie I, Parling T, Arnberg FK. Reporting of harms in randomized controlled trials of psychological interventions for mental and behavioral disorders: A review of current practice. *Contemp Clinical Trials* **2014**:38: 1-8.
92. Jüris L, Larsen HC, Andersson G, Ekselius L. Cognitive behaviour therapy for hyperacusis: A randomized controlled trial. *Behaviour Research and Therapy*, **2014**:24:30-37.
93. Karamanis G, Skalkidou A, Tsakonas G, Brandt L, Ekbom A, Ekselius L, Papadopoulou FC. Cancer incidence and mortality patterns in women with anorexia nervosa. *International Journal of Cancer*. **2014**:134:1751-7.
94. Källstrand J, Lewander T, Baghdassarian E, Nielzén. A new method for analyzing auditory brain-stem response waveforms using a moving-minimum subtraction procedure of digitized analog recordings. *Neuropsychiatr Dis Treat* **2014 Jun** 6;10:1011-6.
95. Nehlin C, Nyberg F, Öster C: The patient's perspective on the link between ADHD and substance use: A qualitative interview study. *Journal of Attention Disorders* **2015**; 19(4), 344-351.
96. Odellius BC, Ramklint M. (2014) Clinical Utility of Proposed Non-Suicidal Self-Injury Diagnosis – a pilot study. *Nordic Journal of Psychiatry*, 68(1): 66-71.

97. Ramirez A, Ekselius L, Ramklint M. (2014) Axis IV – psychosocial and environmental problems – in the DSM-IV. *Journal of Psychiatric and Mental Health Nursing* 20(9): 768-775
98. Scheen L, Brandt L, Bodén R, Tiihonen J, Andersen M, Kieler H, Reutfors J. Predictors for initiation of pharmacological prophylaxis in patients with newly diagnosed bipolar disorder - a nationwide cohort study, *J Affect Disord*, 2014;172:204-210.
99. Sharma H S, Ponten E, Gordh T, Eriksson P, Fredriksson A, Sharma A. Propofol Promotes Blood-Brain Barrier Breakdown and Heat Shock Protein (HSP 72 kd) Activation in the Developing Mouse Brain. *CNS & neurological disorders drug targets* 2014;13, 1595-1603.
100. Silén M, Ramklint M, Hansson MG, Haglund K. 2014. Ethics rounds: An appreciated form of ethics support. *Nurs Ethics*. Dec 18. [Epub ahead of print]
101. Stålberg G, Ekselius L, Lindström LH, Larhammar D, Bodén R. Neuropeptide Y, social function and long-term outcome in schizophrenia. *Schiz Res*. 2014;156:223-7.
102. Sveen J, Sjöberg F, Öster C. Health-related quality of life in Swedish pediatric burn patients and associations with burn and family characteristics. *Burns*, 2014;40:5:987-94.
103. Wettermark B, Brandt L, Kieler H, Bodén R. Pregabalin is increasingly prescribed for neuropathic pain, generalized anxiety disorder and epilepsy but many patients discontinue treatment. *Int J Clin Pract*. 2014;Jan;68(1):104-10.
104. Öster C, Hensing I, Löjdström T, Sjöberg F, Willebrand M. Parents' perceptions of adaptation and family life after burn injuries in children. *J Pediatr Nurs* 2014;29:606-13
105. Öster C, Sveen J. The Psychiatric sequelae of burn injury. *General Hospital Psychiatry* 2014;36:516–522.

### **Agencies that support the work/ Funding**

The Ekhaga Foundation  
 The Fredrik and Ingrid Thuring Foundation  
 The National Board of Health and Welfare  
 The Nicke and Märta Nasvell Foundation  
 The Regional Research Council in Uppsala-Örebro  
 The Research Council of the Swedish Alcohol Retail Monopoly  
 The Selanders Foundation  
 The Swedish Research Council  
 The Swedish Society of Medicine  
 The Söderström-Königska Foundation  
 The Uppsala County Council (ALF)  
 The Uppsala University Hospital

### **Awards**

Josefin Bäckström; Best oral presentation, European Burn Association, Hannover 2016

## Child & Adolescent Psychiatry

**Group leader: Niklas Långström, Professor (from July 1<sup>st</sup> 2016). Mia Ramklint, Associate Professor (from January 1<sup>st</sup> to June 30<sup>th</sup> 2016)**

### **Members of the group during 2016:**

Niklas Långström, Professor	Sandra Löfving-Gupta, PhD student
Ulf Jonsson, Associate professor	Abdulbaghi Ahmad, Associate professor
Iman Alaie, PhD student	Nezar Ismet Taib, PhD student
Hannes Bohman, PhD	Viveka Sundelin Wahlsten, Associate professor
Mia Ramklint, Associate professor	Najah Khalifa, PhD
Vendela Zetterqvist, PhD	Birgitta Johansson Niemelä, PhD
Johan Isaksson, PhD	Frank Lindblad, Professor emeritus
Jenny Meyer, PhD student	Aivar Päären, PhD
Anastasia Karvouni, MD	Anne-Liis von Knorring, Professor emerita
Mimmie Willebrand, Professor	
Vladislav Ruchkin, Associate professor	

### **Introduction**

The research group in child and adolescent psychiatry addresses the development of psychopathology or psychiatric ill-health in children and adolescents, and how psychopathology can be predicted, identified and treated effectively. The overarching theoretical model sees individual genetic and other biological factors, familial and neighborhood environments and more macrosocial risk and protective factors co-occur and interact in both development and desistance of psychiatric symptoms in the young.

Risk and protective factors are studied in both epidemiological and clinical studies. The association of adolescent psychiatric symptomatology to various future outcomes are investigated with long-term follow-up designs. Twin and sibling control study designs are employed to better delineate causal risk factors. Studied risk groups include traumatized children, children who live in psychosocially disadvantaged environments and those with neuropsychiatric disorders. The research group is also studying potential effects of interventions for defined risk groups. The studies are conducted in national and international collaborations with other research groups.

### ***Experience of stress, emotional regulation and physiological stress reactions***

**Participants:** Johan Isaksson (project leader), PhD; Vladislav Ruchkin, Associate professor; Mia Ramklint, Associate professor; Frank Lindblad, Professor emeritus; Jenny Meyer, PhD student; Anastasia Karvouni, MD

**Collaborators:** Kent W Nilsson, Centre for Clinical Research, Västerås; Ulf Högberg, Dept. of Women's and Children's Health; Maria Hallerbäck Unenge, Gillberg Centre, Gothenburg University

In this project, we study the physiological regulation and experience of stress in children. We examine how life events during pregnancy and the early years of life are associated with child physiological stress regulation and long-term mental well-being. We specifically study children with attention deficit hyperactivity disorder (ADHD) and posttraumatic stress

disorder (PTSD) and how they experience and react to stress.

Our research suggests that young people with ADHD, particularly girls, rate their stress levels as higher than their non-ADHD peers. This is possibly a consequence of symptom effects on everyday functioning or a result of stress regulation system inflexibility.

The body reacts to stress partly through the activation of the sympathetic nervous system, our "fight or flight"-system, and partly by a hormonal response conveyed through the pituitary to the adrenal glands where the stress hormone cortisol is released; the HPA-axis. Regarding the physiological stress response in children with ADHD, we identified lower cortisol levels in the HPA-axis, previously found in children with PTSD.

In our ongoing projects, we continue to explore potential differences between boys and girls with ADHD. We attempt to examine the effectiveness of psychological treatment for ADHD and the perceived associated stress. We also try to identify stress reactions related to PTSD as well as biomarkers for PTSD.

### ***Outcomes of Adolescent Depression***

**Participants:** Ulf Jonsson, Associate professor (project leader), Anne-Liis von Knorring, Professor emerita, Hannes Bohman, PhD, Aivar Päären, PhD, Iman Alaie, PhD student

**Collaborators:** Tord Næssén, Professor, Department of Women's & Children's Health, Margareta Möller, UCF, Örebro, Inna Feldman, Department of Women's & Children's Health

In this long-term follow-up of depressed teenagers, we study the socio-economic outcomes on mental and physical health among those who suffered from a depressive disorder in adolescence.

The follow-up is based on an epidemiological survey of affective disorders comprising all 16-17 year-old high school students in Uppsala during the early 1990s. Participants were followed-up until age 30-33 years, and continued follow-ups are planned for the participants who are currently in their 40s. The formerly depressed individuals are compared to matched, non-depressed controls.

The research team has been able to show, among other things, that teenage depression is related to poorer adult mental and physical health, lower education and more psychosocial stress.

### ***Risk factors for the development of child psychiatric problems***

**Participants:** Vladislav Ruchkin, Associate professor (project leader), Mimmie Willebrand, Professor, Johan Isaksson, PhD, Frank Lindblad, Professor emeritus, Sandra Löfving-Gupta, PhD student

**Collaborators:** Elena Grigorenko, Child Study Center, Yale Medical School, USA; Roman Kuposov, Child Psychiatric Unit, Tromsø University, Norway; Denis Sukhodolsky, Child Study Center, Yale Medical School, USA; Andrew Stickley, Tokyo University, Japan; Marek Blatný, National Academy of Science, Brno, Czech Republic; Michal Hrdlička, Dept of Child

Psychiatry, Charles University, Prague, Czech Republic; Britt af Klinteberg, Stockholm University

We address risk factors for the development of antisocial behavior and alcohol abuse and, specifically, such development following trauma. We focus a particularly vulnerable group of children, i.e. institutionalized children, and perform cross-cultural comparisons.

Based on a bio-psycho-social model, we conceptualize the development of psychopathology following an interaction between biological, psychological and social risk factors. Such risk factors can include genetic risk, emotional attachment patterns, exposure to traumatic events and psychosocial adversities such as poverty, crime and substance abuse.

Our research is characterized by broad methodological variety, from genetic analyses to psychiatric epidemiological studies and clinical child psychiatric studies.

### ***Mental illness and antisocial behaviour: Causal factors, developmental trajectories, and treatment development***

**Participants:** Niklas Långström, Professor (project leader); Martin Lardén, PhD student (KI); Kelly Babchishin, PhD; post-doc (KI/University of Ottawa)

**Collaborators:** Pia Enebrink, Dept of Psychology, KI; Paul Lichtenstein, Dept Medical Epidemiology & Biostatistics, KI; Seena Fazel, Dept of Psychiatry, Oxford University, UK; Mats Forsman and Lena Lundholm, Swedish Correctional Services R&D; Kelly Donahue, Dept of Pediatrics, Indiana University Medical School, USA.

This project complements *Risk factors for the development of child psychiatric problems* by Ruchkin and co-workers. We study developmental pathways, causal risk factors, concurrent difficulties such as substance use disorders, and various outcomes of mental illness in children and young people.

Our main interest is in the development and persistence of violent and sexual abusive behaviours and we use methods such as twin and sibling control designs to manage confounding and delineate true causal risk factors from risk markers. We collaborate with epidemiologists on large prospective cohorts with young twins that are followed prospectively with repeated data collection waves and data from self-reports, parents, and registers.

Additionally, we conduct observational studies of the effects of pharmacological treatment on violence risk, controlling for stable, within-individual risk factors. These studies use interlinked, prospective national registers to allow well-controlled, quasi-experimental effect studies also of crime-preventive psychological interventions against disruptive, aggressive behaviours. Smaller RCTs of psychological interventions and promising treatment components are also conducted.

### ***Children with traumatic experiences***

**Participants:** Abdulbaghi Ahmad, Associate professor (project leader); Viveka Sundelin Wahlsten, Associate professor; Nezar Ismet Taib, PhD student

**Collaborators:** Matthew Hodes, Imperial College London, UK; Jacek Kot, Medical University of Gdansk, Poland; Ana de Dios and Sergio Calvo, Perry's partners, Madrid, Spain; Aras Ahmad Seddiq, Azadi Center for Cardiac Diseases and Surgery, Duhok, Iraq; Nashmeel Rasool Hamah Ameen, MHPSS coordinator, Heartland Alliance International; As Sulaimaniyah, Iraq; Jan Ilhan Kizilhan, Baden-Wurtemberg Cooperative State University, Germany; Mamou Farhan Othman, Institute of Psychotherapy and Psychotraumatology, University of Duhok, Iraq.

We are studying children with traumatic experiences during their upbringing, their perception of these events, their perspective on trauma in relation to that of adults, and how they cope with these experiences. We also study children with special needs such as Autism Spectrum Disorder (ASD). Several methods for investigation, prevention and treatment have been developed within the frame of this research and collaboration network.

Based on a salutogenic perspective, we map risk and protective factors for the development of posttraumatic psychopathology such as posttraumatic stress disorder (PTSD). We study the effect of preventive methods in risk groups and early treatment strategies for children with signs of impaired adaptation. The research is carried out in collaboration with the University of Duhok in Iraqi Kurdistan, where child victims of terror and war are identified, investigated and treated. Within the project, assessment instruments such as Genogram, HUTQ-C and PTSS-C were developed to assess children's traumatization and possible intervention effects.

A Crisis Intervention Program for Children and Adolescents (CIPCA) to prevent posttraumatic psychopathology has been developed. It was implemented for the first time at the Metin Health House for Child Mental Health in Duhok, Iraq, in the aftermath of the war with Islamic State (IS) in Iraq, August 2014. A one-year follow-up showed promising results, and a two-year follow-up is currently ongoing.

### **Publications 2014-2016**

Taib NI & Ahmad A. Psychiatric Comorbidity among Street Children in Duhok. *Clinical Medicine; Pediatrics* 2014;10 (8):6-11.

Taib NI & Ahmad A. Psychiatric morbidity among street children in Duhok. *Clinical Medicine Insights: Pediatrics* 2014; 8: 11–16.

Ahmad A. Crisis intervention program for children and adolescents (CIPCA) to prevent posttraumatic psychopathology, preliminary report. *Duhok Med J* 2014;8(2):1-11.

Taib NI & Ahmad A. Mental illness among children working on the streets compared with school children in Duhok. *Psychology* 2015;6:1421-1426.

Johansson Niemelä B, & Tjernström B. Somatic and mental health after leg lengthening with Ilizarov procedure- a clinical report of a prospective study with a 10-year follow-up. *J Depression & Anxiety* 2014,3:2.

Karlsson E, Lindblad F, Ruchkin V. Risk and protective factors for peer victimization: A one-year follow up study of urban American students. *European Child & Adolescent Psychiatry*. 2014;23:773-81.

Isaksson J, Nilsson KW, Lindblad F. The Pressure-Activation-Stress scale in relation to ADHD and cortisol. *Eur Child Adolesc Psychiatry*. 2014 Apr 16. [Epub ahead of print]

Löfving-Gupta S, Lindblad F, Stickley A, Schwab-Stone M, Ruchkin V. Community violence exposure and severe posttraumatic stress in suburban American youth: risk and protective factors. *Soc Psychiatry Psychiatr Epidemiol*. 2014 Oct 10.

Winzer R, Lindblad F, Sorjonen K, Lindberg L. Positive versus negative mental health in emerging adulthood: a national cross-sectional survey. *BMC Public Health*. 2014 Dec 1;14:1238.

Ruchkin, V., Schwab-Stone, M. A longitudinal study of somatic symptoms in adolescents: The role of internalizing psychopathology and somatic anxiety. *Journal of Youth and Adolescence* 2013, Jun 7 [Epub ahead of print], 2014 43:834–845.

Wiklund, G., Ruchkin, V.V., Koposov, R.A., af Klinteberg, B. Pro-bullying attitudes among incarcerated juvenile delinquents: Antisocial behavior, psychopathic tendencies and violent crime. *International Journal of Law & Psychiatry* 2014, Jan 24. [Epub ahead of print]

Stickley, A., Koyanagi, A., Koposov, R., Schwab-Stone, M., Ruchkin, V. Loneliness and health risk behaviours among Russian and U.S. adolescents: a cross-sectional study. *BMC Public Health* 2014, 14(1):366. [Epub ahead of print]

Päären A, Bohman H, von Knorring L, Olsson G, von Knorring A-L, Jonsson U. Early risk factors for adult bipolar disorder in adolescents with mood disorders: a 15-year follow-up of a community sample. *BMC Psychiatry*. 2014 Dec 24;14:363. doi: 10.1186/s12888-014-0363-z.

Päären A, von Knorring A-L, Olsson G, von Knorring L, Bohman H, Jonsson U. Hypomania spectrum disorder in adolescence: A 15-year follow-up of non-mood morbidity in adulthood. *BMC Psychiatry*, 2014 Jan 15;14(1):9. doi: 10.1186/1471-244X-14-9.

Stickley, A., Koyanagi, A., Koposov, R., Blatný, M., Hrdlička, M., Schwab-Stone, M., Ruchkin, V. Correlates of Weapon Carrying in School among Adolescents in Three Countries. *American Journal of Health Behavior* 2015, 39(1):99-108

Stickley A., Koyanagi, A., Koposov, R., McKee, M., Murphy, A., Ruchkin, V. Binge Drinking and Eating Problems in Russian Adolescents. *Alcoholism: Clinical and Experimental Research*. Accepted for publication.

Swartz J, Lindblad F, Arinell H, Theorell T, Alm J. Anthroposophic lifestyle and salivary cortisol are associated with a lower risk of sensitization during childhood. *Pediatric Allergy and Immunology*, 2015 Mar;26(2):153-60.

Lindblad F, Eickhoff M, Forslund AH, Isaksson J, Gustafsson J. Fasting blood glucose and HbA1c in children with ADHD. *Psychiatry Res*. 2015 Apr 30;226(2-3):515-6.

Rindsjö E, Barber M, Theorell T, Lindblad F, Alm J, Scheynius A, Joerink M. Increased mRNA expression of glucocorticoid receptor-P in placenta is associated with a decreased risk of allergen sensitisation in the child. *Acta Paediatr.* 2015 Jun;104(6):638-40.

Lindblad F, Isaksson J, Heiskala V, Kuposov R, Ruchkin V. Comorbidity and Behavior Characteristics of Russian Male Juvenile Delinquents With ADHD and Conduct Disorder. *J Atten Disord.* 2015 Apr 29.

Isaksson J, Allen M, Nilsson KW, Lindblad F. Polymorphisms in the FK506 binding protein 5 gene are associated with attention deficit hyperactivity disorder and diurnal cortisol levels. *Acta Paediatr.* 2015 Sep;104(9):910-5.

Elmelid A, Stickley A, Lindblad F, Schwab-Stone M, Henrich CC, Ruchkin V. Depressive symptoms, anxiety and academic motivation in youth: Do schools and families make a difference? *J Adolesc.* 2015 Oct 15;45:174-182.

Jonsson U, Johanson J, Nilsson E, Lindblad F. Adverse effects of psychological therapy: An exploratory study of practitioners' experiences from child and adolescent psychiatry. *Clin Child Psychol Psychiatry.* 2015 Nov 18.

Isaksson J, Lindblad F, Valladares E, Högberg U. High maternal cortisol levels during pregnancy are associated with more psychiatric symptoms in offspring at age of nine - A prospective study from Nicaragua. *J Psychiatr Res.* 2015 Dec;71:97-102.

Lindblad F, Isaksson J, Heiskala V, Kuposov R, Ruchkin V. Comorbidity and Behavior Characteristics of Russian Male Juvenile Delinquents With ADHD and Conduct Disorder. *J Atten Disord.* 2015.

Isaksson J, Grigorenko EL, Orelan L, Af Klinteberg B, Kuposov RA, Ruchkin V. Exploring possible association between DbetaH genotype (C1021T), early onset of conduct disorder and psychopathic traits in juvenile delinquents. *Eur Arch Psychiatry Clin Neurosci.* 2015.

Rakhlin, N., Hein, S., Doyle, N., Hart, L., Macomber, D., Ruchkin, V., Tan, M., Grigorenko, E.L. Language development of internationally adopted children: Adverse early experiences outweigh the age of acquisition effect. *Journal of Communication Disorders* 2015, 57, 66-80, Sep 2. pii: S0021-9924(15)30004-6.

Jonsson U, Johanson J, Nilsson E, Lindblad F. Adverse effects of psychological therapy: An exploratory study of practitioners' experiences from child and adolescent psychiatry. *Clin Child Psychol Psychiatry*, 2015 Nov 18. [Epub ahead of print]

Stickley, A., Koyanagi, A., Ruchkin, V., Kamio, Y. Attention-deficit/hyperactivity disorder symptoms and suicide ideation and attempts: Findings from the Adult Psychiatric Morbidity Survey 2007. *Journal of Affective Disorders* 2016;189:321-8.

Rakhlin, N., Hein, S., Doyle, N., Hart, L., Kuposov, R., Macomber, D., Ruchkin, V., Strelina, A., Tan, M., Grigorenko, E.L. Sources of Heterogeneity in Developmental Outcomes of Children with Past and Current Experiences of Institutionalization in Russia: A Four-Group Comparison. *American Journal of Orthopsychiatry* 2016 Apr 14. [Epub ahead of print]



- Ruchkin V, Koposov RA, Koyanagi A, Stickley A. Suicidal Behavior in Juvenile Delinquents: The Role of ADHD and Other Comorbid Psychiatric Disorders. *Child Psychiatry Hum Dev*. 2016 Oct 12. [Epub ahead of print]
- Shein-Szydlo J, Sukhodolsky DG, Kon DS, Tejada MM, Ramirez E, Ruchkin V. A Randomized Controlled Study of Cognitive-Behavioral Therapy for Posttraumatic Stress in Street Children in Mexico City. *J Trauma Stress*. 2016 Oct;29(5):406-414.
- Isaksson J, Comasco E, Åslund C, Rehn M, Tuvblad C, Andershed H, Nilsson KW. Associations between the FKBP5 haplotype, exposure to violence and anxiety in females. *Psychoneuroendocrinology*. 2016, 72,196-204.
- Isaksson J, Ruchkin V, Lindblad F. Unseen and stressed? Gender differences in parent and teacher ratings of ADHD symptoms and associations with perceived stress in children with ADHD. *Journal of Attention Disorders*. 2016, July 7. [Epub ahead of print]
- Isaksson J, Lindblad F, Valladares E, Högberg U. Associations between psychiatric symptoms and cortisol levels in Nicaraguan young school-age. *Psychiatry Research*. 2016, 240:376-80.
- Lainpelto J, Isaksson J, Lindblad F. Does Information about Neuropsychiatric Diagnoses Influence Evaluation of Child Sexual Abuse Allegations? *Journal of Child Sexual Abuse*. 2016, 25(3):276-92.
- Stickley A, Koyanagi A, Koposov R, Blatný M, Hrdlička M, Schwab-Stone M, Ruchkin V. Loneliness and its association with psychological and somatic health problems among Czech, Russian and U.S. adolescents. *BMC Psychiatry*. 2016 May 4;16:128.
- Quinn P. D., Pettersson E., Lundström S., Anckarsäter H., Långström N., Gumpert C. H., Larsson H., Lichtenstein P., & D'Onofrio B. M. (2016). Childhood attention-deficit/hyperactivity disorder symptoms and the development of adolescent alcohol problems: A prospective, population-based study of Swedish twins. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 2016, 171, 968-970.
- Baur E., Forsman M., Santtila P., Johansson A., Sandnabba K., & Långström N. (2016). Paraphilic sexual interests and sexually coercive behavior: A population-based twin study. *Archives of Sexual Behavior* 2016, 45, 1163-1172.
- Lysell H., Dahlin M., Långström N., Lichtenstein P., & Runeson B. (2016). Killing the mother of one's child: Psychiatric risk factors among male perpetrators and offspring health consequences. *Journal of Clinical Psychiatry*, 2016, 77, 342-347.
- Cederlöf M., Petterson E., Sariaslan A., Larsson H., Kähler A. K. Östberg P., Kelleher I., Långström N., Anckarsäter H., Gumpert C. H., Lundström S., & Lichtenstein P. (2016). The association between childhood autistic traits and subsequent psychotic experiences is explained by general neuropsychiatric problems. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 2016, 171, 153-159.
- Sariaslan A., Fazel S., D'Onofrio B. M., Långström N., Larsson H., Bergen S. E., Kuja-Halkola R., & Lichtenstein P. (2016). Schizophrenia and subsequent neighbourhood

deprivation: Revisiting the social drift hypothesis using population, twin and molecular genetic data. *Translational Psychiatry*, 2016, e796.

Fazel S., Chang Z., Fanshawe T., Långström N., Lichtenstein P., Larsson H., & Mallett S. (2016). Prediction of violent reoffending on release from prison: derivation and external validation of a scalable tool. *Lancet Psychiatry*, 3, 535-543.

Fazel S., Chang Z., Fanshawe T., Långström N., Lichtenstein P., & Mallett S. (2016). OxRec model for assessing risk of recidivism: ethics Reply. *Lancet Psychiatry*, 3, 809-810.

Lundh A., Forsman M., Serlachius E., Långström N., Lichtenstein P., & Landén M. (2016). Psychosocial functioning in adolescent patients assessed with Children's Global Assessment Scale (CGAS) predicts negative outcomes from age 18: A cohort study. *Psychiatry Research*, 2016, 242, 295-301.

Chang Z., Lichtenstein P., Långström N., Larsson H. & Fazel S. (2016). Association between prescription of major psychotropic medications and violent reoffending after prison release. *JAMA-Journal of the American Medical Association*, 2016, 316, 1798-1807.

Lindner, P., Carlbring, P., Flodman, E., Hebert, A., Poysti, S., Hagkvist, F., Johansson, R., Zetterqvist Westin, V., & Andersson, G. (2016). Does cognitive flexibility predict treatment gains in Internet-delivered psychological treatment of social anxiety disorder, depression, or tinnitus? *PeerJ*, 4, e1934.

#### **Agencies that support the work/ Funding**

Swedish Research Council: Medicine (VR)

Swedish Council for Working Life and Social Research (FORTE)

Swedish Brain Foundation

Regionala Forskningsrådet i Uppsala-Örebroregionen

National Victim Compensation Authority (Brottsoffermyndigheten)

Canadian Institutes of Health Research (CIHR)

#### **Awards**

Abdoulbaghi Ahmad received “The Martin H:son Holmdahl Scholarship for the promotion of human rights and liberty 2014” at the Winter Conferment Ceremony 30 January 2015.

## ***Experimental Neuroscience***

### **Developmental Genetics**

#### ***Formation and Function of Neuronal Circuits***

**Group leader: Klas Kullander, Professor**

#### **Members of the group during 2016**

Arthur Franca, PhD student  
Angelica Thulin, Master student  
Christiane Peuckert, Post doc  
Ernesto Restrepo, Post doc  
Fabio Caixeta, Post doc  
Jennifer Vieillard, post doc

Markus Hilscher, Guest scientist  
Robin Visvanathar, Master student  
Samer Siwani, PhD student  
Sanja Mikulvic, Post doc  
Sharn Perry, PhD student

Neuronal circuits are essential components of the nervous system and determine various body functions. We are interested in the function of neuronal circuits in the central nervous system. Our goals are to increase the knowledge in how neuronal networks develop into functional units and what the roles are for specified sets of neuronal populations in their circuitries. Our research program is devoted to investigate defined populations of inhibitory interneurons in functions including motor control, memory and cognition. We wish to identify the mechanism by which specific inhibitory interneuron influence the activity of principle cells and the resulting effects on behavior. Two limiting factors in disentanglement of neural circuitry are the identification of defined populations of interneurons and the use of reproducible behaviors. Thus, our developed sharp genetic tools in combination with in vitro and in vivo measurements of network activity and behavior are instrumental. Further, we will apply novel and advanced methods, including virus-based tracing, electrophysiology, pharmacology, optogenetics, imaging and in-vivo recordings of neural activity. Apart from the concerted efforts from talented neuroscientists in the team, a core facility for behavior is already in place, and a facility for light-induced stimulations should be operational in the near future. Our research should provide insights into how spinal cord interneurons coordinate locomotion, the functionality of local interneurons in the hippocampus controlling memory, and the contribution of cortical local interneurons to cognition. Inhibitory interneurons are involved in several diseases of the CNS, thus, to find potential remedies in neural circuit dysfunction, we need to achieve insight into the mechanisms for how inhibitory interneurons participate in circuit processing.

#### **Publications 2014-2016**

Chrna2-Martinotti Cells Synchronize Layer 5 Type A Pyramidal Cells via Rebound Excitation. Hilscher MM, Leão RN, Edwards SJ, Leão KE, Kullander K. PLoS Biol. 2017 Feb 9;15(2):e2001392.

Identification of a Neuronal Receptor Controlling Anaphylaxis. Rogoz K, Aresh B, Freitag

FB, Pettersson H, Magnúsdóttir EI, Larsson Ingwall L, Haddadi Andersen H, Franck MC, Nagaraja C, Kullander K, Lagerström MC. *Cell Rep.* 2016 Jan 12;14(2):370-9.

On the photovoltaic effect in local field potential recordings. Mikulovic S, Pupe S, Peixoto HM, Do Nascimento GC, Kullander K, Tort AB, Leão RN. *Neurophotonics.* 2016 Jan;3(1):015002

Multimodal Eph/Ephrin signaling controls several phases of urogenital development. Peuckert C, Aresh B, Holenya P, Adams D, Sreedharan S, Porthin A, Andersson L, Pettersson H, Wöfl S, Klein R, Oxburgh L, Kullander K. *Kidney Int.* 2016 Aug;90(2):373-88.

Mikulovic S, Restrepo CE, Hilscher MM, Kullander K, Leão RN. Novel markers for OLM interneurons in the hippocampus. *Front Cell Neurosci.* 2015 Jun 2;9:201.

Reinius B, Blunder M, Brett FM, Eriksson A, Patra K, Jonsson J, Jazin E, Kullander K. Conditional targeting of medium spiny neurons in the striatal matrix. *Front Behav Neurosci.* 2015 Mar 27;9:71

Perry, S., Gezelius, H., Larhammar, M., Hilscher, M., Lamotte d'Incamps, B., Leao, K., Kullander, K. Firing properties of Renshaw cells defined by *Chrna2*, are modulated by Ih and ISK channels. *Eur J Neurosci* 2015 doi: 10.1111/ejn.12852.

Larhammar M, Patra K, Blunder M, Emilsson L, Peuckert C, Arvidsson E, Rönnlund D, Preobraschenski J, Birgner C, Limbach C, Widengren J, Blom H, Jahn R, Wallén-Mackenzie Å, Kullander K. *SLC10A4* is a vesicular aminergic-associated transporter modulating dopamine homeostasis *Biol Psychiatry* 2015 Mar 15;77(6):526-36

Rogoz K, Stjärne L, Kullander K, Lagerström MC. VGLUT2 controls heat and punctuate hyperalgesia associated with nerve injury via TRPV1-Cre primary afferents. *PLoS One.* 2015, 10:e0116568.

Patra K, Lyons DJ, Bauer P, Hilscher MM, Sharma S, Leão RN, Kullander K. A role for solute carrier family 10 member 4, or vesicular aminergic-associated transporter, in structural remodelling and transmitter release at the mouse neuromuscular junction. *Eur J Neurosci.* 2015, 41:316-27.

Rogoz K, Andersen HH, Lagerström MC, Kullander K. Multimodal use of calcitonin gene-related peptide and substance P in itch and acute pain uncovered by the elimination of vesicular glutamate transporter 2 from transient receptor potential cation channel subfamily V member 1 neurons. *J Neurosci.* 2014, 34:14055-68.

Najet Serradj<sup>1</sup>, Sónia Paixão<sup>2</sup>, Tomasz Sobocki<sup>1</sup>, Mitchell Feinberg<sup>1</sup>, Rüdiger Klein<sup>2</sup>, Klas Kullander<sup>3</sup>, John H. Martin<sup>1</sup>. EphA4-mediated ipsilateral CST misprojections establish bilateral voluntary movements but not bilateral stereotypic locomotion *J Neuroscience* 2014, 34:5211-21

Rogoz K, Andersen HH, Kullander K, Lagerström MC. Glutamate, substance P, and calcitonin gene-related peptide cooperate in inflammation-induced heat hyperalgesia. *Mol Pharmacol.* 2014 Feb;85(2):322-34.

## **Agencies that support the work/ Funding**

Swedish Medical Research Council (SMRC) 2016-2018  
EU FP7 Mindview  
Swedish Brain Foundation  
STINT

## ***Neurodynamics***

**Group leader: Richardson N Leão, MD, PhD**

### **Members of the group during 2016**

Sanja Mikulovic, PhD student  
Ernesto Restrepo, Postdoc  
George Nascimento, Postdoc

### ***Project 1: Generation of theta oscillations and its implication to anxiety***

**Participants:** Sanja Mikulovic, Ernesto Restrepo, George Nascimento, Richardson N. Leão

Theta oscillations is one of the most studied rhythms of the brain. However, this rhythm has wrongfully being correlate only to exploration or sleep. We have found that a much less studied form of form of theta, namely, type 2, is associated to mood. Moreover, we have found that these rhythms are generated in a part of the hippocampus that is not associated to movement. After dissecting the circuits responsible for its generation, we have modulated this rhythm using state-of-the-art optogenetic and chemogenetic methods in order to produce anxiolytic effects. These findings will serve to determine the influence of a hippocampal pacemaker on the synchronisation of limbic system. Besides, our discoveries will determine cellular targets for the control of mood disorders and will help to find targets for new anxiolytic agents.

### ***Project 2. Mobile optical recording of neural activity***

**Participants:** Sanja Mikulovic, George Nascimento, Richardson N. Leão

We have built mobile mini-microscopes that allow mobile recordings of neuronal activity. Using genetically encoded sensors of neuronal activity, we are able to decode the role of specific neuronal populations during cognitive tasks. This revolutionary technique will allow us to understand how genetically determined neuronal populations contribute to psychiatric conditions such as depression or anxiety. We are one of the few laboratories in the world that could successfully register (optically) neuronal activity while animals execute behavioural tasks. We have also tested a variety of genetically encoded calcium indicators in this project. These powerful tools allow the long-term recordings of neuronal activity based on the calcium dynamics. The most used indicators in neuroscience emit green light that is poorly diffused in brain tissue. Therefore, we are currently testing a set of red-shifted indicators to increase the deepness in which we can image.

### **Publications 2014-2016**

1. Lockmann AL, Laplagne DA, Leão RN, Tort AB. (2016) A Respiration-Coupled Rhythm in the Rat Hippocampus Independent of Theta and Slow Oscillations. *J Neurosci.* 36(19):5338-52.
2. Brogini AC, Esteves IM, Romcy-Pereira RN, Leite JP, Leão RN. Pre-ictal increase in theta synchrony between the hippocampus and prefrontal cortex in a rat model of temporal lobe epilepsy. *Exp Neurol.* 279:232-42.
3. Mikulovic S, Pupe S, Peixoto HM, Do Nascimento GC, Kullander K, Tort AB, Leão RN. (2016) On the photovoltaic effect in local field potential recordings. *Neurophotonic.* 3(1):015002
4. Mikulovic S, Restrepo CE, Hilscher MM, Kullander K, Leão RN. (2015) Novel markers for OLM interneurons in the hippocampus. *Front Cell Neurosci.* 9:201.
5. Patra K, Lyons DJ, Bauer P, Hilscher MM, Sharma S, Leão RN, Kullander K. (2015) A role for solute carrier family 10 member 4, or vesicular aminergic-associated transporter, in structural remodelling and transmitter release at the mouse neuromuscular junction. *Eur J Neurosci.* 41(3):316-27.
6. Leão RN, Targino ZH, Colom LV, Fisahn A. (2015) Interconnection and synchronization of neuronal populations in the mouse medial septum/diagonal band of Broca. *J Neurophysiol.* 113(3):971-80.
7. Peixoto HM, Munguba H, Cruz RM, Guerreiro AM, Leao RN. (2014) Automatic tracking of cells for video microscopy in patch clamp experiments. *Biomed Eng Online.* 13:78.
8. Schweizer N, Pupe S, Arvidsson E, Nordenankar K, Smith-Anttila CJ, Mahmoudi S, André A, Dumas S, Rajagopalan A, Lévesque D, Leão RN, Wallén-Mackenzie Å. (2014) Limiting glutamate transmission in a Vglut2-expressing subpopulation of the subthalamic nucleus is sufficient to cause hyperlocomotion. *Proc Natl Acad Sci U S A* 111(21):7837-42.
9. Nordenankar K, Smith-Anttila CJ, Schweizer N, Viereckel T, Birgner C, Mejia-Toiber J, Morales M, Leao RN, Wallén-Mackenzie Å. (2014) Increased hippocampal excitability and impaired spatial memory function in mice lacking VGLUT2 selectively in neurons defined by tyrosine hydroxylase promoter activity. *Brain Struct Funct.* 220(4):2171-90.

#### **Agencies that support the work/ Funding**

Kjell och Märta Beijers Foundation  
The Swedish Research Council

## ***Sensory Circuits***

**Group leader: Malin Lagerström, Associate Professor**

### **Members of the group during 2016**

Marina Franck, postdoctoral fellow  
Tianle Gao, postdoctoral fellow  
Bejan Aresh, PhD student  
Fabio Freitag, PhD student  
Elín Magnúsdóttir, PhD student  
Jon Jakobsson, research assistant/PhD student  
Harmen Koning, Master student  
Hannah Weman, project student

### **Project description**

The neuronal circuit that resides in the spinal cord dorsal horn is responsible for accurately relaying and modulating sensory information. This neuronal network consists of primary afferent neuron, that respond to sensory stimuli e.g. heat, touch, pressure and tissue injury, and transmit stimuli information to the spinal cord, descending neurons from higher brain areas that modulate the sensory signal and dorsal horn interneurons and projection neurons that receive and relay the input from the periphery and the brain. Through these neuronal populations, pain and itch perception can be modulated and regulated both from the periphery and higher brain areas. In states of chronic pain or itch, this system is imbalanced. Current treatments of chronic sensory conditions are most often experienced as inadequate and display severe side effects. To restore the balance in the dorsal horn in a more targeted manner, we need to understand how this circuit is organized in detail. Project 1 is therefore focused on finding the neuronal populations that transmit, fine-tune and regulate different kinds of sensory information in the dorsal horn of the spinal cord. The goal is to increase our understanding of the “gate” of sensory signaling and central processing of especially itch and pain signals. We also aim to find small populations of interneurons with restricted and relevant functions, which can be useful in therapeutic intervention of chronic sensory diseases. We are using techniques such as in situ hybridization, electrophysiology, immunohistochemistry and optogenetics to reach our goals. Project 2 is focused on finding the primary afferent populations and neurotransmitters that mediate and fine-tune the sensations of itch and of heat, cold, chemical, inflammatory and neuropathic pain from the periphery to the spinal cord. One of the projects is focused on the TRPV1 expressing population. TRPV1 is a ligand gated ion channel that is associated with thermosensation, including infrared detection (Gracheva et al, 2011, Neuron; Caterina et al, 1997; Nature). Studies using TRPV1 null mice have also revealed a central function for TRPV1 in inflammation-induced heat hyperalgesia (Caterina et al, 2000, Science; Davis et al, 2000, Nature). We have previously shown that the transmission of heat pain to the spinal cord depends mainly on VGLUT2-mediated glutamatergic transmission (Lagerström et al, 2010, Neuron) and we are now focused on identifying additional aspects of the TRPV1 population.

## Publications 2014-2016

1. Aresh B, Freitag FB, Perry S, Blumel E, Lau J, Franck MCM, Lagerström MC. Spinal cord interneurons expressing the gastrin releasing peptide receptor convey itch through VGLUT2-mediated signaling.  
Accepted in *Pain*.
2. Viereckel T, Dumas S, Smith-Anttila CJ, Vlcek B, Bimpisidis Z, Lagerström MC, Konradsson-Geuken Å, Wallén-Mackenzie Å. Midbrain Gene Screening Identifies a New Mesoaccumbal Glutamatergic Pathway and a Marker for Dopamine Cells Neuroprotected in Parkinson's Disease.  
*Sci Rep*. 2016 Oct 20;6:35203.
3. Rogoz K, Aresh B, Freitag FB, Pettersson H, Magnúsdóttir EI, Ingwall LL, Andersen HH, Franck MCM, Nagaraja C, Kullander K, Lagerström MC. Identification of a neuronal receptor controlling anaphylaxis.  
*Cell Rep*. 2015 Dec 29. pii: S2211-1247(15)01457-6.
4. Lagerström MC. Sinomenine is a promising analgesic and anti-hyperalgesic for pain and hypersensitivity in rheumatoid arthritis.  
*Scandinavian Journal of Pain*, 2015, pp. 15-16.
5. Gao T and Lagerström MC. The anti-inflammatory alkaloid *aloperine* in Chinese herbal medicine is potentially useful for management of pain and itch.  
*Scandinavian Journal of Pain*, 2015, pp. 25-26.
6. Rogoz K, Stjärne L, Kullander K, Lagerström MC. VGUT2 controls heat and punctuate hyperalgesia associated with nerve injury via TRPV1-Cre primary afferents.  
*PLoS One*. 2015 Jan 23;10(1):e0116568.
7. Rogoz K, Andersen HH, Lagerström MC and Kullander K. Multimodal use of calcitonin gene-related Peptide and substance p in itch and acute pain uncovered by the elimination of vesicular glutamate transporter 2 from transient receptor potential cation channel subfamily v member 1 neurons.  
*J Neurosci*. 2014 Oct 15;34(42):14055-68. #shared.
8. Caruso V, Lagerström MC, Olszewski PK, Fredriksson R, Schiöth HB. Synaptic changes induced by melanocortin signalling.  
*Nat Rev Neurosci*. 2014 Feb;15(2):98-110.
9. Rogoz K, Andersen HH, Kullander K and Lagerström MC. Glutamate, substance P, and calcitonin gene-related peptide cooperate in inflammation-induced heat hyperalgesia.  
*Mol Pharmacol*. 2014 Feb;85(2):322-34. #shared.

## Prizes and awards

Malin Lagerström received a Consolidator grant from the Swedish Research Council in 2016.

## Agencies that support the work/ Funding



Ragnar Söderberg Foundation  
Swedish Research Council  
The Konsul Th C Berghs Foundation  
Uppsala University  
The Brain Foundation  
The Royal Swedish Academy of Sciences  
The Olle Engkvist Foundation

## ***Ophthalmology & Retina Biology***

### **Ophthalmology**

#### ***Ophthalmic Biophysics***

**Group leader: Per Söderberg, MD, PhD, Professor Ophthalmology**

#### **Members of the group during 2016**

Galichanin, Konstantin, MD, PhD, Post-doc, part time  
Talibizadeh, Nooshin, MD, MSc, PhD student, part-time  
Yu, Zhaohua, MD, MSc, PhD student, full time  
Malmqvist, Lars, Diploma of Medicine, PhD student, full time  
Sandberg-Melin, Camilla, MD, Ophthalmologist, PhD student, part time  
Mar-Zoega, Gunnar, MD, MSc, Ophthalmologist, PhD student, part time  
Merkoudis, Nikolaus, MD, Ophthalmologist, PhD student, part time

#### **External collaboration 2016**

Bergmanson, Jan, OD, Professor, electron microscopy, College of Optometry, University of Houston, Tx, USA  
Bergquist, Jonas, BSc, Professor, analytical chemistry, Dept. of Analytical Chemistry, UU  
Björklund, Peyman, BSc, PhD, molecular biology, Endocrine surgery, Dept. of Surgical sciences, UU  
Goosey, John, MD, Ophthalmologist, Houston Eye Associates, Tx, USA  
Granstam, Elisabet, MD, PhD, Ophthalmologist, Dept. of Ophthalmology, Västerås Central Hospital  
Henriksson, Julia, MD, Ophthalmologist, Dept. of Ophthalmology, Hudiksvalls sjukhus  
Laurell, Carl-Gustaf, MD, PhD, Ophthalmologist, St. Eriks Eye Hospital, KI  
Manns, Fabrice, BcTechn, Professor, Optics, Bascom Palmer Eye Institute, University of Miami, Fl, USA  
Malmberg, Filip, BSc, PhD, information technology, Division of Visual Information and Interaction, Dept. of Information Technology, UU  
Mathews, Jessica, OD, MSc, College of Optometry, University of Houston, Tx, USA  
Quinlan, Roy, BSc, Professor, biology, School of Biological and Biomedical Sciences, Durham University  
Schulmeister, Karl, BSc, PhD, physics, Seibersdorf Labor GmbH, Vienna, Austria  
Leif Nordh, BSc, electronics, Melerit Medical AB, Sweden  
Skarman, Eva, BSc, PhD, mathematics, Melerit Medical AB, Sweden

Steinvall, Ove, BS, Docent, physics, FoI, Linköping

Varma, Shambu, BSc , Professor, Biochemistry, University of Maryland, School of Medicine, MD, USA

Wählby, Carolina, BSc , Professor, information technology, Division of Visual Information and Interaction, Dept. of Information Technology, UU

### ***Overall aim main project***

Prevent or delay visual impairment due to disease in the optics of the eye and glaucoma, and improve diagnostic procedures for ocular disease, and contribute to safer cataract surgery, using biophysical strategies.

### ***Clinical significance***

Cataract is the most common cause of bilateral blindness in the world and glaucoma is the third most common cause of visual impairment. Both diseases present a rapidly increasing financial burden on society due to an increasing and aging world population and lack of efficient objective diagnostic procedures.

### ***Project 1: Improvement of guidelines for avoidance of cataract after exposure to ultraviolet and near infrared radiation***

***Participants:*** Konstantin Galichanin, Nooshin Talibizadeh, Zhaohua Yu, Fabrice Manns, Jean-Marie Parel, Karl Schulmeister.

### ***Aim***

To improve safety guidelines for exposure of the eye to ultraviolet and infrared radiation (UVR and IRR).

### ***Methods***

Mathematical derivation of methods for estimates of precision of Maximum Tolerable Dose (MTD<sub>2.3:16</sub>), experimental single and repeated exposure of lenses in vitro and in vivo in experimental animals to spectrally and radiometrically defined optical radiation, macroscopic imaging of damage, quantitative measurement of intensity of forward light scattering.

### ***Significance***

Optical radiation has been identified as the most important changeable risk factor for cataract development. Current safety guidelines for optical radiation are partly based on theoretical assumptions and interpolations that need to be experimentally verified, or rejected, to improve the safety guidelines.

### ***Project 2: Molecular mechanisms in ultraviolet radiation cataract formation and possibilities for pharmacological intervention***

***Participants:*** Konstantin Galichanin, Nooshin Talibizadeh, Zhaohua Yu, Jonas Bergquist, Jan Bergmanson, Peyman Björklund, Roy Quinlan, Carolina Wählby

### ***Aim***

To elucidate molecular mechanisms in cataract formation caused by exposure to UVR. To use in vivo UVR-induced cataract as a model for identification of potential pharmaceutical agents for prevention or delay of cataract.

### ***Methods***

Morphologic events during UVR cataract formation are studied with light- and electron microscopy. Genetically modified mice lacking important genes for protection against UVR-induced cataract, are studied. The kinetics of the apoptosis pathway after experimental exposure to UVR is studied with immunohistochemistry, and qPCR. Immunohistochemical images are analyzed with morphometry using automated image analysis. Oxidation defense systems in the lens are studied biochemically. The antioxidant  $\alpha$ -tocopherol is analyzed quantitatively with HPLC coupled with mass spectrometry. The antioxidant caffeine is investigated as a potential anti-cataract agent. Caffeine is detected with UVR-detection after HPLC separation.

### ***Significance***

Better understanding of the pathophysiology of UVR induced cataract is anticipated to provide tools for improvement of safety guidelines. Considering the increasing problem of cataract disease in a world perspective, it would be of substantial value to identify cheap pharmaceuticals for intervention against cataract.

### ***Project 3: Safe cataract surgery***

***Participants:*** Carl-Gustav Laurell, Eva Skarman, Gunnar Zoega

### ***Aims***

1) To develop an instrument that allows fully automatic clinical measurement of corneal endothelial cell density and to study the importance of corneal endothelial cell density for prediction of outcome of cataract surgery. 2) To develop a simulator that enables training in phacoemulsification cataract surgery in a virtual reality learning environment.

### ***Methods***

1) Imaging of the corneal endothelium in the Fourier plane of the imaging optics with video detection and subsequent computerized image analyses. Clinical investigation of the predictive power of endothelial cell density. 2) Virtual reality phacoemulsification cataract surgery: 2.1 Add more functions to developed simulator. 2.2 Develop a strategy for optimal training sessions with the instrument. 2.3 Compare learning with the simulator to current clinical learning of cataract surgery. The software development is done by engineers specialized in medical simulators.

### ***Significance***

1) Pre-operatively undetected relative insufficiency of the corneal endothelium is one of the most significant remaining problems in modern cataract surgery. Current technology for evaluation of the corneal endothelium is too complex to be used in clinical routine. We have developed a fast method that can be used clinically. This now requires clinical evaluation. 2) Modern cataract surgery is performed under local anesthesia making teacher-trainee communication very difficult. Coordination has to be learnt operating a large number of patients under supervision of a teacher. We have developed a virtual reality simulator that aims to reduce acquisition of surgical skill on patients.

### ***Project 4: Contrast sensitivity measurement, Uppsala Contrast Sensitivity Test***

### ***Aim***

To develop a tool for clinical routine measurement of contrast sensitivity.

**Participants:** Lars Malmqvist

**Methods**

Presentation of a target image that contains spatial frequency and contrast simultaneously that allows interactive indication of perceived contrast sensitivity.

**Significance**

All problems in the optics of the eye are associated with decreased contrast sensitivity. However, current contrast sensitivity tests are too slow to be used routinely in the clinic. It is anticipated that with a clinically useful method for contrast sensitivity measurement, indications for procedures such as cataract surgery and Yag laser capsulotomy for secondary cataract can be judged on a sound basis. The method also has the potential to replace visual acuity measurement with a visual acuity chart.

**Project 5: Interactive digital visual acuity charts, AxAnIvIs-Acuity**

**Aim**

To develop an interactive digital visual acuity chart.

**Participants:** Zaohua Yu, Anders Ohlsson, Christian Johansson, Svante Nilsson

**Methods**

Software that allows interactive visual acuity measurement on a digital visual acuity chart was developed. The strategy is being evaluated clinically and compared to the gold standard for visual acuity measurement, the ETDRS-chart.

**Significance**

Currently used visual acuity charts were developed in the 20th century and are static. The simultaneous presentation of a large number of letters creates confusion in children and elderly people and makes currently available refraction and estimation of visual acuity slow. Examiner guided interactive presentation of optotypes has the potential to make both refraction and estimation of visual acuity faster and more accurate.

**Project 6: Detection of glaucoma progress, morphometric analysis of the optic nerve head**

**Aim**

To develop a measurement procedure that allows evaluation of glaucoma progression on the basis of the topography of the optic nerve head.

**Participants:** Camilla Sandberg-Melin, Curt Eriksson, Albert Alm, Filip Malmberg.

**Methods**

1) Statistical analysis of the sources of variability in estimates of the 3-D topography of the optic nerve head recorded with confocal microscopy (HRT). Statistical modelling of optimal clinical strategies for follow up of glaucoma progression. 2) Development of strategies for estimating the 3-D topography of the optic nerve head with optical coherence tomography (OCT). Automatic detection of glaucoma progress with image analysis of OCT images of the optic nerve head.

**Significance:** Glaucoma is the 3rd most significant cause of loss of vision and quickly increasing. The current gold standard for follow up of glaucoma progression, computerized estimation of the visual field, is time consuming and associated with substantial variation, making follow up expensive, inefficient and questionable as a support for pharmacological control of the disease. Imaging of the topographical changes in the optic nerve head has recently become available and is an attractive alternative for follow up of glaucoma progression but the resolution in the images is unknown. Clinically significant morphometric variables have to be identified and an efficient clinical measurement strategy has to be established and validated.

### ***Project 7: Epidemiology of the corneal endothelium***

#### ***Aim***

Estimate risk factors for loss of corneal endothelial cells.

**Participants:** Gunnar Zoega

#### ***Methods***

In vivo specular microscopy images of the corneal endothelium in an age defined, randomly selected cohort of the Icelandic population is analyzed epidemiologically.

#### ***Significance***

Corneal transparency depends on a minimum number of corneal endothelial cells and corneal endothelial cells lost after birth due to trauma and environmental factors are not replaced. To minimize the number of patients suffering from loss of corneal transparency a better understanding of factors that are associated with loss of corneal endothelial cells is required.

### **Additional projects/ collaborations**

#### ***Investigation of effects to the eye and vision at exposure to green laser when driving***

#### ***Aim***

To determine the hazardous effects of exposure to green laser when driving.

**Participants:** Ove Steinvall, Zhaohua Yu

#### ***Methods***

Drivers are exposed to green laser light while driving on a test track. The eyes are examined before and after exposure. The driving behavior during exposure is measured. The psychological reaction to the laser exposure while driving is evaluated.

#### ***Significance***

Better knowledge of effects of blinding drivers with green laser light provide a basis for improved legislation and advice to drivers exposed while driving.

#### ***Clinical evaluation of steroids in treatment of intraocular inflammation***

#### ***Aim***

To evaluate the clinical significance of intraocular slow release administration of steroids in intraocular inflammation.

**Participants:** Nikos Merkoudis, Eva Landgren, Elisabet Granstam, Per Söderberg

### **Methods**

Subconjunctival injection of slow release steroid is compared to topical application of steroids after cataract surgery and for prevention of macular edema in patients with diabetic retinopathy. Intraocular administration of steroid slow release device for treatment of macular edema in after retinal vein occlusion is clinically evaluated. Macular edema is measured with OCT. Intraocular inflammatory proteins are measured.

### **Significance**

Subconjunctival injection of slow release steroids has the potential to increase compliance and therefore decrease postoperative intraocular inflammation after cataract surgery and to prevent macular edema in patients with diabetic retinopathy undergoing cataract surgery. Intraocular administration of a slow steroid release device has the potential to improve vision in patients with macular edema associated with retinal vein occlusion.

### **Ultrastructural changes in keratoconus**

#### **Aim**

Elucidate the mechanism for development of keratoconus.

**Participants:** Jessica Matthews, Jan Bergmanson, John Goosey, Per Söderberg

### **Methods**

Morphometry in transmission electron micrographs of cornea from normal eye bank eyes and from keratoconus eyes.

### **Significance**

Keratoconus is a progressive non inflammatory destruction of the cornea that induces abnormal corneal curvature and in serious cases perforation of the eye that requires corneal transplantation. The mechanism is unknown. It is anticipated that knowledge on ultrastructural changes associated with keratoconus will provide guidance to prevention and treatment.

### **Administrative Commissions**

Chair Subcommittee IV, Optical Radiation, International Commission for Non-Ionizing Radiation Protection (ICNIRP). ICNIRP develops guidelines for safe exposure of the human body to non-ionizing radiation, adopted by most national radiation protection boards.

Co-chair Ophthalmic Technologies, SPIE. International conference for technological development in ophthalmology.

Chair Pascal Rol Foundation for support of new developments in ophthalmic technologies.

### **Publications 2014-2016**

#### **Books**

Manns F, Söderberg PG, Ho A Ophthalmic Technologies XXIV. SPIE Proc 2015;8930:

Manns F, Söderberg PG, Ho A Ophthalmic Technologies XXIV. SPIE Proc 2014;8930:

Manns F, Ho A, Söderberg PG Ophthalmic Technologies XXIII. SPIE Proc 2013;8567:

### ***Review articles***

ICNIRP, Stuck B, Schulmeister K, Sliney DH, Cesarini JP, Thomas R, Greinert R, Söderberg PG Icnirp guidelines on limits of exposure to incoherent visible and infrared radiation. *Health physics* 2013;105:74-91

ICNIRP: ICNIRP, Stuck B, Schulmeister K, Sliney DH, Cesarini, JP, Thomas R, Greinert R, Söderberg PG Icnirp guidelines on limits of exposure to laser radiation of wavelengths between 180 nm AND 1000 µm.. *Health Physics*, 2013; 105: 271-295

### ***Journal articles***

Kronschläger M, Talebizadeh N, Yu Z, Meyer LM, Löfgren S Apoptosis in the rat cornea after in vivo exposure to UVR at 300 nm. *Cornea* 2015;34:945-949

Yu Z, Schulmeister K, Talebizadeh N, Kronschläger M, Söderberg PG 1090 nm infrared radiation at close to threshold dose induces cataract with a time delay. *Acta Ophthalmol* 2015;Ahead of print, 93:E118-E122

Mathew JM, Goosey JG, Söderberg PG, Bergmanson JPG Lamellar Changes in the Keratoconic Cornea. *Acta Ophthalmol* 2015;Ahead of print, :

Yu Z, Schulmeister K, Talebizadeh N, Kronschläger M, Söderberg PG Temperature controlled in vivo ocular exposure to 1090 nm radiation suggests that near infrared radiation cataract is thermally induced. *JBO* 2015;20:015003-1 - 015003-4

Yu Z, Persson R, Öhgren J, Sandberg S, Hörberg U, Berglund F, Karlsson K, Steinvall O, Söderberg PG Green light laser exposure at 532nm near the exposure limit during a human volunteer vehicle driving task does not alter structure or function in the visual system. *J Laser Appl* 2014;Ahead of print, 26:022009-1 - 022009-7

Talebizadeh N, Yu Z, Kronschläger M, Hallböök F, Söderberg PG Specific spatial distribution of caspase-3 in normal lenses. *Acta Ophthalmol* 2014;Ahead of print, :

Talebizadeh N, Yu Z, Kronschläger M, Söderberg PG Time evolution of active caspase-3 labelling after in vivo exposure to UVR-300 nm. *Acta Ophthalmol* 2014;Ahead of print, :

Yu Z, Schulmeister K, Talebizadeh N, Kronschläger M, Söderberg PG 1090 nm infrared radiation at close to threshold dose induces cataract with a time delay. *Acta Ophthalmol* 2014;Ahead of print, :

Yu Z, Schulmeister K, Talebizadeh N, Kronschläger M, Söderberg PG Ocular temperature elevation induced by threshold in vivo exposure to 1090-nm infrared radiation and associated heat diffusion. *JBO* 2014;Ahead of print, 19: 105008-1- 105008-6

Meyer LM, Wegener A, Holz F, Kronschläger M, Bergmanson JPG, Söderberg PG Ultrastructure of UVR-B-induced cataract and repair visualized with electron microscopy. *Acta Ophthalmol* 2014;Ahead of print, :

Galichanin K, Löfgren S, Söderberg PG Cataract after repeated daily in vivo exposure to ultraviolet radiation. *Health physics* 2014;107:523-529

Galichanin K, Yu Z, Söderberg PG Up regulation of GADD45-alpha, TP53 and CASP3 mRNA expression in the rat lens after in vivo exposure to sub-threshold dose of UVR B. *J Ocular Biology* 2014;2:1-5

Kronschläger M, Forsman E, Yu Z, Talebizadeh N, Löfgren S, Meyer LM, Bergquist J, Söderberg PG Pharmacokinetics for topically applied caffeine in the rat. *Exp Eye Res* 2014;122:94-101

Talebizadeh N, Yu Z, Kronschläger M, Söderberg PG Modelling the time evolution of active caspase-3 protein in the lens after in vivo exposure to UVR-B. *PLOS one* 2014;9:e106926

- Kronschläger M, Yu Z, Talebizadeh N, Meyer LM, Söderberg PG Topically applied caffeine induces miosis in the ketamine/xylazine anesthetized rat. *Exp Eye Res* 2014;127:179-183
- Zoega GM, Arnarsson A, Sasaki H, Söderberg PG, Sasaki H The seven-year cumulative incidence of cornea guttata and morphological changes in the corneal endothelium in the Reykjavik Eye Study. *Acta Ophthalmol* 2013;91:212-218
- Meyer LM, Löfgren S, Holz F, Wegener A, Söderberg PG Bilateral cataract induced by unilateral UVR-B exposure- evidence for an inflammatory response. *Acta Ophthalmol* 2013;91:236-242
- Kronschläger M, Yu Z, Talebizadeh N, Meyer LM, Hallböök F, Söderberg PG Evolution of TUNEL-labeling in the Rat Lens After In Vivo Exposure to Just Above Threshold Dose UVB. *Curr Eye Res* 2013;38:880-885
- Kronschläger M, Löfgren S, Yu Z, Talebizadeh N, Varma S, Söderberg PG Caffeine Eye Drops Protect Against Ultraviolet Radiation Cataract. *Exp Eye Res* 2013;113:26-31

### ***Publications in proceedings***

- Söderberg PG, Talebizadeh N, Galichanin K, Kronschläger M, Schulmeister K, Yu Z Near infrared radiation damage mechanism in the lens. *SPIE Proc* 2015;9307:930717-1-5
- Malmqvist L, Söderberg PG The Uppsala Contrast Sensitivity Test (UCST) A fast strategy for clinical assessment of spectral contrast sensitivity. *SPIE Proc* 2014;8930:89300H
- Malmqvist L, Söderberg PG The Uppsala Contrast Sensitivity Test: Fast contrast sensitivity measurements in humans.. *VPO Proc* 2014;:202-205
- Steinvall O, Sandberg S, Persson R, Berglund F, Karlsson K, Öhgren J, Yu Z, Söderberg PG Laser dazzling impacts on car driver performance. *SPIE Proc* 2013;8898:88980H-88980H-16

### **Agencies that supported the work/ Funding**

Uppsala university start-up grant  
 Konung Gustav V:s och Drottning Victorias Frimurarstiftelse  
 Ögonfonden  
 Project grant from Swedish Defence Research Agency (FOI)  
 Carmen och Bertil Regnérs fond för forskning  
 Gun och Bertil Stohnes Stiftelse  
 Ograduerade forskare, Uppsala universitet  
 Wallinders gåva  
 Erik Funks Minnesfond  
 Föreningen Synskadades Vänner i Uppsala Län  
 Stockholms läns landsting research grants (FoUU)  
 Uppsala Läns Landsting research grants (ALF)

## ***Paediatric Ophthalmology***

**Group leader:** Gerd Holmström, MD, PhD, Professor

### **Members of the group during 2016**

Eva Larsson, MD, PhD, Assoc Prof, Ophthalmologist  
 Dordi Austeng, MD, PhD, Ophthalmologist



Hanna Åkerblom, MD, PhD, Ophthalmologist  
Anna Molnar, MD, PhD Student, Ophthalmologist  
Dyrleif Petrusdottir, MD, PhD Student, Ophthalmologist  
Jonina Hreinsdottir, Orthoptist  
Eva Nuija, research nurse

### **Collaborators**

Uwe Ewald, MD, PhD, Professor, Neonatology  
Bo Strömberg, MD, PhD, Assoc Prof Paediatric Neurology, Uppsala University Hospital  
Lena Westas, Professor, Neonatology, Dep Paediatrics, Uppsala University Hospital  
Katarina Strand-Brodd, MD, PhD (2011-GH partly supervisor), Neonatologist  
Marie-Louise Bondesson, PhD, Professor, Dep Genetics, Uppsala University Hospital  
Claes von Hofsten, Prof, Dept of psychology  
Kerstin Rosander, researcher, Dept of psychology, Uppsala University  
Sten Andreasson, MD, PhD, Professor in ophthalmology, University of Lund  
Karel Marsal, Professor, Dep of Gynecology and obstetrics, Lund University  
Karin Källen, professor, statistician and epidemiologist, Tornbladsinstitutet, University of Lund  
Kristina Tornqvist, Professor in ophthalmology, University of Lund  
Mikael Norman, Professor, Neonatology, Karolinska Institute.  
Ann Hellström, Professor, Sahlgrenska Academy, Goteborg.

Our group collaborates with other paediatric ophthalmologists and paediatricians at Uppsala University Hospital, other University Hospitals and other hospitals in Sweden, as well as with international paediatric ophthalmologists and geneticists (Prof Marie-Louise Bondesson and her team, Uppsala). Since 2009 - 2010 we have a close collaboration with Prof Sten Andreasson, University of Lund.

Our major field of research concerns ophthalmologic findings and visual functions in prematurely-born children. Over the last two decades population-based studies on the incidence and risk factors of ROP have been performed, and extensive prospective follow-up studies on various visual functions have been undertaken. G Holmström is in charge of a national register for ROP, which has contributed several scientific papers and improved knowledge.

Various other paediatric ophthalmology studies have been performed on children with, amongst other conditions, haemangioma, x-linked retinoschisis, Down's syndrome, incontinentia pigmentii, neurofibromatosis type II, albinism, aniridia etc. In recent years we have focused on imaging of the retina and optic nerve; during 2009 we set up equipment for ERG and in 2011 for multifocal ERG, and this equipment is now used in our research.

***Project 1: A prospective, population-based, multidisciplinary study on the development of visual perception in infants born very preterm and the relation to cerebral injury (the LOVIS study).***

Commencing in January 2004, with the aim of developing predictive methods for the early detection of deficiencies, the study followed one hundred infants in the County of Uppsala for four years, up to the age of five. In this project we collaborate with neonatologists, paediatric neurologist and psychologists. K Strand-Brodd, PhD 2011. A two and a half year follow-up was completed in 2009. The first preliminary results were presented at ARVO (Association

for Research in Vision and Ophthalmology) in Florida during May 2006 and a Paediatric Research Congress in San Francisco, also in May 2006. In 2011 two papers on Development of Smooth Pursuit Eye Movements in very preterm born infants were published in Acta Paediatrica. The 2.5-year ophthalmological outcome together with a test of visual perception was published in Acta Paediatrica Aug 2013. We are now analysing results from a 6.5-year follow-up of these children in collaboration with paediatricians and psychologists. The LOVIS study will hopefully lead to early detection, possibly prevention and early intervention of future visual perceptual difficulties.

***Project 2: National study on extremely preterm infants born before the 27th week of gestation (the EXPRESS study).***

In collaboration with neonatologists and obstetricians, a national study was undertaken on all preterm infants in Sweden born before the 27th week of gestation over three years (2004-2007). Our aim was to evaluate neonatal mortality and morbidity and also outcome at 2.5 and 6.5 years. GH was responsible for the organization and logistics of the ophthalmologic part of this national project, including eye screening in the neonatal period. Dordi Austeng was a PhD student working on the project - dissertation 12 June 2010. Five papers have been published on the neonatal part of the study, of which one on regional aspects on ROP 2013. Further, an ophthalmological follow-up at 2.5 years was recently published in JAMA Ophthalmology. G Holmström has been a coauthor of one paper on Survival of this extreme population of prematurely-born infants (JAMA 2009), on Incidence and risk factors for neonatal morbidity (Acta Paediatrica 2010) and on one paper on the general follow-up at 2.5 years (JAMA 2013). Ophthalmological data on a national 6.5 year follow-up was published 2016. Further, the results on OCT assessment in preterm and fullterm 6,5 year children within the EXPRESS Study, living in Uppsala and Stockholm, have been accepted for publication 2016 and the results of ERG in the Uppsala children are about to be submitted to a scientific paper (PhD project Anna Molnar, planned dissertation May 2017). A national follow-up at 12 years of age started in June 2016 and around 20 preterm and fullterm children have been examined this autumn.

***Project 3: The SWEDROP register***

A national register for retinal disease (ROP) in prematurely born infants with GH as register holder, was established in 2006. The register (SWEDROP) has a national steering group, it is web based and started collecting national data in Sept 2006 with the aim of covering the whole country. We have a close collaboration with a perinatal register (SNQ), which will enable us to relate ROP data to neonatal findings. This is the first national register for ROP worldwide and will provide unique data on the incidence, natural history and risk factors of ROP, as well as indications and methods of treatment for ROP.

The coverage of the population is around 98 – 99%. During the last years several we have published several scientific reports, the most recent one in 2016, and another one is to be submitted very soon. In November SWEDROP celebrated it's 10<sup>th</sup> birthday with a national meeting at the University Hospital in Uppsala.

***Project 4: Retinal morphology and function in school-aged children born at term and preterm.***

This study is an evaluation of retinal function in children born at term and preterm. Our previous studies have revealed subnormal visual function in prematurely-born children. With the help of imaging techniques such as OCT (Optical coherence tomography) and HRT (Heidelberg tomography), we evaluate the retinal morphology and nerve fibre layer. Our group has previously reported on OCT findings in children with X-linked retinoschisis (Eriksson et al, Acta Ophthalmol 2004) and foveal hypoplasia (Holmström et al – 09). Results on children born at term, regarding both macular thickness and retinal nerve fibre layer, have been published 2009. In 2010 we reported on increased macular thickness in prematurely-born children (Åkerblom et al) and 2012 on reduced retinal nerve fibre layer (Åkerblom et al). Investigations of the retinal function in prematurely-born children 6 – 16 years with the help of ERG have been performed in collaboration with Prof Sten Andreasson, the University of Lund, and the results have been accepted for publication in an American journal, TSV 2014 (Åkerblom et al). The results of the studies on Multifocal ERG (MfERG) have been published in 2016.

***Project 5: Macular morphology and function in children born at term and preterm.***

This study aimed to create a normal material in healthy children, regarding OCT and MfERG, to study the macular development during childhood. We also aimed to study the macular and retinal structure and function in 6.5 years old extremely preterm infants, belonging to the EXPRESS Study, i.e. born before 27 weeks in Sweden 2004 – 2007, and to compare them with children born at term. During 2015 one study on OCT in healthy children was published in Acta Ophthalmologica (Anna Molnar et al) and one study on MfERG in Documenta Ophthalmologica (Anna Molnar et al).

**Publications 2014-2016**

1. Austeng D, Källén KB, Hellström A, Jakobsson PG, Johansson K, Tornqvist K, Wallin A, Holmström GE. Regional differences in [screening for retinopathy of prematurity in infants born before 27 weeks' gestation in Sweden – the EXPRESS study](#). Acta Ophthalmol. 2014 Jun;92(4):311-5.
2. Serenius F, Sjörs G, Blennow M, Fellman V, Holmström G, Maršál K, Lindberg E, Olhager E, Stigson L, Westgren M, Källén K; EXPRESS study group. [EXPRESS study shows significant regional differences in 1-year outcome of extremely preterm infants in Sweden](#). Acta Paediatr. 2014 Jan;103(1):27-37.
3. Vinnars MT, Nasiell J, Holmström G, Norman M, Westgren M, Papadogiannakis N. [Association between placental pathology and neonatal outcome in preeclampsia: a large cohort study](#). Hypertens Pregnancy. 2014 May;33(2):145-58. 2013 Dec 4. [Epub ahead of print]
4. Holmström G, Bondeson ML, Eriksson U, Åkerblom H, Larsson E. ['Congenital' nystagmus may hide various ophthalmic diagnoses](#). Acta Ophthalmol. 2014 Aug;92(5):412-6.
5. Åkerblom H, Andreasson S, Larsson E, Holmström G. Photoreceptor function is affected by preterm birth in school-aged children. TVST. Dec 2014; 1 – 8.

6. Lundgren P, Kistner A, Andersson EM, Hansen Pupp I, Holmström G, Ley D, Niklasson A, Smith LE, Wu C, Hellström A, Löfqvist C. [Low birth weight is a risk factor for severe retinopathy of prematurity depending on gestational age.](#) PLoS One. 2014 Oct 15;9(10):e109460.
7. Larsson E, Holmström G, Rydberg A. [Ophthalmological findings in 10-year-old full-term children--a population-based study.](#) Acta Ophthalmol. 2015 Mar;93(2):192-8.
8. Vinnars MT, Papadogiannakis N, Nasiell J, Holmström G, Westgren M. [Placental pathology in relation to stillbirth and neonatal outcome in an extremely preterm population: a prospective cohort study.](#) Acta Obstet Gynecol Scand. 2015 Jun;94(6):584-90.
9. Serenius F, Blennow M, Maršál K, Sjörs G, Källén K; EXPRESS Study Group. [Intensity of perinatal care for extremely preterm infants: outcomes at 2.5 years.](#) Pediatrics. 2015 May;135(5):e1163-72.
10. Källén K, Serenius F, Westgren M, Maršál K; EXPRESS Group. Impact of obstetric factors on outcome of extremely preterm births in Sweden: prospective population-based observational study (EXPRESS) . Acta Obstet Gynecol Scand. 2015 Nov;94(11):1203-14.
11. Stoltz Sjöström E, Lundgren P, Öhlund I, Holmström G, Hellström A, Domellöf M. [Low energy intake during the first 4 weeks of life increases the risk for severe retinopathy of prematurity in extremely preterm infants.](#) Arch Dis Child Fetal Neonatal Ed. 2016 Mar;101(2):F108-13
12. Molnar A, Holmström G, Larsson E. [Macular thickness assessed with spectral domain OCT in a population-based study of children: normative data, repeatability and reproducibility and comparison with time domain OCT.](#) Acta Ophthalmol. 2015 Aug;93(5):470-5.
13. Molnar A, Andreasson S, Larsson E, Åkerblom H, Holmström G. Macular function measured by binocular mfERG and compared with macular structure in healthy children. Doc Ophthalmol. 2015 Dec;131(3):169-76.
14. Kaul K, Rosander K, von Hofsten C, Strand Brodd K, Holmström G, Kaul K, Böhm B, Hellstrom-Westas L. Visual tracking in very preterm infants at 4 months predicts neurodevelopment at 3 years of age. Pediatr Res. 2016 Mar 8. doi: 10.1038/pr.2016.37. [Epub ahead of print]
15. Hellgren K, Hellström A, Tornqvist, K, Jakobsson P, Lundgren P, Carlsson B, Stjernqvist K, Källén K, Serenius F, Holmström G.. Ophthalmologic outcome of extremely preterm infants at 6.5 years of age; Extremely Preterm Infants in Sweden Study (EXPRESS). JAMA Ophthalmol. 2016 Mar 24. doi: 10.1001/jamaophthalmol.2016.0391. [Epub ahead of print]
16. Holmström G, Hellström A, Jakobsson P, Lundgren P, Tornqvist K, Wallin A. Five years of treatment for retinopathy of prematurity in Sweden – Results from SWEDROP, a national quality register. Br J Ophthalmol. 2016 Mar 11. pii: bjophthalmol-2015-307263. doi: 10.1136/bjophthalmol-2015-307263. [Epub ahead of print]

17. Lundgren P, Lundberg L, Hellgren G, Holmström G, Hård AL, Smith LE, Wallin A, Hallberg B, Hellström A. [Aggressive Posterior Retinopathy of Prematurity Is Associated with Multiple Infectious Episodes and Thrombocytopenia](#). Neonatology. 2016 Sep 16;111(1):79-85. [Epub ahead of print]
18. Åkerblom H, Andreasson S, Holmström G. Macular function in preterm children at school age. Doc Ophthalmol. 2016 Dec;133(3):151-157.
19. Holmström G, Hellström A, Jakobsson P, Lundgren P, Tornqvist K, Wallin A. [Screening for retinopathy of prematurity can be started in postmenstrual week 31 in very premature babies!](#) Eye (Lond). 2016 Nov;30(11):1524-1525.
20. Fahnehjelm KT, Liu Y, Olsson D, Amrén U, Haglind CB, Holmström G, Halldin M, Andreasson S, Nordenström A. [Most patients with long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency develop pathological or subnormal retinal function](#). Acta Paediatr. 2016 Dec;105(12):1451-1460.
21. Anna E.C. Molnar, Rebecka M. Rosén, Maria Nilsson, Eva K.B. Larsson, Gerd E. Holmström, Kerstin M. Hellgren. Central Macular Thickness in 6.5-year-old Children Born Extremely Preterm is Strongly Associated with Gestational Age Even When Adjusted for Risk Factors. In press, Retina.

#### **Agents that support the work/ Funding**

KMA – Kronprinsessan Margarethas stiftelse for synhandikappade  
Carmen och Bertil Regners Foundation  
Läkarsällskapet  
Uppsala University, grants for PhD students  
Uppsala Läns Landsting's Research grants (ALF)  
Ögonfonden

#### **Prices/ awards**

Gerd Holmström has got Marianne Bernadotte-medalj för mycket framstående insatser inom barnoftalmologisk forskning, 2015.

### ***Glaucoma***

**Group leader: Curt Ekström, MD, PhD**

#### **Members of the group during 2016**

Albert Alm, MD, Professor emeritus  
Amelie Botling Taube, MD, PhD student  
Curt Ekström, MD, PhD  
Inger Fällman Hedberg, Orthoptist  
Börje Nordh, Research engineer  
Eva Nuija, Research nurse  
Camilla Sandberg-Melin, MD, PhD student

***Project 1: Incidence of advanced visual field defects in newly diagnosed open-angle glaucoma***

**Participants:** Curt Ekström, Inger Fällman Hedberg.

**Background:** By contrast with numerous reports on the prevalence of glaucoma blindness, information on its incidence in affected patients is sparse.

**Purpose:** Long-term incident rate of glaucoma blindness in open-angle glaucoma is studied.

**Methods:** In 1978-2007, patients examined at the Eye Department in Tierp with a diagnosis of glaucoma were registered in glaucoma case records. The incidence of glaucoma blindness in newly diagnosed open-angle glaucoma is estimated. Blindness is defined as the occurrence of advanced visual field defects. While masked to clinical information, a nurse practised in perimetry evaluates the visual fields.

***Project 2: Risk factors for blindness in incident open-angle glaucoma***

**Participants:** Curt Ekström, Inger Fällman Hedberg.

**Background:** Open-angle glaucoma is an optic neuropathy characterized by progressive loss of optic nerve fibres and reduction of the visual field. Blindness in affected eyes is a possible outcome of the disease.

**Purpose:** Long-term prognosis is studied in a population-based cohort of newly diagnosed cases. The effects of age, comorbid conditions, presence of pseudoexfoliation, stage of visual field defect, and intraocular pressure on the risk of developing glaucoma blindness are tested.

**Methods:** The cohort is composed of patients examined at the Eye Department in Tierp. In the eye under study, blindness is defined as the occurrence of advanced visual field defects. While masked to clinical information, a nurse practised in perimetry evaluates the visual fields. Cox proportional hazards models are used to assess the relationship between potential risk factors and glaucoma blindness.

***Project 3: Predictors for incident open-angle glaucoma in a Swedish population***

**Participants:** Curt Ekström, Albert Alm

**Background:** Increased intraocular pressure, pseudoexfoliation, a positive family history and increasing age are established as the main risk factors for open-angle glaucoma in the Nordic countries, while knowledge of other potential risk factors is sparse.

**Purpose:** Predictors for incident open-angle glaucoma are studied in a sizeable cohort of people 65-74 years of age.

**Methods:** The cohort is based on the glaucoma survey undertaken in Tierp in 1984-86. To expand the sample size, patients examined at the Eye Department in 1978-2007 were enrolled. Information about incident cases is obtained by searching glaucoma case records. A specialist in glaucoma accomplishes classification of cases. Cox proportional hazards models are used to assess the relationship between potential risk factors and open-angle glaucoma.

## **Publications 2014-2016**

1. Ekström C, Kilander L. Pseudoexfoliation and Alzheimer's disease: a population-based 30-year follow-up study. *Acta Ophthalmol* 2014; 92 (4): 355-358.
2. Alm A. Latanoprost in the treatment of glaucoma. *Clin Ophthalmol* 2014 Sep 26;8:1967-85. doi: 10.2147/OPTH.S59162. eCollection 2014. Review.
3. Svensson R, Ekström C. Pseudoexfoliation and mortality: a population-based 30-year follow-up study. *Acta Ophthalmol* 2015; 93 (2): 162-164.
4. Ekström C, Botling Taube A. Pseudoexfoliation and cataract surgery: a population-based 30-year follow-up study. *Acta Ophthalmol* 2015; 93 (8): 774-777.
5. Ekström C, Kilander L. Open-angle glaucoma and Alzheimer's disease: a population-based 30-year follow-up study. *Acta Ophthalmol* 29 Sept 2016; doi: 10.1111/aos.13243.

## **Agencies that support the work/ Funding**

Uppsala Läns Landsting's Research grants (ALF)  
Glaucoma Research Fund at the Department of Ophthalmology, Uppsala University Hospital  
KMA – Kronprinsessan Margarethas stiftelse for synhandikappade  
Uppsala University, grants for PhD students

# Retinal Stem and Progenitor Cell Development

**Group leader: Finn Hallböök, PhD professor**

## **Members of the group during 2016**

Finn Hallböök, PhD professor  
Henrik Ring, Med Mag PhD post doc  
Sonya Stenfelt, MSc, PhD post doc  
Maria Blixt, MSc, PhD student  
Mohammad Harun-Or-Rashid, MSc, PhD student  
Minas Hellsand, Msc, PhD student  
Dardan Konjusha, Master student, Research assistant.  
Mikel Amirola, Master student

Year 2016 has been dominated by two main projects. First, we have established a protocol for producing human retina *in vitro* from human embryonic stem cells. The protocol allows development of human embryonic stem cells towards neuroepithelial progenitor cells from which optic vesicles and bonafide human retina is formed during *in vitro* 3D organogenesis. We use such *in vitro* formed retinas to model human retinal development with focus on the formation of horizontal cells and cone photoreceptors. Experimental evidence, including our own, suggest that those cells are the presumed cells-of-origin for retinoblastoma and the *in vitro* derived human retina is a model for the early steps during Retinoblastoma carcinogenesis. We have therefore focused the work on the early phase of photoreceptor and horizontal cell fate establishment.

Moreover, *in vitro*-formed human cells, in particularly cone photoreceptors are also a base for development of photoreceptor cell therapy to the human eye.

The other main project deals with studies of the behavior of retinal endogenous stem cells after retinal injury. We have focused on Müller cells, which constitute an important source for injury-derived retinal progenitor with potential capacities to generate new retinal neurons. Species differences exists, where cool-blooded non-mammalian vertebrates are able to differentiate these Müller cell-derived progenitor cells into neurons while mammals are less capable or may not have any capacity. We have studied how the activation of Müller cells and their gliotic responses after injuries may be regulated. The role of differentiated or de-differentiated Müller cell-derived cells in the injured retina are studied with respect to their role in neuro-protection of retinal neurons during and after injury and disease.

Main project:

### ***Project 1: Human retina from stemcells in vitro***

**Participants:** Stenfelt, Blixt, Hellsand, Ring, Amirola, Hallböök

An *in vitro* 3D-model for human retinal development.

Recent advances in the field of stem cell technology allow generation of retinal neuroepithelium from ES cells *in vitro*. We have developed a protocol for differentiation of healthy hESCs into 3D neural retinas Figure 1.



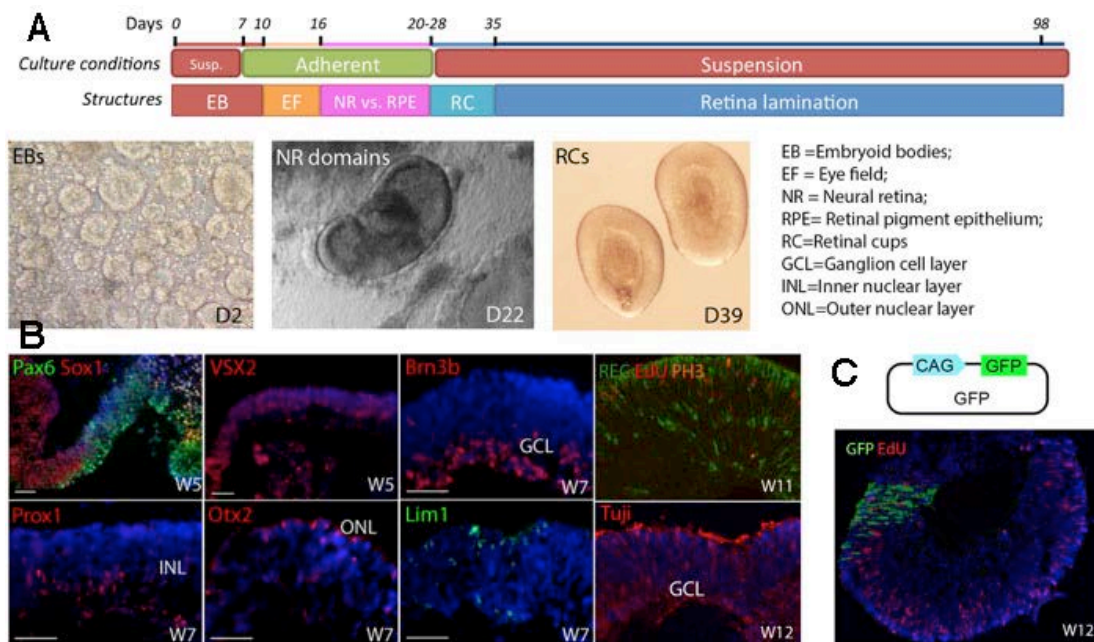


Figure 1: (A) Differentiation protocol via embryoid bodies and with alternating suspension and adherent culture conditions gives rise self-forming NR domains and laminated retinal cups/retinoids. (B) The RCs express eye field markers PAX6 and VSX2 and specific markers for ganglion cells (Brn3b, Tuji), horizontal cells (Prox1, Lim1) and cone photoreceptors (Otx2, REC). (C) GFP positive RCs 70h after electroporation with pZGS-GFP vector (2.5 µg/µl DNA, 15V, 5 pulses à 50ms, 1s intervals)

Establishing iPS cells from patients with the hereditary form of retinoblastoma and development of an in vitro disease model for retinoblastoma.

We will establish iPS cells from skin biopsies from patients diagnosed with the familial form of retinoblastoma and use these cells to generate an in vitro disease model for retinoblastoma using the differentiation protocol in part I. The healthy parents/siblings will be used as controls in this study.

### ***Project 2: Regulation of the final cell division in retinal progenitor cells and their relation to development of childhood Retinoblastoma***

**Participants:** Stenfelt, Blixt, Hellsand, Hallböök

We have shown that the horizontal progenitors in the chicken retina do not activate any p53-cell cycle arrest or apoptosis in response to DNA damage. These progenitors may even perform a truncated terminal mitosis, leaving uneuploid cells that resist apoptosis. These cells in chicken retina lack the normal guard against cancer and resemble a cancer stem cell. Our chicken-based results will be translated to the human context in order to understand exactly what makes the cells prone to undergo carcinogenesis. Human ES cells with a retinoblastoma genotype will then be used for studying bonafide retinoblastoma tumorigenesis.

We have established the self-organising-3D-embryonic body cultures that produce pigmented retina but work still remains before we a proper laminated neural retina. However, we have identified the formation of the retinal progenitors cells that we hypothesize are the

retinoblastoma cell-of-origin. A retinoblastoma hES cell genotype by iPSC from a patient with the familial form of Rb or by manipulating hES cells by Crisper CAS 9 - Rb loss of function. The chick work continues in parallel. We focus on the activation of p53 modulatory system in vivo and study both Rb loss of function as well as MYCN gain of function. Whole genome sequencing of retinoblastoma revealed that MYCN amplification even in the presence of wt Rb+ produces retinoblastoma. Our preliminary results show that chicken horizontal cells are less prone to go into apoptosis after over-expression of hCMYC/MYCN-T58A compared to other retinal progenitors. This project will be important to deepen the knowledge about the mechanisms of retinoblastoma carcinogenesis. Identifying the molecular mechanisms behind the cell of origin becomes increasingly important when threatening children with therapeutic agents developed to target particular molecular pathways. With a deeper knowledge, we are able to aid in the development of complementary pharmacological treatments and a more successful outcome for the patients.

### ***Project 3: Generation of retinal neurons: focus on Nolz1***

**Participants:** Blixt, Konjusha, Ring, Hallböök

The project aims at understanding how early retinal neurons in the lineage of retinal ganglion cells, cones and horizontal cells are generated. The knowledge may be used to instruct progenitor cell development for exploration of possibilities to counteract death of retinal ganglion cells and production of retinal cells for cell therapy. Ganglion cells and cones are relevant from a clinical perspective due to their loss in glaucoma and photoreceptor degenerations.

The transcription factors FoxN4 and Ptf1a have been identified to play a pivotal role in the generation of horizontal and amacrine cells; two types of interneurons in the retina. We are now studying the role of the zinc-finger transcription factor Nolz1.

One important approach has been to establish methods for cell-specific lineage tracing and for transgene expression during embryonic development in the retina. *In ovo* electroporation of expression vectors is used to study gene function and a minimal TATA box promoter in combination with hyperconserved non protein-coding DNA elements are used to drive cell specific gene expression. The Cre-lox piggyBac system is used to achieve constitutive GFP expression in the daughter cells of retinal progenitor cells. This approach is successfully used when studying the cell-of-origin for retinoblastoma.

### ***Project 4: Retinal progenitors and Müller cells in the perinatal and adult retina and their capacities to generate and protect retinal neurons.***

**Participants:** Harun-Or-Rashid, Konjusha, Hallböök

The over-all hypothesis is depicted in figure 2 and addresses the observation that the outcome of injury or disease to the retina is dependent on how Müller cells respond to injury. After injury, the gliotic response of Müller cells includes de-differentiation, proliferation and depending on the species, differentiation and formation of new retinal cells including neurons and new Müller. In mammals the capacity to form neurons (the neurogenic capacity) has become limited and regeneration is much less or non-existing compared to fish, amphibians

and to some extent birds, but never-the-less the mammalian Müller cells become gliotic and de-differentiates.

The project aims at getting control of the de-differentiation of Müller glia by the modulatory factors and signalling pathways that regulate this de-differentiation. We have found that the  $\alpha_2$ -adrenergic receptor agonist; Brimonidine induce a robust negative feed-back

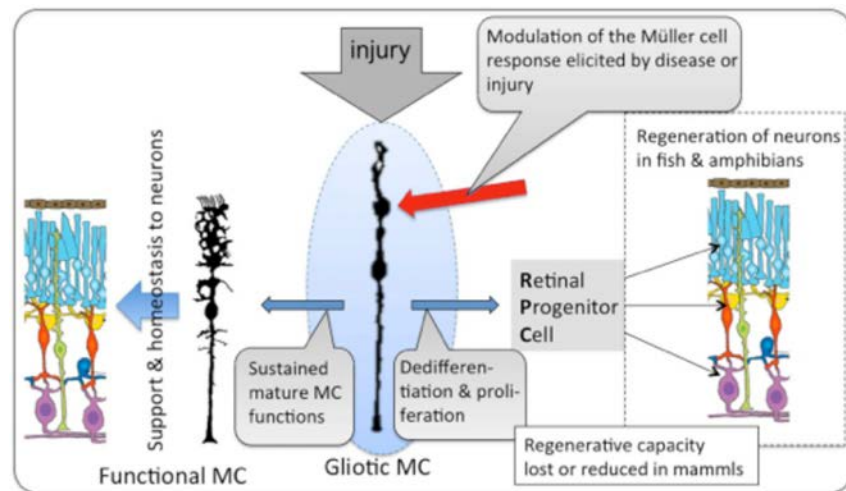


Figure 2. Injury leads to a gliotic response that may lead to de-differentiation and formation of a retinal progenitors (right blue arrow). The possibility to modulate the response (red arrow) may attenuate the de-differentiation and retain the support by mature Müller cells (left blue arrow).

regulation of the epidermal growth factor (EGF)-induced ERK-

signalling in Müller cells.  $\alpha_2$ -Adrenergic receptor signalling therefore acts as a negative regulator of Müller cells during retinal injury and disease (Harun-Or-Rashid et al. 2015; Harun-Or-Rashid et al. 2014). The EGF receptor is an established drug-target with well-proven inhibitory or stimulatory reagents and combined with the novel mechanism of action for Brimonidine, as further investigated in this application. It may open for novel combinatory treatments of retinal disease or injury.

Our results reinforce the role for glial homeostatic functions during an injury or disease situation and the long-term outcome may be improved by reduced Müller cell- activation. Activated Müller cells become gliotic and may in addition to attaining a progenitor role they may also lose their vital homeostatic functions. The work in this proposal will forward the results that we have obtained using animal models and cells and bring it into the human cell system. We will primarily use a cell line with Müller cell characteristics as well as cells derived from human embryonic stem cells.

### ***Project 5: Functional genetics using domestic animals***

**Participants:** Ring, Hallböök (INV) and Andersson (IMBIM) and co-workers

These projects are part of collaborative efforts to utilize domestic animals as a tool for gene discovery in relation to feeding behaviours, results of domestication and morphological development. Performed in collaboration with Leif Andersson's group and other collaborators.

1. One of the most striking differences between wild and domesticated rabbits is that the tamed animals can live and breed in captivity, even when they living among potential predators as dogs. In collaboration with Leif Andersson (IMBIM, Uppsala) and Miguel Carneiro (CIBIO, Portugal) we seek to find the genetics behind the differences. We are using MRI to analyze and compare brains from wt and domesticated rabbits. Volumetric analyses of 10 wt and 10 *dom* brains have been performed using with T2 and dt analyses. Differences are

seen. Based on these results of total brain region analysis as well as RNA sequencing, qRT PCR, immunohistochemistry and *in situ* hybridization techniques are used to visualize the quantitative expression and locations of genes that could explain why this species have such diverse characteristics.

2. Analysis of the function and importance of differentially expressed genes in hypothalamus in two selected lines for high and low body weights. Analysis of regions and comparison of location of differentially expressed genes with QTLs and regions that have been under selection. We investigate the importance of the SH3RF2 gene for the metabolism and cognitive functions in the two chicken lines.

3. Identification and analysis of genes and mutations and their regulatory consequences for morphological growth of soft tissue development. Comb modifiers in Pea-comb (Sox5), Rose-comb, double comb and single-comb.

## Publications 2014-2016

2014

1. Shirazi Fard S, All-Ericsson C, Hallböök F. (2014) The heterogenic final cell cycle of chicken retinal Lim1 horizontal cells is not regulated by the DNA damage response pathway. *Cell Cycle*. 13(3):408-17.
2. Harun-Or-Rashid H, Lindqvist N and Hallböök, F. (2014) Transactivation of EGF Receptors in Chicken Müller Cells by  $\alpha$ 2A-Adrenergic Receptors Stimulated by Brimonidine. *Invest Ophthalmol Vis Sci*. 55(6):3385-94
3. Talebizadeh N, Yu Z, Kronschläger M, Hallböök F, Söderberg P. (2014) Specific spatial distribution of Caspase-3 in normal lenses. *Acta Ophtholmol*. July 14, PMID: 25043765
4. Shirazi Fard S, All-Ericsson C, Thysselius, M and Hallböök F. (2014) The terminal basal mitosis of chicken retinal Lim1 horizontal cells is not sensitive to cisplatin induced cell cycle arrest. *Cell Cycle* 13(23):3698-706

2015

5. Dorshorst B, Harun-Or-Rashid M, Bagherpoor AL, Rubin C-J, Ashwell C, Gourichon D, Tixier-Boichard M, Hallböök F, Andersson J. (2015) A Genomic Duplication is associated with Ectopic Eomesodermin Expression in the Developing Embryonic Chicken comb and Two Duplex-comb Phenotypes. *PLoS Genet*. Mar 19;11(3):e1004947
6. Shirazi Fard, S., Blixt, M. K. E., Hallböök, F. (2015) Whole Retinal Explants from Chicken Embryos for Electroporation and Chemical Reagent Treatments. *J. Vis. Exp*. Sep 30;(104). doi: 10.3791/53202e.
7. Shirazi Fard, S., Blixt, M.K.E. and Hallböök, F. (2015) Over-expression of the p53 coactivator Zac1 does not induce cell cycle arrest of Lim1 expressing horizontal progenitor cells. *Cell death & Discovery*. 1, e15023; doi:10.1038/cddiscovery.2015.23
8. Harun-Or-Rashid M, Díaz-DelCastillo M, Galindo-Romero C, Hallböök F. (2015) Alpha2-adrenergic-agonist brimonidine stimulates negative feedback and attenuates injury-induced phospho-ERK and dedifferentiation of chicken Müller cells. *Invest Ophthalmol Vis Sci*. 56(10):5933-45 DOI:10.1167/iovs.15-16816.
9. Blixt, MKE, Shirazi Fard, S, All-Ericsson C, and Hallböök F. (2015) Adding another piece to the retinoblastoma puzzle. *News and Commentary in Cell Death & Disease*, Oct 29;6:e1957. doi: 10.1038/cddis.2015.317

2016

10. Blixt MKE and Hallböök F. A regulatory sequence from the retinoid X receptor  $\gamma$  gene directs expression to horizontal cells and photoreceptors in the embryonic chicken retina. *Molecular Vision* 2016; 22:1405-1420
11. Galindo-Romero, C. Harun-Or-Rashid, M. Vidal-Sanz M, Agudo M, and Hallböök, F. Neuroprotection by  $\alpha$ 2-Adrenergic Receptor Stimulation after Excitotoxic Retinal Injury: A Study of the Total Population of Retinal Ganglion Cells and Their Distribution in the Chicken Retina. *PLoS One*. 2016 Sep 9;11(9):e0161862.
12. Harun-Or-Rashid M, Konjusha D, Galindo-Romero C, Hallböök F. Endothelin B Receptors on Primary Chicken Müller Cells and the Human MIO-M1 Müller Cell Line Activate ERK Signaling via Transactivation of Epidermal Growth Factor Receptors. *PLoS One*. 2016 Dec 8;11(12):e0167778

2017

### Submitted Manuscripts and Manuscripts in preparation

13. Schwochow Thalmann D, Ring H, Sundström E, Cao X, Larsson M, Kerje S, Wright D, Jemth P, Hallböök F. Bed'Hom B, Dorshorst B, Tixier-Boichard M and Andersson L. The evolution of *Sex-linked barring* alleles in chickens involves both regulatory and coding changes in *CDKN2A* **Submitted with revisions** *PloS Genetics*
14. Blixt MKE, Konjusha D, Ring H and Hallböök F. The zinc finger gene *Nolz1* is controlled by retinoic acid and regulates the formation of chicken retinal progenitors and *Lim3* expressing bipolar cells. **Submitted with revision** *Developmental Dynamics*
15. Harun-Or-Rashid M., and Hallböök F. Alpha 2-Adrenergic Agonist Brimonidine Stimulates ERK1/2 and AKT Signaling Via Transactivation of EGF Receptors in MIO-M1 Human Müller Cells. **In manuscript** *Exp Eye Res*
16. Harun-Or-Rashid M, Lönngren U, Sellés-Navarro I, Lee J Y, Agudo M, Näpänkangas U, Vidal-Sanz M, and Hallböök F. Altered expression of progenitor cell genes in Müller cells following retinal ischemia and treatment with the  $\alpha$ 2-adrenergic receptor agonist brimonidine. **In manuscript.**
17. Hedin J, Al-Baghdadi M, Blixt M, Sandlund D, Larsson E, and Hallböök F. Perception of 3D cinema effects and stereoacuity in young adults. **In manuscript** *Scientific Reports*
18. David Wheatcroft, Mohammad Harun-Or-Rashid, Anna Qvarnström, and Finn Hallböök "No evidence for song discrimination in caudomedial nidopallium of females from two closely related songbird species" **In preparation**

### Agencies that support the work /Funding

Faculty grants

Swedish Research Council (M)

Barncancerfonden

Ögonfonden

Kronprinsessan Margaretas arbetsnämnd för synskadade KMA

# ***Physiology and Pharmacology***

## **Physiology**

### ***Gastrointestinal Physiology***

**Group leaders: Olof Nylander, Professor and Markus Sjöblom, Associate Professor**

#### **Members of the group during 2016**

Olof Nylander, Professor in Physiology  
Markus Sjöblom, Associate Professor  
Annika Jägare, Technician (40%)  
Hedvig Olander, Project student  
Asraa Youssef, Project student  
Johanna Bergfeldt, Project student  
Mawj Al Ibraheemi, Project student

#### **External collaborations**

Professor Hans Lennernäs, Dept of Pharmacy, Uppsala University, Sweden  
Professor Dr Ursula Seidler, Hannover Medical School, Germany.  
Professor Per Hellström, Dept. of Medical Sciences, Uppsala University, Sweden

The duodenum, which is the first segment of the small intestine, has a number of important physiological functions. Beside its important task to absorb nutrients, vitamins, electrolytes and water, it also has to neutralize the acidic juice discharged from the stomach, adjust luminal osmolality and prevent absorption of potentially injurious agents and microbes that may be present in water and food. To perform these functions the duodenum must be able to recognize various constituents in the lumen and respond appropriately to the changes in the luminal environment by regulating motility, fluid absorption and secretion, mucosal permeability and the secretion of antibacterial agents and immunoglobulins. The endocrine cells of the gut, the enteric nervous system and the mucosal immune system possibly cooperate in an extremely complicated manner to maintain gut homeostasis.

The overall aim of research is to identify, in the living animal, how different luminal constituents are “sensed” by the duodenal mucosa and to reveal those mechanisms that participate in the response to different provocations such as luminal hypo- and hypertonicity, gastric juice, ethanol, microbes and systemic hypoxia.

#### **Publications 2014-2016**

1. Sommansson A, Nylander O & Sjöblom M. Melatonin decreases duodenal epithelial paracellular permeability via a nicotinic receptor-dependent pathway in rats *in vivo*. *Journal of Pineal Research* 2013 Apr;54(3):282-291.
2. Sedin J, Sjöblom M, & Nylander O. The selective cyclooxygenase-2 inhibitor parecoxib markedly improves the ability of the duodenum to regulate luminal hypertonicity in anaesthetized rats. *Acta Physiol (Oxf)*. 205:433-451, 2012.

3. Seidler U & Sjöblom M. Gastroduodenal Bicarbonate Secretion. In Leonard R. Johnson (Eds), *Physiology of the Gastrointestinal Tract*, 5th edition, Academic Press, Oxford, 2012, pp. 1311-1340.
4. Sommansson A, Nylander O, Sjöblom M. Melatonin decreases duodenal epithelial paracellular permeability via a nicotinic receptor-dependent pathway in rats in vivo. *Journal of Pineal Research*. 2013 Apr;54(3):282-291.
5. Sjöblom M, Lindqvist R, Bengtsson MW, Jedstedt G, Flemström G. Cholecystokinin but not ghrelin stimulates mucosal bicarbonate secretion in rat duodenum: Independence of feeding status and cholinergic stimuli. *Regul Pept*. 2013 Mar 13;183:46-53.
6. Sommansson A, Saudi WS, Nylander O, Sjöblom M. Melatonin inhibits alcohol-induced increases in duodenal mucosal permeability in rats in vivo. *Am J Physiol Gastrointest Liver Physiol*. 2013 Jul 1;305(1):G95-G105.
7. Sedin J, Sjöblom M, Nylander O. Prevention of duodenal ileus reveals functional differences in the duodenal response to luminal hypertonicity in Sprague-Dawley and Dark Agouti rats. *Acta Physiol (Oxf)*. 2013 Nov 19. doi: 10.1111/apha.12201.
8. Sommansson A, Saudi WS, Nylander O, Sjöblom M. The ethanol-induced stimulation of rat duodenal mucosal bicarbonate secretion in vivo is critically dependent on luminal Cl<sup>-</sup>. *PLoS One*. 2014 Jul 17;9(7):e102654. doi: 10.1371/journal.pone.0102654. eCollection 2014.
9. Sommansson A, Yamskova O, Schiöth HB, Nylander O, Sjöblom M. Long-term oral melatonin administration reduces ethanol-induced increases in duodenal mucosal permeability and motility in rats. *Acta Physiol (Oxf)*. 2014 Oct;212(2):152-65. doi: 10.1111/apha.12339. Epub 2014 Jul 22.
10. Sommansson A, Wan Saudi WS, Nylander O, Sjöblom M. The ethanol-induced stimulation of rat duodenal mucosal bicarbonate secretion in vivo is critically dependent on luminal Cl<sup>-</sup>. *PLoS One*. 2014 Jul 17;9(7): e102654.
11. Wan Saudi WS, Halim MA, Rudholm-Feldreich T, Gillberg L, Rosenqvist E, Tengholm A, Sundbom M, Karlbom U, Näslund E, Webb DL, Sjöblom M, Hellström PM. Neuropeptide S inhibits gastrointestinal motility and increases mucosal permeability through nitric oxide. *American Journal of Physiology (Gastrointest Liver Physiol)*. 2015;309(8):G625-G634.

### **Agencies that support the work/ Funding**

Uppsala University, Medical Faculty

## ***Neurophysiology of Motion Vision***

**Group leader: Karin Nordström, PhD, Assoc. Professor**

### **Members of the group during 2016**

Karin Nordström, Docent  
Olga Dyakova, PhD student  
Malin Thyselius, PhD student  
Josefin Dahlbom, researcher

### **Collaborators**

Shannon Olsson, NCBS, India  
Paloma Gonzalez-Bellido, University of Cambridge, UK  
Emily Baird, Lund University  
David Outomuro, Uppsala University

### ***Motion vision***

Animals successfully navigate in a natural world full of highly complex information. Many animals have evolved sensory systems that are optimized for rapidly extracting vital information from a continuous, noisy flow constantly approaching the senses. What mechanisms allow the extraction of salient features extracted from a noisy surround? This broadly interesting question has received a reignited interest in recent years, as it is interesting not just for vision scientists, but the findings additionally have many potential applications, for example in the development of unmanned vehicles, and for information processing of large data sets (so called Big data).

Visual motion can be crudely sub-divided in two types: Wide-field optic flow, which is generated by the animal's own motion through the world, and the motion of objects that move independently of the rest of the surround. For humans, such focal motion may represent an approaching ball during a game of tennis, or a flying bird. Many animals are quite good at rapidly detecting focal object motion, even though the mechanisms are complex, and still difficult to solve reliably in silico. In our lab we investigate both these types of motion vision.

### ***Natural scenes***

We recently described a novel neuron in the fly lobula plate that clearly does not derive its input from classic EMDs (De Haan et al., J Neurosci, 2013). Centrifugal stationary inhibited flicker excited (cSIFE) is strongly excited by flicker, up to very high temporal frequencies. The non-EMD driven flicker sensitivity leads to strong, non-directional responses to high-speed, wide-field motion. Furthermore, cSIFE is strongly inhibited by stationary patterns, within a narrow wavelength band. cSIFE's outputs overlap with the inputs of well-described optic flow sensitive lobula plate tangential cells (LPTCs). Driving cSIFE affects the active dendrites of LPTCs, and cSIFE may therefore play a large role in motion vision.

We are currently investigating the spatial characteristics of scenes that inhibit the neuron. Natural scenes may appear random, but they are not. Instead they contain feature distributions that are surprisingly predictable. Such redundancy has led to animal eyes and brains that are adapted to the spatial characteristics of natural scenes, and the human visual cortex, for example, is strongly tuned to their second-order statistics. However, very little has been known about how the fly brain responds to similar images. We redress this striking omission and show that cSIFE is strongly tuned to the spatial statistics in natural scenes, thus, in strong analogy with the vertebrate visual cortex.



### *Fly behavior*

We are using several techniques for measuring fly behavior. Malin Thyselius has developed a free flight arena, which is big and bright enough for hoverflies to display conspecific interactions. By filming the flies with 2 cameras, we can reconstruct the 3D flight trajectories of flies in the arena.

We also have a trackball set-up where we record the behavioral responses of hoverflies to many different stimuli for which we know the neurophysiological responses. Olga is particularly interested in natural images, so this will be a major component of the planned experiments.

### *Flower visitation project*

The world's bee and bumblebee populations are declining, though an estimated 80% of European crops are directly dependent on insects for pollination. Preserving and promoting wild pollinators is therefore crucial for sustainable agriculture. In addition to maintaining natural habitats and reducing pesticide use, an increased understanding of why and how wild pollinators utilize certain sources will allow us to propose efficient planting and maintenance strategies that maximize crop pollination. Hoverflies are ecologically important alternative pollinators and provide an extremely valuable alternative to the world's wavering bee populations.

In this project we utilize a multimodal and multivariate approach to determine the cues that attract hoverflies to specific pollination sites. We have a unique ability to measure multimodal parameters on a very local scale. Our pilot data suggests that a combination of visual, chemical, and abiotic cues create an optimal hoverfly signature for increased attraction to certain sites.

After quantitatively characterizing this signature in several sites, we test our hypotheses using artificial and/or natural lures to increase wild pollination in unattractive sites. Finally, in conjunction with local, national, and international garden and agricultural organizations, this data will ultimately allow us to publically offer specific ecologically-based strategies to maximize the attractiveness of crops to wild pollinators.

### **Publications 2013-2015**

1. Gonzalez-Bellido, PT, Fabian, ST, and *Nordström, K* (2016) "Target detection in insects: Optical, neural and behavioral optimizations", **Curr Opin Neurobiol**, 41:122-128
2. Outomoro, D, Söderquist, L, Johansson, F, Ödéén, A and *Nordström, K* (2016) "The price of looking sexy: Visual ecology of a three level predator-prey system", **Functional Ecology**
3. *Thyselius, M* and *Nordström, K* (2016) "Hoverfly locomotor activity is resilient to external influence and intrinsic factors", **J Comp Physiol A**, 202 (1): 45–54
4. Dyakova, O, Lee, Y-J, Longden KD, Kiselev, VG and Nordström, K (2015) "A higher-order visual neuron tuned to the spatial amplitude spectra of natural scenes", **Nature Comm**, 6: 8522. doi: 10.1038/ncomms9522
5. Lee, Y-J, Jönsson O and Nordström, K (2015) "Spatio-temporal dynamics of impulse responses to figure motion in optic flow neurons", **PLoS ONE**, 10 (5): e0126265.
6. Wardill, T, Knowles, K, Barlow, L, Tapia, G, Nordström, K, Olberg, R and Gonzalez-Bellido, P (2015) "The killer fly hunger games: Target size and speed predict decision to pursuit", **Brain, Behav Evol**, 86 (1): 28-37; DOI:10.1159/000435944
7. Hidayat, E, Medvedev, A and Nordström, K (2015) "Identification of the Reichardt Elementary Motion Detector Model", In Advances in experimental medicine and biology;

Signal and Image Analysis for Biomedical and Life Sciences, Editors C. Sun, T. Bednarz, T. D. Pham, P. Vallotton and D. Wang, Springer Verlag, 01/2015; 823: 83-105.

8. Hidayat, E, Medvedev, M and Nordström, K (2014) "Identification of a Layer of Spatially Distributed Motion Detectors in Insect Vision", 6th International Congress on Ultra Modern Telecommunications and Control Systems and Workshops (ICUMT), 372-379
9. Hidayat, E, Soltanalian, M, Medvedev, M and Nordström, K (2014) "Stimuli Design for Identification of Spatially Distributed Motion Detectors in Biological Vision Systems". 13th International Conference on Control, Automation, Robotics and Vision (ICARCV) paper ID P0201, pp 740-745

### **Agencies that support the work/ Funding**

Discovery Project, Australian Research Council (ARC, DP170100008, 18% success rate), "Target detection in 3D optic flow", AUD 325,000, with Paloma Gonzalez-Bellido, Cambridge, 2017-2019

Faculty of Medicine, Nursing and Health Sciences Small Grants (seeding), "Multi-unit electrode recordings of motion vision networks", 19,200 AUD, 2016-2017

Stiftelsen Olle Engkvist Byggmästare (2016/348), "Multi-modala faktorer i blomflugpollinering: beteende och neurovetenskap", collaboration with Shannon Olsson, NCBS, 900,000 Skr, 2016 – 2018

The Craaford Foundation (20150516), "From Flies to Robots: How Miniature Brains Navigate Through Complex Environments", 300,000 Skr in collaboration with Emily Baird, Lund University, 2015 – 2016

US Air Force Office of Scientific Research (AFOSR, FA9550-15-1-0188, Neural basis of target tracking in insects: Impact of body size and flight strategy), 302,553 USD to my lab, collaboration with Paloma Gonzalez-Bellido, University of Cambridge, 2015 – 2018

### **Prices and awards**

Centre for Neuroscience Publication Prize 2016 for "The price of looking sexy: Visual ecology of a three-level predator-prey system" in Functional Ecology.

## ***Molecular Physiology and Neuroscience***

**Group leader: Bryndis Birnir, Professor**

### **Members of the group during 2016**

Zhe Jin, researcher

Sergiy Korol, researcher

Aikeremu Ahemaiti postdoctoral fellow

Omar Babateen, PhD student

Amol Bhandage, PhD student

Louise Flood Md/PhD student

Atieh Tafreshiha PhD student

Hayma Hammoud, Ms student

Chang Li, Ms student

Karin Nygren, technical engineer

### ***Project 1: Regulation of neuronal inhibition by metabolic hormones***

A major focus of the lab has been on GABA-generated neuronal inhibition in the hippocampus. We are particularly interested in the so-called tonic inhibition. Tonic GABA-generated currents are a relatively new discovery and we were the first to describe the underlying extrasynaptic GABA-A receptors (Birnir *et al.*, 1994). Tonic currents have been shown to significantly alter neuronal excitability and neuronal survival. The extrasynaptic GABA-A receptors, unlike their synaptic counterparts, are activated by very low extracellular ambient GABA concentrations and are probably also the main targets of drugs such as benzodiazepines and other medicines that target the inhibitory system.

We have discovered that insulin and GLP-1 at physiological concentrations induce tonic GABA-activated currents in hippocampal neurons (Jin *et al.*, 2011, Korol *et al.*, 2015). This has important implications as the hippocampus is the centre for memory and learning plus has a vital role in metabolic homeostasis. Our results are relevant for diseases like diabetes, dementia and Alzheimer's disease but also epilepsy, multiple sclerosis (MS) and a number of psychiatric diseases. We are continuing these studies with the aim of understanding metabolic hormones, and their mimetics, like exendin-4 and liraglutide, modulation of GABAergic inhibition in the hippocampus in health and Alzheimer disease.

### ***Project 2: GABA signalling in the pancreatic islets***

GABA is produced by the insulin-releasing beta cells and in humans, both the beta cells and the glucagon-producing alpha cells plus the delta cells have GABA-A receptors. In rats and mice only the alpha cells have GABA-A receptors (Jin *et al.*, 2013). Our studies today are, therefore, exclusively carried out in human pancreatic islets as no good animal models are available for the human pancreatic islet GABA signalling. Building on our experience of working with brain slices, we have now been able to use the patch-clamp technique to record from cells in intact human islets. Our results show that the ambient GABA concentration in the islets affects the electrical activity of both the alpha and beta cells thus affecting hormone secretion and the balance of insulin and glucagon release. If this balance is disturbed, it may be a part of the underlying cause of type 2 diabetes (Taneera *et al.*, 2012). In addition, our qPCR data shows that in islets from type 2 diabetic patients specific GABA-A subunits are down-regulated as compared to healthy controls. The results very clearly identify GABA-generated tonic currents and thus GABA-A receptors as central parts of the normal physiology of healthy islets as well as the pathophysiology in type 2 diabetes. We are continuing these studies and are in the process of characterising at the single-channel level the

subtypes of GABA-A receptors expressed in a identified subtype of the cells e.g  $\alpha$ ,  $\beta$  or  $\delta$  cells, in the intact human pancreatic islet. We examine their functional and pharmacological properties and further the roles these receptors have in determining the insulin and glucagon secretion from the cells. We then study how these receptors are modulated by medicines like exendin-4 and liraglutide as well as GABA-A receptors specific drugs some the benzodiazepines. We obtain the human tissue from the Uppsala Human Tissue Lab within the strategic research initiative EXODIAB.

### ***Project 3: GABA is a natural immunomodulatory molecule***

Extrasynaptic GABA-A receptors affinity for GABA is in the pM - nM range or more than million times higher affinity than synaptic channels (Lindquist and Birnir, 2006, Jin *et al.*, 2011). After making this discovery we decided to examine if lymphocytes expressed GABA-A receptors as there are low concentrations of GABA present in the blood. And yes, lymphocytes have GABA-A receptors and activation of these channels decreased the T cell proliferation. We have proposed that the GABA-activated brake on immune cell proliferation is an important mechanism in keeping toxic lymphocytes in check and if this “brake” is malfunctioning, diseases like MS and type 1 diabetes may arise or progress more rapidly (Bjurström *et al.*, 2008, Mendu *et al.*, 2011). We are further characterizing by what mechanism GABA is able to decrease lymphocyte proliferation and what subtypes of the receptors are expressed. Recently, we examined, in human peripheral blood mononuclear cells, if the GABA receptors varied between men and women and if pregnancy or depression influenced their mRNA expression. It turned out that gender, pregnancy and depression modulated the expression of the receptors in the cells! The results imply that in humans the GABA signalling system in immune cells is finely tuned to physiology (Bhandage *et al.*, 2014). These results may open up interesting treatment and diagnostic possibilities in a number of diseases. We are currently investigating effects of GABA on immune cells from type 1 diabetes patients and depressed patients, collaboration with professor Lisa Ekselius and others at the Psychiatry division of the Department of Neuroscience.

### ***Project 4: GABA-A receptors in cancer***

In collaboration with professors A. Smits (Uppsala University) and E. Aronica (Neuropathologist, Netherlands) we have characterized expression of GABA-A receptors subunits in human gliomas of various malignancy. Our results show that GABA-A subunit expression in human glioma correlates with tumor histology and clinical outcome (Smits *et al.*, 2012). The results indicate that if we can boost the GABA system we may be able to decrease tumor malignancy/proliferation. In a cell-line derived from human glioblastoma, in collaboration with professors K. Forsberg-Nilsson, B. Westermark and L. Uhrbom, we demonstrated that the GABA-A receptors were functional and modulated by drugs and in particular by the anaesthetic etomidate (Babateen *et al.*, 2014).

### ***Project 5: In brains of human alcoholics there are selective brain areas that have specific changes in GABA-A and Glutamate receptors subunits***

In a series of papers (Jin *et al.*, 2011, 2014a, b; Bhandage *et al.*, 2014) we have shown in samples from postmortem human brains that a decrease or an increase in the inhibitory GABAergic signalling system is mirrored by changes in the glutamate excitatory signalling system. Moreover, changes in the brains of alcoholics take place in specific brain areas with the greatest alterations in areas where new memories are formed, like the hippocampus and

amygdala. Our results further indicate that there is an altered balance between caudate-mediated voluntarily controlled and automatic behaviors in alcoholics, including diminished executive control on goal-directed alcohol-seeking behavior. This conclusion has important implications for relapse and potentially ways of inhibiting relapse.

It is not known why some brain areas are vulnerable to alcohol exposure when other areas are not. Whether the changes in one neurotransmitter system drives changes in the other or if they change independently but change in order to maintain neuronal networks functional integrity, is currently an active research area.

### ***Project 6: ENABLE: European Gram-negative Antibacterial Engine***

Antimicrobial resistance is a major public health threat. Infections caused by resistant bacteria are increasing. Despite the strong need for new antimicrobials, very few new, effective antibiotics have been brought to the market in the last decades. The ENABLE project is collaboration between many Universities and pharmaceutical companies, working to advance the development of potential antibiotics against Gram-negative bacteria, such as *Escherichia coli*. The ultimate goal of the project is to develop attractive antimicrobial candidates for testing in the clinic, bringing the possibility of new antibiotics to treat Gram-negative infections one step closer to patients. Our laboratory participates in the project by testing compounds on specific voltage-gated ion channels.

### **Publications 2014-2016**

1. Losch BF, Korol SV, Ganor Y, Gu S, Cooper I, Eilam R, Besser M, Goldfinger M, Chowes Y, Wank R, Birnir B, Levite M (2016) Normal human CD4+ helper T cells express Kv1.1 voltage-gated K+ channels, and selective Kv1.1 block in T cells induce by itself robust TNF $\alpha$  production and secretion and activation of the NF $\kappa$ B non-canonical pathway *J Neural Transmission*. 123(3):137-57. doi: 10.1007/s00702-015-1446-9.
2. Korol SV, Jin Z, Babateen O, Birnir B (2015) GLP-1 and Exendin-4 Transiently Enhance GABAA Receptor-Mediated Synaptic and Tonic Currents in Rat Hippocampal CA3 Pyramidal Neurons. *Diabetes*. 64(1):79-89. doi: 10.2337/db14-0668. Epub 2014 Aug 11
3. Korol SV, Jin Z, Birnir B. (2015) The GLP-1 Receptor Agonist Exendin-4 and Diazepam Differentially Regulate GABAA Receptor-Mediated Tonic Currents in Rat Hippocampal CA3 Pyramidal Neurons. *PLoS One*. 10(4):e0124765. doi: 10.1371/journal.pone.0124765. eCollection 2015.
4. Bhandage AK, Jin Z, Bazov I, Kononenko O, Bakalkin G, Korpi ER, Birnir B (2014) GABA-A and NMDA receptor subunit mRNA expression is altered in the caudate but not the putamen of the postmortem brains of alcoholics. *Front Cell Neurosci*. 8:415. doi: 10.3389/fncel.2014.00415. eCollection 2014
5. Jin Z, Bhandage AK, Bazov I, Kononenko O, Bakalkin G, Korpi ER, Birnir B (2014) Expression of specific ionotropic glutamate and GABA-A receptor subunits is decreased in central amygdala of alcoholics. *Front Cell Neurosci*. 8:288. doi: 10.3389/fncel.2014.00288. eCollection 2014

6. Jin Z, Bhandage AK, Bazov I, Kononenko O, Bakalkin G, Korpi ER, Birnir B. (2014) Selective increases of AMPA, NMDA, and kainate receptor subunit mRNAs in the hippocampus and orbitofrontal cortex but not in prefrontal cortex of human alcoholics. *Front Cell Neurosci.* 8:11. doi: 10.3389/fncel.2014.00011. eCollection 2014
7. Bhandage AK, Hellgren C, Jin Z, Olafsson EB, Sundström-Poromaa I, Birnir B (2015) Expression of GABA receptors subunits in peripheral blood mononuclear cells is gender dependent, altered in pregnancy and modified by mental health. *Acta Physiol (Oxf).* doi: 10.1111/apha.12440.
8. Babateen O, Jin Z, Bhandage A, Korol SV, Westermark B, Forsberg Nilsson K, Uhrbom L, Smits A, Birnir B (2014) Etomidate, propofol and diazepam potentiate GABA-evoked GABA currents in a cell line derived from human glioblastoma. *Eur J Pharmacol.* 1748C:101-107. doi: 10.1016/j.ejphar.2014.12.001.
9. Alenkvist I, Dyachok O, Tian G, Li J, Mehrabanfar S, Jin Y, Birnir B, Tengholm A, Welsh M (2014) Absence of Shb impairs insulin secretion by elevated FAK activity in pancreatic islets. *J Endocrinol.* 2014 Dec;223(3):267-75. doi: 10.1530/JOE-14-0531.

## Reviews

1. Barragan A, Weidner JM, Jin Z, Korpi ER and Birnir B (2015) GABAergic signaling in the immune system. *Acta Physiol.* 213(4):819-27. doi: 10.1111/apha.12467.

## Agencies that support the work/ Funding

Swedish Research Council  
 The Swedish Brain Foundation  
 EXODIAB (Excellence of Diabetes Research in Sweden)  
 Inslamlingsstiftelsen Diabetes Wellness Network Sverige  
 The Swedish Diabetes Foundation  
 The Swedish Children's Diabetes Foundation  
 ENABLE (European Gram-negative Antibacterial Engine)  
 Thuring Stiftelse  
 Ernfors Stiftelse

## Prices, awards and other

Birnir, 2016, became Chair, Swedish National Committee for Pharmacol, Physiol and Neurosci, <http://www.kva.se/en/contact/NationalICSU-kommitteer/Pharmacology/>

## ***Behavioural Neuroendocrinology***

**Group leader: Svante Winberg, Professor**

### **Members of the group during 2016**

Per-Ove Thörnqvist, PhD, Research Associate  
Josefin Sundin, PhD, postdoc  
Arianna Cocco, PhD-student  
Laura Vossen, PhD-student  
Johanna Axling, PhD-student  
Arshi Mustaffa, PhD-student  
Imdad Ullah Salar PhD-student (Quaid-i-Azam University, Islamabad, Pakistan)  
Oly Sensarma, master student  
Helen Nilsson, master student  
Nikita Tjernström, master student  
Kathryn McKay, master student  
Katherine Valdivieso, master student  
Harmen Koning, master student

### **External collaboration**

Evolutionary Biology Centre, Uppsala University  
Dept. of Zoology, Göteborg University  
Sahlgrenska Academy at Göteborg University  
Swedish University of Agricultural Sciences, Umeå, Sweden  
Danish Technical University, Hirtshals, Denmark  
Norwegian University of Life Sciences, Aas, Norway  
Norwegian School of Veterinary Science, Oslo, Norway  
University of Oslo, Norway  
Linköping University  
Göteborg University  
Centre for Environment Fisheries and Aquaculture Science (CEFAS), UK  
Norwegian Institute of Water Research (NIVA)  
French Research Institute for Exploitation of the Sea (IFREMER), France  
Food and Agricultural Research Institute (IRTA), Spain  
Italian health authority and research organization for animal health and food safety (IZSVE), Italy  
Universidad Politécnica de Madrid, Spain

Our research is focused on neuroethology and comparative neuroendocrinology, and we are especially interested in the adaptive value of variable individualized stress responses and possible behavioural correlates of various neuroendocrine stress response profiles. A role of social experience in modifying the behavioural output of an individual seems to be well established, but the physiological background of differing life histories and behavioural tactics is largely unknown.

***Project 1: Personality traits in zebrafish (Danio rerio): Behaviour and neuroendocrine mechanisms***

**Participats:** Per-Ove Thörnqvist, Arshi Mustaffa, Gonzalo Andre and Svante Winberg

The aim of this project is to use zebrafish as a model to study personality traits and neuroendocrine and molecular mechanisms controlling these traits. As well as being a major model organism in terms of developmental anatomy, the zebrafish is also an excellent, if under-used, model for studies on behavioral genetics. The short generation time (about 3 months) is a clear advantage when creating divergent strains by selective breeding. In the present project we will create two strains of zebrafish differing in personality traits. These strains will be used to study correlations between behavioral and physiological traits.

***Project 2: Mechanisms of improved stress tolerance and welfare of farmed fish***

**Participants:** Per-Ove Thörnqvist, Svante Winberg

We have found that divergent inherent stress coping strategies akin to those described as proactive and reactive coping strategies in mammals exists also in fish. However, recent studies suggest that stress coping strategies are modulated by the epigenetic effects of social interaction. Previous studies show that the behavior and physiology of fish is dramatically affected by social interactions, and that the brain serotonergic system plays a key for these effects. The serotonergic (5-HT) system is also known to be important for the expression of coping strategies. We will now explore to what extent behavior and neuroendocrine stress responses of reactive and proactive rainbow trout is affected by social interaction. Moreover we will study the effects of stimulation on the 5-HT system on behavioral profiles and stress responses in a non-selected hatchery population as well as in rainbow trout strains selectively bred for high (HR) and low (LR) post-stress plasma cortisol, respectively. There is a large interest in generating stress tolerant fish strain that could cope with the unavoidable stress in aquaculture. This task is complicated by the fact that traits like stress tolerance and boldness is linked to aggressiveness. Moreover, environmental enrichment is often discussed, and is believed to have positive effects on fish welfare and performance. Still our knowledge on the effects of environmental enrichment on fish performance is very limited.

***Project 3: Effects of increasing ocean CO<sub>2</sub> on fish neurophysiology and behaviour***

**Participants:** Svante Winberg, Bryndis Birnir, Arianna Cocco, Laura Vossen, Josefin Sundin (collaboration with Fredrik Jutfelt, Göteborg University, Göran Nilsson, Oslo University).

Ocean CO<sub>2</sub> concentration increases in line with atmospheric CO<sub>2</sub> resulting in ocean acidification. In addition, rising ocean CO<sub>2</sub> concentrations may by itself have severe disturbing effects on fish behaviour. Recent studies have shown that near future CO<sub>2</sub> levels, can cause a behavioural reversal in larval fish, significantly reducing settling success. In fish, high pCO<sub>2</sub> could lead to a shift in the gradients of Cl<sup>-</sup> and/or HCO<sub>3</sub><sup>-</sup> across neural membranes, resulting in a reversal of the GABA-A receptor action, i.e. making it excitatory instead of inhibitory. This hypothesis is supported by a recent report that treatment with a GABA-A receptor antagonist counteracts the behavioural effects of elevated pCO<sub>2</sub>. The effect could be widespread among marine fish species since GABA-A receptor mechanisms appear conserved. However, the time-course of the behavioural effects of elevated pCO<sub>2</sub> suggests that effects on gene expression may be involved. Moreover, it is likely that fresh water fish living shallow eutrophic environments, where pCO<sub>2</sub> may fluctuate, display adaptations to high pCO<sub>2</sub>. The current proposal will apply a comparative approach,



comparing marine fish to zebrafish in order to assess behavioural effects of GABA-A receptor ion permeability and subunit composition. This will provide information on the mechanisms behind the behavioural changes, which can subsequently be used to predict the sensitivity of different species to rising ocean CO<sub>2</sub> concentrations.

The project started 2013 and is financed for 4 years by VR.

#### ***Project 4: Welfare, Health and Individuality in Farmed FISH: The WIN-FISH project***

**Participants:** Svante Winberg<sup>1</sup>, Leif Andersson<sup>1</sup>, Marie-Laure Bégout<sup>2</sup>, Ana Roque<sup>3</sup>, Amedeo Manfrin<sup>4</sup>, Morris Villarroel<sup>5</sup>, Manuel Gestó<sup>6</sup>.

<sup>1</sup>Uppsala Universitet, Sweden; <sup>2</sup>IFREMER, France; <sup>3</sup>IRTA, Spain; <sup>4</sup>IZSVe, Italy;

<sup>5</sup>Universidad Politécnica de Madrid, Spain; <sup>6</sup>DTU Aqua, Denmark.

An ERA-net ANIHW project

In modern aquaculture, fish are exposed to farming-inherent stressors that can be detrimental to animal health and welfare. However, it is increasingly clear that stress reactions are different for each individual and therefore, individuality should be included in the concept of animal welfare. Individual differences often take the form of suites of traits, or stress coping styles (SCS), where traits like sympathetic reactivity, aggression and the tendency follow and develop routines show positive relationships. In addition, these traits show a negative relationship with plasma cortisol levels and are also associated with differences in immune function. The main aim of the WIN-FISH project is to investigate the relevance of fish individuality when assessing fish welfare and performance under different culture conditions. The WIN-FISH consortium, consisting of 6 partners in 5 countries, will validate behavioral and physiological welfare indicators for sea bass, sea bream and rainbow trout at the individual and rearing unit level. This will generate new information about responses to environmental factors, knowledge that can be applied to improve husbandry and management practices. Modern recirculating aquaculture systems (RAS) related-stressors such as higher rearing densities and water quality parameters may challenge the welfare of fish. In WIN-FISH, health, welfare and production related effects of RAS rearing of sea bass and sea bream kept at different densities will be monitored. In order to account for individual variation, these studies will be performed on fish screened for SCS. Similarly, in flow through systems, health, welfare and production related effects of rearing densities will be further investigated in sea bream differing in SCS. It is also known that, in general, environmental enrichment has positive effects on animal welfare. WIN-FISH will investigate effects of environmental enrichment on rainbow trout with contrasting SCS. In an attempt to generate genetic markers for selective breeding to optimize performance and welfare of farmed Atlantic salmon, a genome-wide association analysis will be performed on salmon with divergent SCS, focusing on proactive fish differing in aggressive behavior. Finally, zebrafish will be used as a model to gain additional knowledge on mechanisms underlying SCS and aggressive behavior.

#### **Publications 2014-2016**

1. Kotrschal, A., Lievens, E.J.P., Dahlbom, J., Bundsen, A., Semenova, S., Sundvik, M., Maklakov, A.A., Winberg, S., Panula, P. & Kolm, N. (2014). Artificial selection on relative brain size reveals a positive genetic correlation between brain size and proactive personality in the guppy. *Evolution* 68: 1139-1149.
2. Amcoff, M., Hallsson, L.R., Winberg, S. & Kolm, N. (2014). Male courtship pheromones affect female behaviour in the swordtail characin (*Corynopoma riisei*). *Ethology* 120:463-470.

3. Thörnqvist, P.-O., Höglund, E. & Winberg, S. (2015). Natural selection constrains personality and brain gene expression differences in Atlantic salmon (*Salmo salar*). *J. Exp. Biol.* 218: 1077-1083.
4. Sebire, M., Davis, J. E., Hatfield, R., Winberg, S. & Katsiadaki, I. (2015). Prozac affects stickleback nest quality without altering androgen, spiggin or aggression levels during a 21-day breeding test. *Aquat. Toxicol.* 168: 78-89.
5. Backström, T., Heynen, M., Brännäs, E., Nilsson, J., Winberg, S. & Magnhagen, C. (2015). Social stress effects on pigmentation and monoamines in Arctic charr. *Behav. Brain Res.* 291: 103-107.
6. Fraser, T. W. K., Vindas, M. A., Fjellidal, P. G., Winberg, S., Thörnqvist, P.-O., Øverli, Ø., Skjæraasen, J.-E., Hansen, T. J. & Mayer, I. (2015). Increased reactivity and monoamine dysregulation following stress in triploid Atlantic salmon (*Salmo salar*). *Comp. Biochem. Physiol. A* 185: 125-131.
7. Magnhagen, C., Backström, T., Øverli, Ø., Winberg, S., Nilsson, J., Vindas, M. A. & Brännäs, E. (2015). Behavioural responses in a net restraint test predict interrenal reactivity in Arctic charr *Salvelinus alpinus*. *J. Fish Biol.* 87: 88-99.
8. Larsen, M. H., Johnsson, J. I., Winberg, S., Wilson, A. D. M., Hammenstig, D., Thörnqvist, P.-O., Midwood, J. D., Aarestrup, K. & Höglund, E. (2015). Effects of emergence time and early social rearing environment on behaviour of Atlantic salmon: Consequences for juvenile fitness and smolt migration. *PlosOne* 10: e0119127.
9. Moltesen, M., Vindas, M. A., Winberg, S., Ebbesson, L. O. E., Ruiz-Gomez, M. L., Skov, P. V., Dabelsteen, T., Øverli, Ø. & Höglund, E. (2016). Cognitive appraisal of aversive stimulus differs between individuals with contrasting stress coping styles; evidences from selected rainbow trout (*Oncorhynchus mykiss*) strains. *Behav.* 153: 1567-1587.
10. Moltesen, M., Laursen, D. L., Thörnqvist, P.-O., Åberg Andersson, M., Winberg, S. & Höglund, E. (2016). Effects of acute and chronic stress on telencephalic neurochemistry and gene expression in rainbow trout (*Oncorhynchus mykiss*). *J. Exp. Biol.* 219: 3907-3914.
11. Vossen, L. E., Jutfelt, F., Cocco, A., Thörnqvist, P.-O. & Winberg, S. (2016). Zebrafish (*Danio rerio*) behaviour is largely unaffected by elevated pCO<sub>2</sub>. *Conservation Physiology* 4: cow065.
12. Rosengren, M., Thörnqvist, P.-O., Johnsson, J.I., Sandblom, E., Winberg, S., & Sundell, K. (2017). High risk no gain-metabolic performance of hatchery reared Atlantic salmon smolts, effects of nest emergence time, hypoxia avoidance behaviour and size. *Physiol. Behav.* (in press).
13. Backström, T., Heynen, M., Brännäs, M., Nilsson, J., Winberg, S. & Magnhagen, C. (2017). Anaesthesia and handling stress effects on pigmentation and monoamines in Arctic charr. *Environ. Biol. Fish* (doi: 10.1007/s10641-016-0563-0).
14. Ullah, I., Zuberi, I., Khan, K. U., Ahmad, S., Thörnqvist, P.-O. & Winberg, S. (2017). Effects of enrichment on the development of behaviour in an endangered fish mahseer (*Tor putitora*). *Appl. Anim. Behav. Sci.* 186: 93-100.
15. Vindas, M. A., Gorissen, M., Höglund, E., Flik, G., Tronci, V., Damsgård, B., Thörnqvist, P.-O., Nilsen, T. O., Winberg, S., Øverli, Ø. & Ebbesson, L. O. E. (2017). How do individuals cope with stress? Behavioural, physiological and neuronal differences between proactive and reactive coping styles in fish. *J. Exp. Biol.* (doi: 10.1242/jeb.153213).
16. Cocco, A., Rönnerberg, A. M. C., Jin, Z., André, G. I., Vossen, L. E., Bhandage, A. K., Thörnqvist, P.-O., Birnir, B. & Winberg, S. (2017). Characterization of the  $\gamma$ -aminobutyric acid signaling system in the zebrafish (*Danio rerio* Hamilton) central nervous system by reverse transcription-quantitative polymerase chain reaction. *Neurosci.* 343: 300-321.

### Reviews articles

1. Winberg, S. & Thörnqvist, P.-O. (2016). Role of brain serotonin in modulating fish behavior. *Curr. Zool.* 62: 317-323.

### Books and book chapters

1. Winberg, S., Höglund, E. & Øverli, Ø. (2016). Variation in the neuroendocrine stress response, In: *Biology of Stress in Fish* (Fish Physiology Vol. 35, series eds. Anthony P. Farrell & Colin

J. Branner), pp. 35-75, eds. Carl B. Schreck & Luis Tort, Elsevier Academic Press (ISBN: 978-0-12-802728-8)

2. Nunes, A. R., Ruhl, N., Winberg, S. & Oliveira, R. F. (2017). Social Phenotypes in Zebrafish, In: *The rights and wrongs of zebrafish: Behavioral phenotyping of zebrafish*, pp. 95-139, Allan V. Kalueff ed., Springer International Publishing (ISBN: 978-3-319-33773-9)

### **Agencies that support the work/ Funding**

The Swedish Research Council (VR), The Swedish Research Council for Environment Agricultural Sciences and Spatial Planning (FORMAS), FACIAS, Uppsala University Medical Faculty, ERA-net ANIHW

## **Pharmacology**

### ***Pharmacology***

**Group leader: Dan Larhammar, PhD, Professor**

### **Members of the group during 2016**

Bo Xu, PhD  
Christina Bergqvist, research engineer  
David Lagman, PhD  
Helen Haines, PhD student  
Ingrid Lundell, PhD, reader (lecturer) em.  
Jasna Pruner, PhD student  
Julia Pedersen, PhD student  
Kateryna Shebanits, PhD student  
Lars G. Lundin, PhD, docent, reader (lecturer) em.  
Xesús Abalo, PhD, researcher  
Xiao Zhang, PhD, researcher, adjunct lecturer

### Project students

Gabriel Heras Arribas, project student  
Harmen Koning, project student  
James Janani, project student

### **Our research has two primary aims:**

- 1) To deduce the evolution of important gene families in vertebrates, particularly gene families expressed in the nervous system and in the endocrine system. We wish to find out when new genes and functions have arisen and how functions have changed during evolution. We are primarily investigating gene families involved in vision and in learning and long-term memory.
- 2) To characterize the NPY (neuropeptide Y) system of peptides and receptors of importance in appetite regulation.

Thousands of vertebrate gene families are now known to have expanded in the two genome doublings (tetraploidizations) that took place approximately 500 million years ago. A third

genome doubling occurred in the ancestor of teleost fishes. These dramatic events explain a great deal of the complexity of the vertebrates. We combine phylogenetic sequence analyses with chromosome comparisons across species to determine gene duplication time points. This allows identification of corresponding genes (orthologs) in different species for comparisons of functions. This helps explain how functions arise, change, and even disappear during evolution. We have recently resolved several gene families including the opioid peptides (enkephalins etc.) and receptors, growth hormone and prolactin and their receptors, oxytocin-vasopressin and somatostatin receptors, sodium and calcium channels, gene families involved in vision (such as opsins) and gene families involved in learning and long-term memory.

NPY is an abundant neuropeptide in the brains of all mammals including humans. NPY and its two related peptides PYY and PP regulate appetite, metabolism and numerous other physiological functions. We investigate how these peptides bind to their 4-7 receptors in different vertebrate species, primarily the four human receptors. We are especially exploring the opposing roles of NPY and PYY/PP in appetite regulation. The methods used include molecular biology, functional expression and in vitro pharmacology. We also investigate how genetic variation in one of the human receptor genes correlates with body weight and obesity.

***Project 1: Evolution of vertebrate neuronal and endocrine gene families***

**Participants:** Christina Bergqvist, Helen Haines, Julia Pedersen, David Lagman, Lars G. Lundin

Our studies have shown that many neuronal and endocrine gene families gained new gene copies in the two early vertebrate tetraploidizations. These duplications have allowed evolution of many new and more highly specialized functions. We are presently investigating several families of neuropeptides, G protein-coupled receptors and ion channels.

***Project 2: Functional and genetic studies of the neuropeptide Y (NPY) system***

**Participants:** Bo Xu, Jasna Pruner, Kateryna Shebanits

In mammals, NPY stimulates appetite primarily via receptor subtypes Y1 and Y5, whereas the related gut endocrine peptide PYY reduces appetite via receptor Y2. The effects of pancreatic polypeptide (PP) via Y4 are still obscure. We investigate the ligand-binding properties of the human Y2 receptor by mutagenesis, functional expression and in vitro pharmacology. We have identified important points of interaction between peptides and receptors. The results will facilitate drug development to reduce appetite.

Recent studies have shown that the PP receptor Y4 is associated with childhood obesity and adult body weight. We have found strong correlation between Y4 gene copy number variation (CNV) body weight, suggesting a causal role for the Y4 receptor..

***Project 3: Evolution of vision in vertebrates***

**Participants:** Xesús Abalo, David Lagman

Numerous gene families are involved in vertebrate vision. We have found that the early vertebrate genome doublings generated gene duplicates that became specialized on expression in cones or rods, respectively. A surprising conclusion from these comparisons is that colour vision arose before dim-light vision. We have found distinct expression patterns for gene

duplicates in the eye in zebrafish. For instance, some duplicates differ in the circadian regulation. Thus, the genome doublings have contributed to functional specialization.

#### ***Project 4: Evolution of memory molecules***

**Participants:** Helen Haines, Christina Bergqvist, Julia Pedersen

Learning and long-term memory are exceedingly complex processes involving multiple types of receptors and ion channels and a large repertoire of modulating proteins. So far, most studies have used rat and mouse as model systems to characterize the molecular mechanisms. However, such complicated machineries can best be understood by taking an evolutionary approach to deduce how they have originated and become so complicated. We are therefore investigating how and when the gene duplications took place that have generated the gene families involved in learning and memory. Many of the gene families expanded in the early vertebrate genome doublings, and zebrafish often has more such genes than mammals. Future studies will combine phylogenetic analyses with comparisons of expression patterns in the brain, primarily aiming to compare zebrafish with rat/mouse.

#### ***Project 5: Involvement of heparan sulfate in reward and Alzheimer's disease***

**Participants:** Xiao Zhang

Heparan sulfate (HS) proteoglycans have numerous roles and influence a range of physiological functions, for instance by binding to peptides and proteins. It has been found that HS and degradation of HS by heparanase affect feeding and that HS binds to the appetite-stimulating peptide AgRP. This will be investigated further by exploring the role of HS and AgRP in the reward circuitry of dopamine neurons in genetically modified mice. In Alzheimer's disease, HS seems necessary for macrophage-mediated clearance of the A $\beta$  peptide. The mechanisms for this are explored further in mouse models. Also, changes in heparanase during aging are investigated.

#### **Publications 2014-2016**

1. Larhammar, D. and Lagman, D. Turtle ghrelin. Comment on: "The draft genomes of soft-shell turtle and green sea turtle yield insights into the development and evolution of the turtle-specific body plan." *Nature Genetics* 46, 524-525 (2014). PMID: 24866184.
2. Ståhlberg, G., Ekselius, L., Lindström, L. H., Larhammar, D., and Boden, R. Neuropeptide Y, social function and long-term outcome in schizophrenia. *Schizophr. Res.* 156, 223-227 (2014). PMID: 24799298.
3. Tostivint, H., Ocampo Daza, D., Bergqvist, C. A., Quan, F. B., Bougerol, M., Lihrmann, I., and Larhammar, D. Molecular evolution of somatostatin and urotensin II systems. *J. Mol. Endocrinol.* 52, T61-86 (2014). PMID: 24740737.
4. Cardoso, J. C. R., Félix, R. C., Bergqvist, C. A., and Larhammar, D. New insights into the evolution of vertebrate CRH (corticotropin-releasing hormone) and invertebrate DH44 (diuretic hormone 44) receptors in metazoans. *Gen. Comp. Endocrinol.* 209, 162-170 (2014). PMID: 25230393.

5. Larhammar, D., Xu, B., and Bergqvist, C. A. Unexpected multiplicity of QRFP receptors in early vertebrate evolution. *Front. Neurosci.* 8, 337 (2014). PMID: 25386115.
6. Xu, B., Bergqvist, C. A., Sundström, G., Lundell, I., Vaudry, H., Leprince, J., and Larhammar, D. Characterization of peptide QRFP (26RFa) and its receptor from amphioxus, *Branchiostoma floridae*. *Gen. Comp. Endocrinol.* Epub 2014 Oct 25. PMID: 25449662.
7. Zhang, X., Wang, B., Li, J. P. Implications of heparan sulfate and heparanase in neuroinflammation. *Matrix Biol.* 35, 174-181 (2014). PMID: 24398134.
8. Zhang, G. L., Zhang, X., Wang, X. M., Li, J. P. Towards understanding the roles of heparan sulfate proteoglycans in Alzheimer's disease. *Biomed Res Int.* 2014:516028. PMID: 25157361.
9. O'Callaghan, P., Noborn, F., Sehlin, D., Li, J. P., Lannfelt, L., Lindahl, U., and Zhang, X. Apolipoprotein E increases cell association of amyloid- $\beta$  40 through heparan sulfate and LRP1 dependent pathways. *Amyloid* 21, 76-87 (2014). PMID: 24491019.
10. Jendresen, C. B., Cui, H., Zhang, X., Vlodavsky, I., Nilsson, L. N., Li, J. P. Overexpression of heparanase lowers amyloid burden in A $\beta$ PP transgenic mice. *J. Biol. Chem.* 2014 (Dec. 29).
11. Xu, B., Bergqvist, C. A., Sundström, G., Lundell, I., Vaudry, H., Leprince, J., and Larhammar, D. Characterization of peptide QRFP (26RFa) and its receptor from amphioxus, *Branchiostoma floridae*. *Gen. Comp. Endocrinol.* 210, 107-113 (2015). PMID: 25449662.
12. Lagman, D., Callado-Pérez, A., Franzén, I. E., Larhammar, D.<sup>\*,+</sup> and Abalo, X. M.<sup>\*\*</sup>) These authors have contributed equally. Transducin duplicates in the zebrafish retina and pineal complex: differential specialisation after the teleost tetraploidisation. *PLoS One*, 10(3):e0121330 (2015). PMID: 25806532.
13. O'Callaghan, P., Li, J.-P., Lannfelt, L., Lindahl, U., and Zhang, X. Microglial heparan sulfate proteoglycans facilitate the cluster-of-differentiation 14 (CD14)/Toll-like receptor 4 (TLR4)-dependent inflammatory response. *J. Biol. Chem.* 290, 14904-14914 (2015). PMID: 25869127.
14. Jendresen, C. B., Cui, H., Zhang, X., Vlodavsky, I., Nilsson, L.N., and Li, J.-P. Overexpression of heparanase lowers the amyloid burden in amyloid- $\beta$  precursor protein transgenic mice. *J. Biol. Chem.* 290, 5053-5064 (2015). PMID: 25548284.
15. Xu, B., Lagman, D., Sundström, G., and Larhammar, D. Neuropeptide Y family receptors Y1 and Y2 from sea lamprey, *Petromyzon marinus*. *Gen. Comp. Endocrinol.* 222, 106-115 (2015). PMID: 26255155.
16. Cui, H., Tan, Y.-X., Österholm, C., Zhang, X., Hedin, U., Vlodavsky, I., and Li, J.-P. Heparanase expression upregulates platelet adhesion activity and thrombogenicity. *Oncotarget* 2016, 7:39486-39496. PMID: 27129145.

17. Cardoso, J. C., Bergqvist, C. A., Félix, R. C., and Larhammar, D. Corticotropin-releasing hormone family evolution: five ancestral genes remain in some lineages. *J. Mol. Endocrinol.* 57, 73-86 (2016). PMID: 27220618.

18. Lagman, D., Franzén, I. E., Eggert, J., Larhammar, D. and Abalo, X. M. Evolution and expression of phosphodiesterase 6 genes unveils vertebrate novelty to control photosensitivity. *BMC Evol. Biol.*, 16:124 (2016). PMID: 27296292.

### **Book chapters and web articles**

1. Larhammar, D., Bergqvist, C. A., and Sundström, G. Ancestral vertebrate complexity of the opioid system. In "Nociceptin Opioid", Ed.: G. Litwack. *Vitam. Horm.* 97, 95-122 (2015). Academic Press/Elsevier Inc.

### **Commentaries**

1. Larhammar, D. Comment on study of acupuncture against dry eyes. *Focus on Alternative and Complementary Therapies* 20(3-4), 144-145 (2015).

2. Larhammar, D. Comment on systematic review of trials of valerian against insomnia: "No effect of valerian against insomnia". *Focus on Alternative and Complementary Therapies* 21(1), 42-43.

3. Larhammar, D. and Larsson, I. Comment on study of weight reduction: "Proprietary weight-reduction supplement: evidence inconclusive". *Focus on Alternative and Complementary Therapies* 21(1), 64-65 (2016).

### **Popular Science Articles**

1. Larhammar, D. "Ingen effekt på psoriasis" - artikel om sprängticka, *Inonotus obliquus*. *Psoriasis-tidningen* 1/2015, sid 40-41.

2. Larhammar, D. "Alternativmedicinens brister belysta inifrån". Recension av "A scientist in Wonderland - A memoir of search for truth and finding trouble" by Edard Ernst. *Läkartidningen* 2015;112:DMIT, 2015-08-11.

### **Agencies that support the work/ Funding**

Carl Tryggers Stiftelse

### **Honours**

Dan Larhammar is 3rd vice president of the Royal Swedish Academy of Sciences 2015-2018 and chairperson for the the Academy's Education Committee.

Dan Larhammar was appointed 'Pharmacist of the Year' 2016 by the Swedish Pharmacists (Sveriges Farmaceuter), the pharmacists' union, for 'being a strong advocate of evidence-based medicine and the pharmaceutical profession', and for criticizing pseudoscientific alternative medicine.

Dan Larhammar was appointed as the Karl Johan Öbrink lecturer 2016 by the Biomedical Center of Uppsala University. The prize committee's motivation: "Dan is a transboundary researcher with scientific integrity and good dissemination of his research." (Swedish: "Dan är en gränsöverskridande forskare med vetenskaplig integritet och god spridning av sin forskning.")

## ***Functional Pharmacology***

**Group leader: Helgi B. Schiöth, Professor, director of PhD studies, course leader**

**Senior leaders: Madeleine Le Grevés, Lecturer and director of studies in pharmacology, Michael Williams, Associate prof. and Christian Benedict, Associate prof., PI sleep group.**

### **Members of the team during 2016**

Helgi B. Schiöth, professor  
Madeleine Le Grevés, lecturer,  
Christian Benedict, associate professor  
Michael Williams, associate professor  
Jonathan Cedernaes, post doc  
Jörgen Jonsson, adjunct  
Staffan Uhlén, researcher  
Erik Svensson, post doc.  
Pleunie Högenkamp, post doc  
Xiao Tan, post doc  
Martina Blunder, post doc  
Vanni Caruso, post doc  
Lyle Wiemerslage, post doc  
Jessica Mwinyi, associate professor  
Samantha Brooks, affiliated researcher  
Gudrun Skuladottir, guest professor  
Sahar Roshanbin, PhD student

Sarah Voisin, PhD student  
Sofie Hellsten, PhD student  
Marcus Bandstein, PhD student  
Emilia Lekholm, PhD student  
Emilie Perland, PhD student  
Colin Chapman, PhD student  
Olga Titova, PhD student  
Frida Rångtell, PhD student  
Nathalie Bringeland, PhD student  
Wei Zhou, PhD student  
Sofia Kanders, PhD student  
Gaia Olivo, PhD student  
Hao Cao, PhD student  
Ahmed Mohammed Alsheli, PhD student  
Andreas Johansson, PhD student, part-time  
Maria Ling, PhD student, part-time  
Björn Sundberg, PhD student, part-time

**General:** The team studies pharmacology/toxicology, genetics, neuroendocrinology and behaviour. Studies on peripheral and central nervous system energy metabolism, sleep/wake regulation, hedonic behaviors, control of emotional health, and memory functions are performed both in human and animal models. We perform molecular biology and neuroanatomical studies in a fully equipped molecular biology lab as well as transgenic fly work linked with behavioural characterisation. We have also built a human neurometabolic lab at BMC to conduct human experiments (including sleep interventions) in the context of psychiatric and metabolic health. We use bioinformatics studies with focus on evolution of membrane proteins and perform several types of genetic, epigenetic and biostatic studies. The research team was ranked in 2011 at the highest category of "top international class" by external international panel evaluation of Uppsala University (KoF2011) stating that the "research output of this group is exceptional" with projects "highly relevant for society".



Benedict has built his own research group within this unit with two post docs and two PhD students as main tutor, one medical postdoc, one master student, and term students.

**Progress 2016:** We have been very productive during 2016 with more than 35 papers published. We continued to publish papers in high impact journals during year 2016. This includes papers in Williams et al., *Plos Genetics*, Cedernaes et al., *Sleep Med Rev*. Rask-Andersen et al., *Am J Clin Nutr*. Cedernaes et al., *Psychoneuroendocrinology*, Benedict et al., *Mol Med*. Hogenkamp et al., *Int J Obes*. Wiemerslage et al., *Int J Obes*. Titova et al., *Neurobiol Aging*, Gaudio et al., *Neurosci Biobehav Rev*.

According to the central database DIVA, the team at this unit is currently the most productive at the department of neuroscience considering the total impact of the published papers during the last four years. This is also evidenced by the fact that Schiöth has the highest cumulative impact of all researchers in the neuroscience department, followed by Benedict during the past four years. The unit contributes with papers of total impact of above 100 (total impact of papers) in average per year the recent years. Recent papers have continued to receive high number of citations, and the total number of citations received by Schiöth HB (Google Scholar) are above 2000 during 2016 and more than 18000 citations in total. Benedict C has more than 700 citations during year 2016 and more than 4000 citations in total. Schiöth has published more than 30 papers (27 original papers and 6 reviews) that have received more than 100 citations and has h index of 70. Benedict has during reached a milestone in that he has been able to publish his hundredth peer-reviewed articles, thereof 61 articles either as first or senior author (h index= 34). Schiöth has an evaluated score based on impact of papers during years 2012-2015 of 140 (average of the other professors at the department is 17.4), while Benedict has 85, the second highest at the department, and highest of all persons without a permanent position. Schiöth is on Thomson Reuters list of the worlds highly cited researchers (also called the list of “most influential researchers”) and is one of four scientists from Uppsala on the current version of this list.

**Grants:** The unit for functional pharmacology has been very successful during year 2015 in receiving external grants. The unit had three VR-projects grants. Schiöth has two grants at VR-M, main grant of 0.7 mSEK/year for 3 years “Central regulation of food intake and reward” and another grant, 3R, “Development of a replacement model to determine short and long term effects of environmental toxin mixtures using *Drosophila*” of 0.7 mSEK per years in 3 years. Benedict has been awarded a young researcher VR-M grant (5 mSEK; only 27 out of 320 applications were approved) on sleep (Intra-and transgenerational health consequences of shift work in humans) and a Novo Nordisk excellence award for endocrinological research (5 mDKK) to conduct studies about the role of sleep on health. Cedernaes has international post doctoral grant for 3 years or about 1 mSEK per year about sleep as well as several other smaller grants. Schiöth has also grant at Hjärnfonden 0.5 mSEK/year for studies on biomarkers, Benedict another one for 0.5 mSEK/year for sleep research and Cedernaes 0.5 mSEK/year for sleep research. AFA has granted Benedict/Schiöth 0.6 mSEK per year for three years for sleep research.

**Development of the laboratory and techniques:** 1) molecular pharmacology and genetic laboratory, 2) human neurometabolic lab and 3) behavioural genetic fly lab. *The molecular pharmacology and genetic laboratory* is the core facility used for various human, rodent and fly studies. This is a fully equipped lab for molecular biology, including cloning, PCR etc as well as equipment for pharmacology and toxicology experimentation.

***The human neurometabolic lab*** is led by Christian Benedict and Helgi Schiöth. This lab currently encompasses an array of physiological and psychological tests that can be utilized for studies at the interface of neuroscience and metabolism. This includes measurements of heart rate variability and body movements, neurobehavioral testing, electroencephalography (EEG), electromyography (EMG), and electrooculography (EOG). The metabolic testing capabilities include protocols for both short- and long-term disruption of sleep and circadian rhythms; where we collect biomarkers (hair, feces, blood, saliva, fat and muscle tissues). In these labs we also collect cohort material in studies related to behaviour with focus on food intake regulation. We are now in the process of purchasing compatible eye tracking technology, ambulatory EEG/ERP amplifier and fNIR Imager as well as other equipment.

***The behavioural genetic fly lab*** studies the genetics of obesity and molecular mechanisms of behaviour in drosophila under the leadership of researcher Michael Williams and Helgi Schiöth. This has enabled us to study gene knock outs in large number of genes involved in behaviour. This lab currently encompasses an array of equipment that allows for behavioural, general fitness and metabolic assays. This includes the Drosophila Activity Monitoring System (DAMS) that can be used for high-throughput measurements of general activity, sleep/wake behaviour, circadian rhythm, as well as being utilized for measuring anxiety and depression-like behaviour (e.g. neophobia and prepulse inhibition (PPI)). We have the Locomotory Activity Monitoring System (LAMS) that uses the flies natural negative geotaxis behaviour (flies climb away from gravity) to measure general fitness, this can also be employed to measure depression-like behaviour. A new piece of equipment being invented in the lab is the Behavioural Activity Monitoring System (BAMS) that can be used for high-throughput measurements of thigmotaxis (centrophobism), neophobism, as well as being employed in a manner similar to the rodent elevated plus maze to measure anxiety. We have two apparatus for automated measurements of food intake. The fly Proboscis and Activity Detector (flyPAD) allows for high-throughput quantification of the different micro-activities that make up feeding behaviour. This apparatus is also used for food preference tests, which can be used to measure choices based on either homeostatic or hedonic feeding. Furthermore, we are developing the DAMPAD, which marries the capabilities of the DAMS and flyPAD to monitor both general activity and feeding behaviour for up to a week. This allows us to measure feeding patterns over a 24 hour period, as well as measure how anxiety and depression-like behaviour, variations in sleep/wake behaviour or changes in circadian rhythm disrupt normal feeding behaviour. Finally, we have the capability for high-throughput measurements of both triglycerides and carbohydrate levels.

The team also performs functional magnetic resonance imaging (fMRI) studies in humans, performed in collaboration with professor Elna-Marie Larsson, head of radiology at the University Hospital in Uppsala on several studies including evaluating the treatment effect of anorexia and bariatric surgery, as well as the role of specific genetics. We collaborate with professor Lars Lind, Acute and Internal Medicine, related to the PIVUS, ULSAM, EpiHealth cohort studies.

### **Publications 2014-2016**

Synaptic changes induced by melanocortin signalling. Caruso V, Lagerström MC, Olszewski PK, Fredriksson R, Schiöth HB. *Nat Rev Neurosci*. 2014 Feb;15(2):98-110. Review.

Obesity-linked homologues TfAP-2 and Twz establish meal frequency in *Drosophila melanogaster*. Williams MJ, Goergen P, Rajendran J, Zheleznyakova G, Hägglund MG, Perland E, Bagchi S, Kalogeropoulou A, Khan Z, Fredriksson R, Schiöth HB. *PLoS Genet*. 2014 Sep 4;10(9):e1004499.

Advances in kinase targeting: current clinical use and clinical trials. Rask-Andersen M, Zhang J, Fabbro D, Schiöth HB. *Trends Pharmacol Sci*. 2014 Nov;35(11):604-620.

The *Drosophila* small GTPase Rac2 is required for normal feeding and mating behaviour. Goergen P, Kasagiannis A, Schiöth HB, Williams MJ. *Behav Genet*. 2014 Mar;44(2):155-64.

Acute sleep deprivation increases serum levels of neuron-specific enolase (NSE) and S100 calcium binding protein B (S-100B) in healthy young men. Benedict C, Cedernaes J, Giedraitis V, Nilsson EK, Hogenkamp PS, Vågesjö E, Massena S, Pettersson U, Christoffersson G, Phillipson M, Broman JE, Lannfelt L, Zetterberg H, Schiöth HB. *Sleep*. 2014 Jan 1;37(1):195-8.

BDNF polymorphisms are linked to poorer working memory performance, reduced cerebellar and hippocampal volumes and differences in prefrontal cortex in a Swedish elderly population. Brooks SJ, Nilsson EK, Jacobsson JA, Stein DJ, Fredriksson R, Lind L, Schiöth HB. *PLoS One*. 2014 Jan 23;9(1):e82707.

Cholecystokinin-Like Peptide (DSK) in *Drosophila*, Not Only for Satiety Signaling. Nässel DR, Williams MJ. *Front Endocrinol (Lausanne)*. 2014 Dec 18;5:219.

The role of common and rare MC4R variants and FTO polymorphisms in extreme form of obesity. Rovite V, Petrovska R, Vaivade I, Kalnina I, Fridmanis D, Zaharenko L, Peculis R, Pirags V, Schiöth HB, Klovins J. *Mol Biol Rep*. 2014 Mar;41(3):1491-500.

Exposure to a high-fat high-sugar diet causes strong up-regulation of proopiomelanocortin and differentially affects dopamine D1 and D2 receptor gene expression in the brainstem of rats. Alsjö J, Rask-Andersen M, Chavan RA, Olszewski PK, Levine AS, Fredriksson R, Schiöth HB. *Neurosci Lett*. 2014 Jan 24;559:18-23.

Exposure to bisphenol A affects lipid metabolism in *Drosophila melanogaster*. Williams MJ, Wang Y, Klockars A, Monica Lind P, Fredriksson R, Schiöth HB. *Basic Clin Pharmacol Toxicol*. 2014 May;114(5):414-20.

Regulation of aggression by obesity-linked genes TfAP-2 and Twz through octopamine signaling in *Drosophila*. Williams MJ, Goergen P, Rajendran J, Klockars A, Kasagiannis A, Fredriksson R, Schiöth HB. *Genetics*. 2014 Jan;196(1):349-62.

The GPCR repertoire in the demosponge *Amphimedon queenslandica* : insights into the GPCR system at the early divergence of animals. Krishnan A, Dnyansagar R, Almén M, Williams MJ, Fredriksson R, Manoj N, Schiöth HB. *BMC Evol Biol*. 2014 Dec 21;14(1):270.

Gabaergic control of anxiety-like behavior, but not food intake, induced by ghrelin in the intermediate medial mesopallium of the neonatal chick. Gastón MS, Schiöth HB, De Barioglio SR, Salvatierra NA. *Horm Behav*. 2015 Jan;67:66-72.

Ghrelin increases memory consolidation through hippocampal mechanisms dependent on glutamate release and NR2B-subunits of the NMDA receptor. Ghersi MS, Gabach LA, Buteler F, Vilcaes AA, Schiöth HB, Perez MF, de Barioglio SR. *Psychopharmacology (Berl)*. 2014 Dec 4.

Obsessive-compulsivity and working memory are associated with differential prefrontal cortex and insula activation in adolescents with a recent diagnosis of an eating disorder. Brooks SJ, Solstrand Dahlberg L, Swenne I, Aronsson M, Zarei S, Lundberg L, Jacobsson JA, Rask-Andersen M, Salonen-Ros H, Rosling A, Larsson EM, Schiöth HB. *Psychiatry Res*. 2014 Dec 30;224(3):246-53.

Associations of self-reported sleep disturbance and duration with academic failure in community-dwelling Swedish adolescents: Sleep and academic performance at school. Titova OE, Hogenkamp PS, Jacobsson JA, Feldman I, Schiöth HB, Benedict C. *Sleep Med*. 2014 Sep 19. pii: S1389-9457(14)00386-4.

New functions and signaling mechanisms for the class of adhesion G protein-coupled receptors. Liebscher I, Ackley B, Araç D, Ariestanti DM, Aust G, Bae BI, Bista BR, Bridges JP, Duman JG, Engel FB, Giera S, Goffinet AM, Hall RA, Hamann J, Hartmann N, Lin HH, Liu M, Luo R, Mogha A, Monk KR, Peeters MC, Prömel S, Ressler S, Schiöth HB, Sigoillot SM, Song H, Talbot WS, Tall GG, White JP, Wolfrum U, Xu L, Piao X. *Ann N Y Acad Sci*. 2014 Dec;1333(1):43-64.

Häggglund MG, Hellsten SV, Bagchi S, Philippot G, Löfqvist E, Nilsson VC, Almkvist I, Karlsson E, Sreedharan S, Tafreshiha A, Fredriksson R. Transport of L-glutamine, L-alanine, L-arginine and L-histidine by the neuron-specific Slc38a8 (SNAT8) in CNS. *J Mol Biol*. 2014 Oct 30. pii: S0022-2836(14)00567-1.

Comment on Laker et al. Exercise prevents maternal high-fat diet-induced hypermethylation of the *pgc-1 $\alpha$*  gene and age-dependent metabolic dysfunction in the offspring. Cedernaes J, Benedict C. *Diabetes*. 2014 May;63(5):e5.

*Drosophila* insulin-producing cells are differentially modulated by serotonin and octopamine receptors and affect social behavior. Luo J, Lushchak OV, Goergen P, Williams MJ, Nässel DR. *PLoS One*. 2014 Jun 12;9(6):e99732.

Human obesity: FTO, IRX3, or both? Cedernaes J, Benedict C. *Mol Metab*. 2014 May 17;3(5):505-6.

PAT4 is abundantly expressed in excitatory and inhibitory neurons as well as epithelial cells. Roshanbin S, Hellsten SV, Tafreshiha A, Zhu Y, Raine A, Fredriksson R. *Brain Res*. 2014 Apr 4;1557:12-25. doi: 10.1016/j.brainres.2014.02.014. Epub 2014 Feb 14.

Sleep duration and energy intake: timing matters. Cedernaes J, Benedict C. *Am J Clin Nutr*. 2014 Nov;100(5):1402-3

Histological analysis of SLC38A6 (SNAT6) expression in mouse brain shows selective expression in excitatory neurons with high expression in the synapses. Bagchi S, Baomar HA, Al-Walai S, Al-Sadi S, Fredriksson R. *PLoS One*. 2014 Apr 21;9(4):e95438.

Efficacy of antibody-based therapies to treat Alzheimer's disease: just a matter of timing?  
Cedernaes J, Schiöth HB, Benedict C. *Exp Gerontol*. 2014 Sep;57:104-6.

The *Drosophila* Kctd-family homologue Kctd12-like modulates male aggression and mating behaviour. Williams MJ, Goergen P, Phad G, Fredriksson R, Schiöth HB.  
*Eur J Neurosci*. 2014 Aug;40(3):2513-26.

CDKAL1-related single nucleotide polymorphisms are associated with insulin resistance in a cross-sectional cohort of Greek children. Rask-Andersen M, Philippot G, Moschonis G, Dedoussis G, Manios Y, Marcus C, Fredriksson R, Schiöth HB. *PLoS One*. 2014 Apr 2;9(4):e93193.

Insights into the origin of nematode chemosensory GPCRs: putative orthologs of the *Srw* family are found across several phyla of protostomes. Krishnan A, Almén MS, Fredriksson R, Schiöth HB. *PLoS One*. 2014 Mar 24;9(3):e93048.

Ghrelin effects expression of several genes associated with depression-like behavior. Poretti MB, Rask-Andersen M, Kumar P, Rubiales de Barioglio S, Fiol de Cuneo M, Schiöth HB, Carlini VP. *Prog Neuropsychopharmacol Biol Psychiatry*. 2015 Jan 2;56:227-34.

The G protein-coupled receptor GPR162 is widely distributed in the CNS and highly expressed in the hypothalamus and in hedonic feeding areas. Caruso V, Hägglund MG, Badiali L, Bagchi S, Roshanbin S, Ahmad T, Schiöth HB, Fredriksson R. *Gene*. 2014 Dec 10;553(1):1-6

Dietary fat quality impacts genome-wide DNA methylation patterns in a cross-sectional study of Greek preadolescents. Voisin S, Almén MS, Moschonis G, Chrousos GP, Manios Y, Schiöth HB. *Eur J Hum Genet*. 2014 Jul 30.

Replacement of short segments within transmembrane domains of MC2R disrupts retention signal. Fridmanis D, Petrovska R, Pjanova D, Schiöth HB, Klovins J. *J Mol Endocrinol*. 2014 Oct;53(2):201-15.

Genome-wide analysis reveals DNA methylation markers that vary with both age and obesity. Almén MS, Nilsson EK, Jacobsson JA, Kalnina I, Klovins J, Fredriksson R, Schiöth HB. *Gene*. 2014 Sep 10;548(1):61-7.

Long-term oral melatonin administration reduces ethanol-induced increases in duodenal mucosal permeability and motility in rats. Sommansson A, Yamskova O, Schiöth HB, Nylander O, Sjöblom M. *Acta Physiol (Oxf)*. 2014 Oct;212(2):152-65.

Watching TV and food intake: the role of content. Chapman CD, Nilsson VC, Thune HÅ, Cedernaes J, Le Grevès M, Hogenkamp PS, Benedict C, Schiöth HB. *PLoS One*. 2014 Jul 1;9(7):e100602.

Melanocortin 4 receptor activation inhibits presynaptic N-type calcium channels in amygdaloid complex neurons. Agosti F, López Soto EJ, Cabral A, Castrogiovanni D, Schiöth HB, Perelló M, Raingo J. *Eur J Neurosci*. 2014 Sep;40(5):2755-65.

Fat mass and obesity-associated gene (FTO) is linked to higher plasma levels of the hunger hormone ghrelin and lower serum levels of the satiety hormone leptin in older adults. Benedict C, Axelsson T, Söderberg S, Larsson A, Ingelsson E, Lind L, Schiöth HB. *Diabetes*. 2014 Nov;63(11):3955-9.

Acute sleep deprivation in healthy young men: impact on population diversity and function of circulating neutrophils. Christofferson G, Vågesjö E, Pettersson US, Massena S, Nilsson EK, Broman JE, Schiöth HB, Benedict C, Phillipson M. *Brain Behav Immun*. 2014 Oct;41:162-72.

Increased impulsivity in response to food cues after sleep loss in healthy young men. Cedernaes J, Brandell J, Ros O, Broman JE, Hogenkamp PS, Schiöth HB, Benedict C. *Obesity (Silver Spring)*. 2014 Aug;22(8):1786-91.

Benedict C, Byberg L, Cedernaes J, Hogenkamp PS, Giedratis V, Kilander L, Lind L, Lannfelt L, Schiöth HB. (2015) Self-reported sleep disturbance is associated with Alzheimer's disease risk in men. *Alzheimers Dement*. Sep;11, 1090-7.

Titova OE, Hogenkamp PS, Jacobsson JA, Feldman I, Schiöth HB, Benedict C. Associations of self-reported sleep disturbance and duration with academic failure in community-dwelling Swedish adolescents: Sleep and academic performance at school. *Sleep Med*. 16, 87-93.

GABA and its B-receptor are present at the node of Ranvier in a small population of sensory fibers, implicating a role in myelination. Corell M, Wicher G, Radomska KJ, Dağlıkoca ED, Godskenen RE, Fredriksson R, Benedikz E, Magnaghi V, Fex Svenningsen A. *J Neurosci Res*. 2015 Feb;93(2):285-95.

Krishnan A, Dnyansagar R, Almén M, Williams MJ, Fredriksson R, Manoj N, Schiöth HB. (2014) The GPCR repertoire in the demosponge *Amphimedon queenslandica*: insights into the GPCR system at the early divergence of animals. *BMC Evol Biol*. 14, 270.

Gherzi MS, Gabach LA, Buteler F, Vilcaes AA, Schiöth HB, Perez MF, de Barioglio SR. (2015) Ghrelin increases memory consolidation through hippocampal mechanisms dependent on glutamate release and NR2B-subunits of the NMDA receptor. *Psychopharmacology (Berl)*. 232, 1843-57.

Gastón MS, Schiöth HB, De Barioglio SR, Salvatierra NA. (2015) Gabaergic control of anxiety-like behavior, but not food intake, induced by ghrelin in the intermediate medial mesopallium of the neonatal chick. *Horm Behav*. 67, 66-72.

Machado I, Gonzalez PV, Vilcaes A, Carniglia L, Schiöth HB, Lasaga M, Scimonelli TN. (2015) Interleukin-1 $\beta$ -induced memory reconsolidation impairment is mediated by a reduction in glutamate release and zif268 expression and  $\alpha$ -melanocyte-stimulating hormone prevented these effects. *Brain Behav Immun*. 46, 137-46.

Rask-Andersen M, Almén MS, Lind L, Schiöth HB. (2015) Association of the LINGO2-related SNP rs10968576 with body mass in a cohort of elderly Swedes. *Mol Genet Genomics*. 290, 1485-91.

Nilsson EK, Ernst B, Voisin S, Almén MS, Benedict C, Mwinyi J, Fredriksson R, Schultes B, Schiöth HB. (2015) Roux-en Y gastric bypass surgery induces genome-wide promoter-specific changes in DNA methylation in whole blood of obese patients. *PLoS One*. 10, e0115186.

Harty BL, Krishnan A, Sanchez NE, Schiöth HB, Monk KR. (2015) Defining the gene repertoire and spatiotemporal expression profiles of adhesion G protein-coupled receptors in zebrafish. *BMC Genomics*. 16, 62.

Bandstein M, Schultes B, Ernst B, Thurnheer M, Schiöth HB, Benedict C. (2015) The Role of FTO and Vitamin D for the Weight Loss Effect of Roux-en-Y Gastric Bypass Surgery in Obese Patients. *Obes Surg*. 25, 2071-7.

Hogekamp PS, Sundbom M, Nilsson VC, Benedict C, Schiöth HB (2015) Patients lacking sustainable long-term weight loss after gastric bypass surgery show signs of decreased inhibitory control of prepotent responses. *PLoS One*. 10, e0119896.

Zheleznyakova GY, Nilsson EK, Kiselev AV, Maretina MA, Tishchenko LI, Fredriksson R, Baranov VS, Schiöth HB. (2015) Methylation levels of SLC23A2 and NCOR2 genes correlate with spinal muscular atrophy severity. *PLoS One*. 10, e0121964.

Eriksson A, Williams MJ, Voisin S, Hansson I, Krishnan A, Philippot G, Yamskova O, Herisson FM, Dnyansagar R, Moschonis G, Manios Y, Chrousos GP, Olszewski PK, Fredriksson R, Schiöth HB. (2015) Implication of coronin 7 in body weight regulation in humans, mice and flies. *BMC Neurosci*. 16, 13.

Krishnan A, Mustafa A, Almén MS, Fredriksson R, Williams MJ, Schiöth HB. (2015) Evolutionary hierarchy of vertebrate-like heterotrimeric G protein families. *Mol Phylogenet Evol*. 91, 27-40.

Caruso V, Le Grevés M, Shirazi Fard S, Haitina T, Olszewski PK, Alsiö J, Schiöth HB, Fredriksson R. (2015) The Orphan G Protein-Coupled Receptor Gene GPR178 Is Evolutionary Conserved and Altered in Response to Acute Changes in Food Intake. *PLoS One*. 10, e0122061.

288. Schiöth HB, Ferriday D, Davies SR, Benedict C, Elmståhl H, Brunstrom JM, Hogekamp PS. (2015) Are You Sure? Confidence about the Satiating Capacity of a Food Affects Subsequent Food Intake. *Nutrients*. 7, 5088-97.

Cedernaes J, Rångtall FH, Axelsson EK, Yeganeh A, Vogel H, Broman JE, Dickson SL, Schiöth HB, Benedict C. (2015) Short Sleep Makes Declarative Memories Vulnerable to Stress in Humans. *Sleep*. 38, 1861-8.

Williams MJ, Eriksson A, Shaik M, Voisin S, Yamskova O, Paulsson J, Thombare K, Fredriksson R, Schiöth HB. (2015) The obesity-linked gene *Nudt3* Drosophila homolog *Aps* is associated with insulin signalling. *Mol Endocrinol*. 2015, 29, 1303-19.

Cedernaes J, Osler ME, Voisin S, Broman JE, Vogel H, Dickson SL, Zierath JR, Schiöth HB, Benedict C. (2015) Acute sleep loss induces tissue-specific epigenetic and transcriptional alterations to circadian clock genes in men. *J Clin Endocrinol Metab*. 100, E1255-61.

Le Duc D, Renaud G, Krishnan A, Almén MS, Huynen L, Prohaska SJ, Ongyerth M, Bitarello BD, Schiöth HB, Hofreiter M, Stadler PF, Prüfer K, Lambert D, Kelso J, Schöneberg T. (2015) Kiwi genome provides insights into evolution of a nocturnal lifestyle. *Genome Biol.* 16, 147.

Rask-Andersen M, Almén MS, Schiöth HB. (2015) Scrutinizing the FTO locus: compelling evidence for a complex, long-range regulatory context. *Hum Genet.* 134, 1183-93.

Rask-Andersen M, Sällman Almén M, Jacobsson JA, Ameer A, Moschonis G, Dedoussis G, Marcus C, Gyllensten U, Fredriksson R, Schiöth HB. (2015) Determination of obesity associated gene variants related to TMEM18 through ultra-deep targeted re-sequencing in a case-control cohort for pediatric obesity. *Genet Res (Camb).* 97, e16.

Voisin S, Almén MS, Zheleznyakova GY, Lundberg L, Zarei S, Castillo S, Eriksson FE, Nilsson EK, Blüher M, Böttcher Y, Kovacs P, Klovins J, Rask-Andersen M, Schiöth HB. (2015) Many obesity-associated SNPs strongly associate with DNA methylation changes at proximal promoters and enhancers. *Genome Med.* 7, 103.

Krishnan A, Schiöth HB. (2015) The role of G protein-coupled receptors in the early evolution of neurotransmission and the nervous system. *J Exp Biol.* 218, 562-571.

Hamann J, Aust G, Araç D, Engel FB, Formstone C, Fredriksson R, Hall RA, Harty BL, Kirchhoff C, Knapp B, Krishnan A, Liebscher I, Lin HH, Martinelli DC, Monk KR, Peeters MC, Piao X, Prömel S, Schöneberg T, Schwartz TW, Singer K, Stacey M, Ushkaryov YA, Vallon M, Wolfrum U, Wright MW, Xu L, Langenhan T, Schiöth HB. (2015) International Union of Basic and Clinical Pharmacology. XCIV. Adhesion G protein-coupled receptors. *Pharmacol Rev.* 67, 338-67.

Benedict C, Schiöth HB, Cedernaes J. (2015) Television watching and effects on food intake: distress vs eustress. *JAMA Intern Med.* 175, 468.

Cedernaes J, Schiöth HB, Benedict C. (2015) Determinants of shortened, disrupted, and mistimed sleep and associated metabolic health consequences in healthy humans. *Diabetes.* 64, 1073-80.

A genetic risk score is significantly associated with statin therapy response in the elderly population. Ciuculete DM, Bandstein M, Benedict C, Waeber G, Vollenweider P, Lind L, Schiöth HB, Mwinyi J. *Clin Genet.* 2016 Oct 13.

Classification, Nomenclature, and Structural Aspects of Adhesion GPCRs.  
Krishnan A, Nijmeijer S, de Graaf C, Schiöth HB. *Handb Exp Pharmacol.* 2016;234:15-41.

A resting-state fMRI study of obese females between pre- and postprandial states before and after bariatric surgery. Wiemerslage L, Zhou W, Olivo G, Stark J, Hogenkamp PS, Larsson EM, Sundbom M, Schiöth HB. *Eur J Neurosci.* 2017 Feb;45(3):333-341.

A systematic review of resting-state functional-MRI studies in anorexia nervosa: Evidence for functional connectivity impairment in cognitive control and visuospatial and body-signal



integration. Gaudio S, Wiemerslage L, Brooks SJ, Schiöth HB. *Neurosci Biobehav Rev*. 2016 Dec;71:578-589.

Sleep restriction alters plasma endocannabinoids concentrations before but not after exercise in humans. Cedernaes J, Fanelli F, Fazzini A, Pagotto U, Broman JE, Vogel H, Dickson SL, Schiöth HB, Benedict C. *Psychoneuroendocrinology*. 2016 Dec;74:258-268.

Psychological intervention with working memory training increases basal ganglia volume: A VBM study of inpatient treatment for methamphetamine use. Brooks SJ, Burch KH, Maiorana SA, Cocolas E, Schiöth HB, Nilsson EK, Kamaloodien K, Stein DJ. *Neuroimage Clin*. 2016 Aug 24;12:478-91.

One-night sleep deprivation induces changes in the DNA methylation and serum activity indices of stearoyl-CoA desaturase in young healthy men. Skuladottir GV, Nilsson EK, Mwinyi J, Schiöth HB. *Lipids Health Dis*. 2016 Aug 26;15(1):137.

Two hours of evening reading on a self-luminous tablet vs. reading a physical book does not alter sleep after daytime bright light exposure. Rångtjell FH, Ekstrand E, Rapp L, Lagermalm A, Liethof L, Búcaro MO, Lingfors D, Broman JE, Schiöth HB, Benedict C. *Sleep Med*. 2016 Jul;23:111-118. doi: 10.1016/j.sleep.2016.06.016.

Recurrent Sleep Fragmentation Induces Insulin and Neuroprotective Mechanisms in Middle-Aged Flies. Williams MJ, Perland E, Eriksson MM, Carlsson J, Erlandsson D, Laan L, Mahebalu T, Potter E, Fredriksson R, Benedict C, Schiöth HB. *Front Aging Neurosci*. 2016 Aug 2;8:180. doi: 10.3389/fnagi.2016.00180.

Association between shift work history and performance on the trail making test in middle-aged and elderly humans: the EpiHealth study. Titova OE, Lindberg E, Elmståhl S, Lind L, Schiöth HB, Benedict C. *Neurobiol Aging*. 2016 Sep;45:23-9.

Postprandial alterations in whole-blood DNA methylation are mediated by changes in white blood cell composition. Rask-Andersen M, Bringeland N, Nilsson EK, Bandstein M, Olaya Búcaro M, Vogel H, Schürmann A, Hogenkamp PS, Benedict C, Schiöth HB. *Am J Clin Nutr*. 2016 Aug;104(2):518-25.

Higher resting-state activity in reward-related brain circuits in obese versus normal-weight females independent of food intake. Hogenkamp PS, Zhou W, Dahlberg LS, Stark J, Larsen AL, Olivo G, Wiemerslage L, Larsson EM, Sundbom M, Benedict C, Schiöth HB. *Int J Obes (Lond)*. 2016 Nov;40(11):1687-1692.

A new, simple and robust radioligand binding method used to determine kinetic off-rate constants for unlabeled ligands. Application at  $\alpha 2A$ - and  $\alpha 2C$ -adrenoceptors. Uhlén S, Schiöth HB, Jahnsen JA. *Eur J Pharmacol*. 2016 Oct 5;788:113-21.

Epigenomics of Total Acute Sleep Deprivation in Relation to Genome-Wide DNA Methylation Profiles and RNA Expression. Nilsson EK, Boström AE, Mwinyi J, Schiöth HB. *OMICS*. 2016 Jun;20(6):334-42.

A targeted analysis reveals relevant shifts in the methylation and transcription of genes responsible for bile acid homeostasis and drug metabolism in non-alcoholic fatty liver

disease. Schiöth HB, Boström A, Murphy SK, Erhart W, Hampe J, Moylan C, Mwinyi J. *BMC Genomics*. 2016 Jun 14;17:462. doi:

The *Drosophila* ETV5 Homologue Ets96B: Molecular Link between Obesity and Bipolar Disorder. Williams MJ, Klockars A, Eriksson A, Voisin S, Dnyansagar R, Wiemerslage L, Kasagiannis A, Akram M, Kheder S, Ambrosi V, Hallqvist E, Fredriksson R, Schiöth HB. *PLoS Genet*. 2016 Jun 9;12(6):e1006104.

BDNF DNA methylation changes as a biomarker of psychiatric disorders: literature review and open access database analysis. Zheleznyakova GY, Cao H, Schiöth HB. *Behav Brain Funct*. 2016 Jun 6;12(1):17.

A genetic variant in proximity to the gene *LYPLAL1* is associated with lower hunger feelings and increased weight loss following Roux-en-Y gastric bypass surgery. Bandstein M, Mwinyi J, Ernst B, Thurnheer M, Schultes B, Schiöth HB. *Scand J Gastroenterol*. 2016 Sep;51(9):1050-5.

Chenodeoxycholic acid significantly impacts the expression of miRNAs and genes involved in lipid, bile acid and drug metabolism in human hepatocytes. Krattinger R, Boström A, Lee SM, Thasler WE, Schiöth HB, Kullak-Ublick GA, Mwinyi J. *Life Sci*. 2016 Jul 1;156:47-56.

High leptin levels are associated with migraine with aura. Pisanu C, Preisig M, Castelao E, Glaus J, Cunningham JL, Del Zompo M, Merikangas KR, Schiöth HB, Mwinyi J. *Cephalalgia*. 2016 May 10.

Oxytocin Acting in the Nucleus Accumbens Core Decreases Food Intake. Herisson FM, Waas JR, Fredriksson R, Schiöth HB, Levine AS, Olszewski PK. *J Neuroendocrinol*. 2016 Apr;28(4).

Longitudinal genome-wide methylation study of Roux-en-Y gastric bypass patients reveals novel CpG sites associated with essential hypertension. Boström AE, Mwinyi J, Voisin S, Wu W, Schultes B, Zhang K, Schiöth HB. *BMC Med Genomics*. 2016 Apr 22;9:20.

Dibutyl Phthalate Exposure Disrupts Evolutionarily Conserved Insulin and Glucagon-Like Signaling in *Drosophila* Males. Williams MJ, Wiemerslage L, Gohel P, Kheder S, Kothegala LV, Schiöth HB. *Endocrinology*. 2016 Jun;157(6):2309-21.

microRNA-192 suppresses the expression of the farnesoid X receptor. Krattinger R, Boström A, Schiöth HB, Thasler WE, Mwinyi J, Kullak-Ublick GA. *Am J Physiol Gastrointest Liver Physiol*. 2016 Jun 1;310(11):G1044-51.

Topology based identification and comprehensive classification of four-transmembrane helix containing proteins (4TMs) in the human genome. Attwood MM, Krishnan A, Pivotti V, Yazdi S, Almén MS, Schiöth HB. *BMC Genomics*. 2016 Mar 31;17:268.

The *Drosophila* ortholog of *TMEM18* regulates insulin and glucagon-like signaling. Wiemerslage L, Gohel PA, Maestri G, Hilmarsson TG, Mickael M, Fredriksson R, Williams MJ, Schiöth HB. *J Endocrinol*. 2016 Jun;229(3):233-43.

Bis-(2-ethylhexyl) Phthalate Increases Insulin Expression and Lipid Levels in *Drosophila melanogaster*. Cao H, Wiemerslage L, Marttila PS, Williams MJ, Schiöth HB. *Basic Clin Pharmacol Toxicol*. 2016 Sep;119(3):309-16.

Candidate mechanisms underlying the association between sleep-wake disruptions and Alzheimer's disease. Cedernaes J, Osorio RS, Varga AW, Kam K, Schiöth HB, Benedict C. *Sleep Med Rev*. 2017 Feb;31:102-111.

Learning and sleep-dependent consolidation of spatial and procedural memories are unaltered in young men under a fixed short sleep schedule. Cedernaes J, Sand F, Liethof L, Lampola L, Hassanzadeh S, Axelsson EK, Yeganeh A, Ros O, Broman JE, Schiöth HB, Benedict C. *Neurobiol Learn Mem*. 2016 May;131:87-94.

Resting-State Brain and the FTO Obesity Risk Allele: Default Mode, Sensorimotor, and Salience Network Connectivity Underlying Different Somatosensory Integration and Reward Processing between Genotypes. Olivo G, Wiemerslage L, Nilsson EK, Solstrand Dahlberg L, Larsen AL, Olaya Búcaro M, Gustafsson VP, Titova OE, Bandstein M, Larsson EM, Benedict C, Brooks SJ, Schiöth HB. *Front Hum Neurosci*. 2016 Feb 17;10:52.

A Genetic Risk Score Is Associated with Weight Loss Following Roux-en Y Gastric Bypass Surgery. Bandstein M, Voisin S, Nilsson EK, Schultes B, Ernst B, Thurnheer M, Benedict C, Mwinyi J, Schiöth HB. *Obes Surg*. 2016 Sep;26(9):2183-9.

mRNA GPR162 changes are associated with decreased food intake in rat, and its human genetic variants with impairments in glucose homeostasis in two Swedish cohorts. Caruso V, Sreedharan S, Carlini VP, Jacobsson JA, Haitina T, Hammer J, Stephansson O, Crona F, Sommer WH, Risérus U, Lannfelt L, Marcus C, Heilig M, de Barioglio SR, Fredriksson R, Schiöth HB. *Gene*. 2016 May 1;581(2):139-45.

An obesity-associated risk allele within the FTO gene affects human brain activity for areas important for emotion, impulse control and reward in response to food images. Wiemerslage L, Nilsson EK, Solstrand Dahlberg L, Ence-Eriksson F, Castillo S, Larsen AL, Bylund SB, Hogenkamp PS, Olivo G, Bandstein M, Titova OE, Larsson EM, Benedict C, Brooks SJ, Schiöth HB. *Eur J Neurosci*. 2016 May;43(9):1173-80.

Reduced vasopressin receptors activation mediates the anti-depressant effects of fluoxetine and venlafaxine in bulbectomy model of depression. Poretti MB, Sawant RS, Rask-Andersen M, de Cuneo MF, Schiöth HB, Perez MF, Carlini VP. *Psychopharmacology (Berl)*. 2016 Mar;233(6):1077-86.

A single night of partial sleep loss impairs fasting insulin sensitivity but does not affect cephalic phase insulin release in young men. Cedernaes J, Lampola L, Axelsson EK, Liethof L, Hassanzadeh S, Yeganeh A, Broman JE, Schiöth HB, Benedict C. *J Sleep Res*. 2016 Feb;25(1):5-10.

Gut microbiota and glucometabolic alterations in response to recurrent partial sleep deprivation in normal-weight young individuals. Benedict C, Vogel H, Jonas W, Woting A, Blaut M, Schürmann A, Cedernaes J. *Mol Metab*. 2016 Oct 24;5(12):1175-1186.

Circadian Clock Interaction with HIF1 $\alpha$  Mediates Oxygenic Metabolism and Anaerobic Glycolysis in Skeletal Muscle. Peek CB, Levine DC, Cedernaes J, Taguchi A, Kobayashi Y, Tsai SJ, Bonar NA, McNulty MR, Ramsey KM, Bass J. *Cell Metab.* 2017 Jan 10;25(1):86-92.

A single night of partial sleep loss impairs fasting insulin sensitivity but does not affect cephalic phase insulin release in young men. Cedernaes J, Lampola L, Axelsson EK, Liethof L, Hassanzadeh S, Yeganeh A, Broman JE, Schiöth HB, Benedict C. *J Sleep Res.* 2016 Feb;25(1):5-10.

Reduced vasopressin receptors activation mediates the anti-depressant effects of fluoxetine and venlafaxine in bulbectomy model of depression. Poretti MB, Sawant RS, Rask-Andersen M, de Cuneo MF, Schiöth HB, Perez MF, Carlini VP. *Psychopharmacology (Berl).* 2016 Mar;233(6):1077-86.

Decoding obesity in the brainstem. Cedernaes J, Bass J. *Elife.* 2016 May 9;5. pii: e16393.  
Neural correlates of olfactory and visual memory performance in 3D-simulated mazes after intranasal insulin application. Brünner YF, Rodriguez-Raecke R, Mutic S, Benedict C, Freiherr J. *Neurobiol Learn Mem.* 2016 Oct;134 Pt B:256-63.

Antihypertensive medication prior to nocturnal sleep reduces the risk of new-onset type 2 diabetes in hypertensive patients: a role for slow-wave sleep? Benedict C. *Diabetologia.* 2016 Feb;59(2):390-1.

Central Nervous Insulin Signaling in Sleep-Associated Memory Formation and Neuroendocrine Regulation. Feld GB, Wilhem I, Benedict C, Rüdell B, Klameth C, Born J, Hallschmid M. *Neuropsychopharmacology.* 2016 May;41(6):1540-50.

The raspberry Gene Is Involved in the Regulation of the Cellular Immune Response in *Drosophila melanogaster*. Kari B, Csordás G, Honti V, Cinege G, Williams MJ, Andó I, Kurucz É. *PLoS One.* 2016 Mar 4;11(3):e0150910.

Elevated total plasma-adiponectin is stable over time in young women with bulimia nervosa. Syk M, Ramklint M, Fredriksson R, Ekselius L, Cunningham JL. *Eur Psychiatry.* 2016 Dec 29;41:30-36.

The Novel Membrane-Bound Proteins MFSD1 and MFSD3 are Putative SLC Transporters Affected by Altered Nutrient Intake. Perland E, Hellsten SV, Lekholm E, Eriksson MM, Arapi V, Fredriksson R. *J Mol Neurosci.* 2016 Dec 16. [Epub ahead of print]

Histological characterization of orphan transporter MCT14 (SLC16A14) shows abundant expression in mouse CNS and kidney. Roshanbin S, Lindberg FA, Lekholm E, Eriksson MM, Perland E, Åhlund J, Raine A, Fredriksson R. *BMC Neurosci.* 2016 Jul 1;17(1):43.

The Putative SLC Transporters Mfsd5 and Mfsd11 Are Abundantly Expressed in the Mouse Brain and Have a Potential Role in Energy Homeostasis. Perland E, Lekholm E, Eriksson MM, Bagchi S, Arapi V, Fredriksson R. *PLoS One.* 2016 Jun 7;11(6):e0156912.

NAFLD is associated with methylation shifts with relevance for the expression of genes involved in lipoprotein particle composition. Mwinyi J, Boström AE, Pisanu C, Murphy SK,

Erhart W, Schafmayer C, Hampe J, Moylan C, Schiöth HB. *Biochim Biophys Acta*. 2017 Mar;1862(3):314-323.

Adolescents newly diagnosed with eating disorders have structural differences in brain regions linked with eating disorder symptoms. Solstrand Dahlberg L, Wiemerslage L, Swenne I, Larsen A, Stark J, Rask-Andersen M, Salonen-Ros H, Larsson EM, Schiöth HB, Brooks SJ. *Nord J Psychiatry*. 2016 Nov 15:1-9. [Epub ahead of print]

### **Agencies that support the work/ Funding**

Swedish Research Council  
Hjärnfonden  
Åhlens Foundation  
Novo Nordisk Foundation  
Åke Wiberg Foundation,  
Magnus Bergvall Foundation,  
Tore Nilsons Foundation,  
AFA  
Bissen Brainwalk

## ***Neuropsychopharmacology***

**Group leader: Erika Comasco, Associate Professor**

### **Members of the group during 2016**

Lars Orelund, Prof. em.	Gianvito Lagravinese, researcher
Jarmila Hallman, Prof.	Julia Breedh, MD student
Aniruddha Todkar, PhD student (defended Jun 2016)	Matilda Karlsson, MD student
Megha Bendre, PhD student	Haro de Grauw, Master student
Maria Vrettou, PhD student	Miguel Sanz Puebla, Bachelor student

Research during 2016 has focussed on the psychoneurobiology of psychiatric disorders, comprising:

- Clinical research on the effect of gonadal sex hormone on women's mental health, using a complementary approach including genetics, endocrinology, neurophysiology and neuroimaging;
- Translational research on (epi)gene–environment interactive effects related to alcohol use disorder, including experiments with rodents as well as human population-based and clinical samples, with a special focus on the adolescence period.

### **Publications 2014-2016**

1. Nylander I, Todkar A, Granholm L, Vrettou M, Bendre M, Boon W, Andershed H, Tuvblad C, Nilsson KW, Comasco E. Evidence for a Link Between Fkbp5/FKBP5, Early Life Social Relations and Alcohol Drinking in Young Adult Rats and Humans. *Mol Neurobiol*. 2016 Oct

5. [Epub ahead of print] PMID: 27709495.
2. Comasco E, Gulinello M, Hellgren C, Skalkidou A, Sylven S, Sundström-Poromaa I. Sleep duration, depression, and oxytocinergic genotype influence prepulse inhibition of the startle reflex in postpartum women. *Eur Neuropsychopharmacol*. 2016 Apr;26(4):767-76. doi: 10.1016/j.euroneuro.2016.01.002. PMID: 26857197.
3. Spies M, Hahn A, Kranz GS, Sladky R, Kaufmann U, Hummer A, Ganger S, Kraus C, Winkler D, Seiger R, Comasco E, Windischberger C, Kasper S, Lanzenberger R. Gender transition affects neural correlates of empathy: A resting state functional connectivity study with ultra high-field 7T MR imaging. *Neuroimage*. 2016 Sep;138:257-65. doi: 10.1016/j.neuroimage.2016.05.060. PMID: 27236082.
4. Vachon-Preseau E, Tétréault P, Petre B, Huang L, Berger SE, Torbey S, Baria AT, Mansour AR, Hashmi JA, Griffith JW, Comasco E, Schnitzer TJ, Baliki MN, Apkarian AV. Corticolimbic anatomical characteristics predetermine risk for chronic pain. *Brain*. 2016 Jul;139(Pt 7):1958-70. doi: 10.1093/brain/aww100. PMID: 27190016.
5. Iliadis SI, Comasco E, Hellgren C, Kollia N, Sundström Poromaa I, Skalkidou A. Associations between a polymorphism in the hydroxysteroid (11-beta) dehydrogenase 1 gene, neuroticism and postpartum depression. *J Affect Disord*. 2017 Jan 1;207:141-147. doi: 10.1016/j.jad.2016.09.030. PMID: 27721188.
6. Agnafors S, Svedin CG, Orelund L, Bladh M, Comasco E, Sydsjö G. A Biopsychosocial Approach to Risk and Resilience on Behavior in Children Followed from Birth to Age 12. *Child Psychiatry Hum Dev*. 2016 Sep 15. [Epub ahead of print] PMID: 27628896.
7. Isaksson J, Comasco E, Åslund C, Rehn M, Tuvblad C, Andershed H, Nilsson KW. Associations between the FKBP5 haplotype, exposure to violence and anxiety in females. *Psychoneuroendocrinology*. 2016 Oct;72:196-204. doi: 10.1016/j.psyneuen.2016.07.206. PMID: 27448712.
8. Sundström Poromaa I, Comasco E, Georgakis MK, Skalkidou A. Sex differences in depression during pregnancy and the postpartum period. *J Neurosci Res*. 2017 Jan 2;95(1-2):719-730. doi: 10.1002/jnr.23859. Review. PMID: 27870443.
9. Agnafors S, Sydsjö G, Comasco E, Bladh M, Orelund L, Svedin CG. Early predictors of behavioural problems in pre-schoolers - a longitudinal study of constitutional and environmental main and interaction effects. *BMC Pediatr*. 2016 Jun 7;16:76. doi: 10.1186/s12887-016-0614-x. PMID: 27267363.
10. Iliadis SI, Sylvén S, Hellgren C, Olivier JD, Schijven D, Comasco E, Chrousos GP, Sundström Poromaa I, Skalkidou A. Mid-pregnancy corticotropin-releasing hormone levels in association with postpartum depressive symptoms. *Depress Anxiety*. 2016 May 27. doi: 10.1002/da.22529. [Epub ahead of print] PMID: 27232288.
11. Tuvblad C, Narusyte J, Comasco E, Andershed H, Andershed AK, Collins OF, Fanti KA, Nilsson KW. Physical and verbal aggressive behavior and COMT genotype: Sensitivity to the environment. *Am J Med Genet B Neuropsychiatr Genet*. 2016 Jul;171(5):708-18. doi: 10.1002/ajmg.b.32430. PMID: 26888414.

12. Todkar A, Granholm L, Aljumah M, Nilsson KW, Comasco E, Nylander I. HPA Axis Gene Expression and DNA Methylation Profiles in Rats Exposed to Early Life Stress, Adult Voluntary Ethanol Drinking and Single Housing. *Front Mol Neurosci.* 26;8:90. doi: 10.3389/fnmol.2015.00090. PMID: 26858597.
13. Harro J, Orelund L. The role of MAO in personality and drug use. *Prog Neuropsychopharmacol Biol Psychiatry.* 2016 Aug 1;69:101-11. doi: 10.1016/j.pnpbp.2016.02.013. PMID: 26964906.
14. Isaksson J, Grigorenko EL, Orelund L, Af Klinteberg B, Kuposov RA, Ruchkin V. Exploring possible association between DBH genotype (C1021T), early onset of conduct disorder and psychopathic traits in juvenile delinquents. *Eur Arch Psychiatry Clin Neurosci.* 2016 Dec;266(8):771-773. PMID: 26616837.
15. Bendre M, Comasco E, Nylander I, Nilsson KW. Effect of voluntary alcohol consumption on Maa expression in the mesocorticolimbic brain of adult male rats previously exposed to prolonged maternal separation. *Transl Psychiatry.* 2015 Dec 8;5:e690. doi: 10.1038/tp.2015.186. PMID: 26645625.
16. Vrettou M, Granholm L, Todkar A, Nilsson KW, Wallén-Mackenzie Å, Nylander I, Comasco E. Ethanol affects limbic and striatal presynaptic glutamatergic and DNA methylation gene expression in outbred rats exposed to early-life stress. *Addict Biol.* 2015 Nov 27. doi: 10.1111/adb.12331. [Epub ahead of print] PMID: 26610727.
17. Comasco E, Gustafsson PA, Sydsjö G, Agnafors S, Aho N, Svedin CG. Psychiatric symptoms in adolescents: FKBP5 genotype--early life adversity interaction effects. *Eur Child Adolesc Psychiatry.* 2015 Dec;24(12):1473-83. doi: 10.1007/s00787-015-0768-3. PMID: 26424511.
18. Iliadis S, Sylvén S, Jocelien O, Hellgren C, Hannefors AK, Elfström D, Sundström-Poromaa I, Comasco E, Skalkidou A. Corticotropin-releasing hormone and postpartum depression: A longitudinal study. *Psychoneuroendocrinology.* 2015 Nov;61:61. doi: 10.1016/j.psyneuen.2015.07.556. PMID: 26383443.
19. Iliadis SI, Comasco E, Sylvén S, Hellgren C, Sundström Poromaa I, Skalkidou Prenatal and Postpartum Evening Salivary Cortisol Levels in Association with Peripartum Depressive Symptoms. *PLoS One.* 2015 Aug 31;10(8):e0135471. doi: 10.1371/journal.pone.0135471. PMID: 26322643.
20. Comasco E, Sundström-Poromaa I. Neuroimaging the Menstrual Cycle and Premenstrual Dysphoric Disorder. *Curr Psychiatry Rep.* 2015 Oct;17(10):77. doi: 10.1007/s11920-015-0619-4. Review. PMID: 26272540.
21. Comasco E, Hellgren C, Olivier J, Skalkidou A, Sundström Poromaa I. Supraphysiological hormonal status, anxiety disorders, and COMT Val/Val genotype are associated with reduced sensorimotor gating in women. *Psychoneuroendocrinology.* 2015 Oct;60:217-23. doi: 10.1016/j.psyneuen.2015.06.019. PMID: 26189199.
22. Comasco E, Todkar A, Granholm L, Nilsson KW, Nylander I. Alpha 2a-Adrenoceptor Gene Expression and Early Life Stress-Mediated Propensity to Alcohol Drinking in Outbred

- Rats. *Int J Environ Res Public Health*. 2015 Jun 25;12(7):7154-71. doi: 10.3390/ijerph120707154. PMID: 26121187.
23. Hannerfors AK, Hellgren C, Schijven D, Iliadis SI, Comasco E, Skalkidou A, Olivier JD, Sundström-Poromaa I. Treatment with serotonin reuptake inhibitors during pregnancy is associated with elevated corticotropin-releasing hormone levels. *Psychoneuroendocrinology*. 2015 Aug;58:104-13. doi: 10.1016/j.psyneuen.2015.04.009. PMID: 25978816.
24. Oreland L. Henrik Sjöbring and the concept of individual psychology in psychiatry. *Ups J Med Sci*. 2015 May;120(2):95-103. doi: 10.3109/03009734.2015.1027428. PMID: 25906975.
25. Comasco E, Frokjaer VG, Sundström-Poromaa I. Functional and molecular neuroimaging of menopause and hormone replacement therapy. *Front Neurosci*. 2014 Dec 8;8:388. doi: 10.3389/fnins.2014.00388. Review. PMID: 25538545.
26. Nilsson KW, Comasco E, Hodgins S, Oreland L, Åslund C. Genotypes do not confer risk for delinquency but rather alter susceptibility to positive and negative environmental factors: gene-environment interactions of BDNF Val66Met, 5-HTTLPR, and MAOA-uVNTR [corrected]. *Int J Neuropsychopharmacol*. 2014 Dec 10;18(5). pii: pyu107. doi: 10.1093/ijnp/pyu107. Erratum in: *Int J Neuropsychopharmacol*. 2015 Jun;18(8). pii: pyv048. doi: 10.1093/ijnp/pyv048. PMID: 25522433.
27. Toffoletto S, Lanzenberger R, Gingnell M, Sundström-Poromaa I, Comasco E. Emotional and cognitive functional imaging of estrogen and progesterone effects in the female human brain: a systematic review. *Psychoneuroendocrinology*. 2014 Dec;50:28-52. doi: 10.1016/j.psyneuen.2014.07.025. Review. PMID: 25222701.
28. Kiive E, Laas K, Akkermann K, Comasco E, Oreland L, Veidebaum T, Harro J. Mitigating aggressiveness through education? The monoamine oxidase A genotype and mental health in general population. *Acta Neuropsychiatr*. 2014 Feb;26(1):19-28. doi: 10.1017/neu.2013.34. PMID: 25142096.
29. Culverhouse RC, Bowes L, Breslau N, Nurnberger JI Jr, Burmeister M, Fergusson DM, Munafò M, Saccone NL, Bierut LJ; 5-HTTLPR, Stress, and Depression Consortium.. Protocol for a collaborative meta-analysis of 5-HTTLPR, stress, and depression. *BMC Psychiatry*. 2013 Nov 12;13:304. doi: 10.1186/1471-244X-13-304. PMID: 24219410.
30. Nilsson KW, Sonnby K, Nordquist N, Comasco E, Leppert J, Oreland L, Sjöberg RL. Transcription Factor Activating Protein-2 $\beta$  (TFAP-2 $\beta$ ) genotype and symptoms of attention deficit hyperactivity disorder in relation to symptoms of depression in two independent samples. *Eur Child Adolesc Psychiatry*. 2014 Apr;23(4):207-17. doi: 10.1007/s00787-013-0450-6. PMID: 23824473.
31. Comasco E, Hallman J, Wallén-Mackenzie A. Haplotype-tag single nucleotide polymorphism analysis of the vesicular glutamate transporter (VGLUT) genes in severely alcoholic women. *Psychiatry Res*. 2014 Oct 30;219(2):403-5. doi: 10.1016/j.psychres.2014.05.052. PMID: 24953423.
32. Comasco E, Hahn A, Ganger S, Gingnell M, Bannbers E, Oreland L, Wikström J, Epperson CN, Lanzenberger R, Sundström-Poromaa I. Emotional fronto-cingulate cortex



activation and brain derived neurotrophic factor polymorphism in premenstrual dysphoric disorder. *Hum Brain Mapp.* 2014 Sep;35(9):4450-8. doi: 10.1002/hbm.22486. PMID: 24615932.

### **Books/book chapters**

1. Om barns sjukdomar i början av 1800-talet. Professor Pehr Afzelius föreläsningar Morbi infantum med kommentarer. Blomquist H, Jonsell R, Orelund L. Publisher: Medicinhistoriska museet (2014). ISBN 978-91-637-5652-8
2. Drogerias historia by Orelund L. In: "Mot en ny drogpolitik". Eds Almqvist K, Gröning L. Publisher: Axel & Margaret Ax:son Johnson stiftelse (2014). ISBN 978-91-89672-57-4
3. Läkarutbildningen i Sverige 400 år - tillkomst och de första åren by Orelund L. In: Medicin och Farmaci 400 år vid Uppsala universitet. Eds Hulter-Åsberg K, Östlund K. Publisher: Uppsala universitet (2014). ISBN 978-91-554-8972-4.

### **Agencies that supported the work/ funding**

Alcohol Research Council of the Swedish Alcohol Retailing Monopoly  
European Union  
Lundqvist foundation  
Swedish Foundation for International Cooperation in Research and Higher Education  
Söderström-Königska sjukhemmet foundation  
Swedish Research Council  
Swedish Society of Medicine

## ***Neurotrauma & Restorative Neuroscience***

### **Neurosurgery**

**The Neurosurgical research comprises two major research programs:**

#### ***Clinical Brain Injury Program – Neurocritical care***

##### **Group leader: Per Enblad, Professor**

Traumatic Brain Injury and Subarachnoid Haemorrhage are the major patient groups treated in the Uppsala Neurointensive care unit (NICU). The continual refinement of neurointensive care and improved knowledge of secondary brain injury mechanisms are the corner stones of this program. With a translational approach combining basic research in animal models with clinical research in the NICU, we strive to find novel therapeutical interventions to minimise secondary brain damage and improve patient outcomes.

#### ***Experimental Brain Injury Programme – Neurotrauma***

##### **Group leader: Lars Hillered, Professor**

The basic goal of this program is to provide new knowledge on important brain injury mechanisms in animal models, to be translated for exploration in the NICU. Several group

members are active in both neurosurgical programs, which is instrumental for achieving the translational goals of the research. Our neurotrauma research is organized in a translational network named the Uppsala Brain Injury Center – UBIC (<http://www.neuro.uu.se/collaboration/uppsala-brain-injury-center-ubic/>) with the overall goal of conducting multidisciplinary research to combat Traumatic Brain Injury – a major global public health problem - from molecule to man. The ultimate goal of the research is to find new targets for therapeutic intervention to restore brain function following TBI. Both neurosurgical programs are integral parts of the Centre of Excellence Neurotrauma at the Uppsala University Hospital (<http://www.akademiska.se/neurotrauma/>). A close interaction between these centers and the Uppsala Berzelii Technology Centre for Neurodiagnostics ([www.berzelii.uu.se](http://www.berzelii.uu.se)) is currently in action.

### **Members of the group during 2016**

Per Enblad, MD, PhD, Professor of Neurosurgery  
Lars Hillered, MD, PhD, Professor of Neurochemistry  
Fredrik Clausen, PhD, Research Engineer, Animal modelling  
Philip Dyhrfort, Neurosurgery Resident  
Andreas Dahlin, Researcher, Materials science and proteomics  
Johanna Flygt, PhD student  
Henrik Engquist, Neuroanesthesiologist, PhD Student  
Sami Abu Hamdeh, Neurosurgery Resident, PhD Student  
Anders Hånell, BSc, PhD, post doc at Karolinska Institute, Stockholm  
Tim Howells, PhD, Researcher, Computer science  
Ulf Johnson, MD, Radiology Resident, PhD Student (dissertation completed in November, 2016)  
Anders Lewén, MD, PhD, Neurosurgeon, Associate professor (50% research time)  
Camilla Lööv, BSc, PhD, currently post-doc at MIND, Boston, USA  
Sara Magnéli, Neurosurgery resident  
Niklas Marklund, MD, PhD, Neurosurgeon, Professor (translocated to Chair of Neurosurgery, University of Lund in December 2016)  
Pelle Nilsson, MD, PhD, Neurosurgeon, Pediatric neurosurgery chief  
Christoffer Nyberg, MD, Neuroradiology Resident, PhD Student  
Lena Nyholm, NICU Nurse, PhD Student  
Elisabeth Ronne, MD, PhD, Adjunct professor, Neurosurgeon (20% research time)  
Elham Rostami, MD, PhD, Neurosurgery resident (Forskar-ST block)  
Mats Ryttefors, MD, PhD, Neurosurgeon  
Inger Ståhl-Myllyaho, NICU Technician  
Parmenion Titsopoulos, Neurosurgeon, PhD Student  
Pavlos Vlachogiannis, Neurosurgeon, PhD Student  
Maria Zetterling, MD, PhD, Neurosurgeon

### **Undergraduate students and project researchers**

Amanda Norberg, Project student

***Project 1: Clinical brain injury program – Neurocritical care***

Participants: Per Enblad (Group leader), Lars Hillered, Philip Dyhrfort, Tim Howells, Ulf Johnson, Anders Lewén, Sara Magnéli, Niklas Marklund, Pelle Nilsson, Christoffer Nyberg, Lena Nyholm, Elisabeth Ronne, Elham Rostami, Mats Ryttefors, Inger Ståhl, Pavlos Vlachogiannis, Parmenion Titsopoulos, Maria Zetterling.

### ***Background***

Traumatic brain injury (TBI) and subarachnoid hemorrhage (SAH) are common and critical medical conditions. The development of modern neurointensive care has markedly reduced mortality and improved patient outcomes, while clinical trials of neuroprotective drug candidates have to date been unsuccessful. Basic research has identified a number of secondary injury mechanisms following TBI and SAH. The challenge ahead is to translate this knowledge into the clinical setting, in order to find new treatment strategies to hinder secondary injuries and improve patient outcomes even further. The neurointensive care unit (NICU) with highly standardised health care, a multitude of monitoring methods and powerful computerised data collection systems provides an excellent platform for this translational research.

### ***Overall goal***

To study secondary brain injury mechanisms in patients with TBI and SAH in the NICU, utilising the available multimodality monitoring and computerised data collection systems.

To specifically study secondary injury mechanisms caused by intracranial secondary insults/complications (e.g. intracranial hypertension owing to brain swelling) and secondary systemic insults (e.g. hypotension with a reduced cerebral blood perfusion).

### ***Methods, Networks and Biobanking facilities***

Multimodality monitoring – The technical equipment available in our NICU allows for continuous monitoring of intracranial pressure, systemic blood pressure, cerebral perfusion pressure, CBF pressure autoregulation status (PRx), intracerebral neurochemistry changes (e.g. energy metabolic perturbations and biomarkers), neurophysiology (e.g. post traumatic seizure activity), brain temperature and brain tissue oxygen pressure, jugular venous oxygen saturation, cerebral blood flow velocity, intracranial compliance. Neuroimaging (CT, CT/PET and MRI) are important complimentary methods for monitoring the brain injury process. A mobile CT scanner with a xenon CBF device makes it possible to measure regional CBF bedside at the NIC unit.

Computerised data collection systems – A computer system has been developed and implemented in the NICU allowing for collection, analysis and illustration of clinical data (e.g. type of brain injury, CT findings), physiological data (e.g. intracranial pressure, brain tissue oxygen pressure) and treatment data (e.g. ventricular CSF drainage to lower the intracranial pressure). A TBI database has been established in the NICU in collaboration with the Uppsala Clinical Research Centre (UCR) to facilitate patient follow up and outcome assessment ([www.ucr.uu.se/tbi](http://www.ucr.uu.se/tbi)). All TBI patients treated in our NICU during the last 5 years are included in the database to date.

Approved systems for biobanking of body fluid samples, brain biopsies and resected brain tissue are established.

The NICU as a “clinical laboratory” – A standardised clinical protocol corresponding to the concept of “good laboratory practice” has been developed and implemented in the NICU. The clinical protocol, the multimodality monitoring system and the computer data collection system together enable extensive control and monitoring of the clinical condition, resembling

a basic science laboratory environment. The facilities thus create an excellent platform for neurointensive care and clinical research of top international quality.

Brain IT group – We have, in collaboration with distinguished colleagues in the field, established an international research network comprising over 20 centers in Europe, with focus on neurointensive care of TBI patients ([www.brainit.org](http://www.brainit.org)). Information technology (IT) is used to collect patient data for a common web-based database for TBI research. This provides a powerful research tool for international multi-center trials on e.g. novel treatment strategies and neurosurgical methods.

Uppsala Brain Injury Center (UBIC) – This is a translational research network with focus on TBI research that was established in 2004. The basic objective of this multidisciplinary endeavour is to combat TBI with a broad spectrum of competencies ranging from molecule to man, i.e. from molecular genetics, cell-culture systems, animals models, TBI patients in the NICU to rehabilitation and follow-up (<http://www.neuro.uu.se/collaboration/uppsala-brain-injury-center-ubic/>). The Uppsala NICU is of top international standard, providing one of the major research platforms within the UBIG. The UBIG concept received top marks regarding research quality, research environment and future potential by the external international review board in the recent evaluations “Quality and Renewal 2007 and 2011” of the research at Uppsala University.

The Centre of Excellence Neurotrauma (<http://www.akademiska.se/neurotrauma/>) is a joint effort between Uppsala University Hospital and Uppsala University, launched in 2008. The purpose of this venture is to stimulate the synergies between highly specialised neurointensive care and research, in order to further improve patient outcomes. The effort involves financial support for dedicated research time (50%) for one neurosurgeon, one NICU technician (50%), one researcher in Computer science (50%) and one PhD student nurse (50%).

Another multidisciplinary project was launched in 2007 in a collaborative effort between UBIG and the Uppsala Berzelii Technology Center for Neurodiagnostics ([www.berzelii.uu.se](http://www.berzelii.uu.se)) combining clinical microdialysis technology with modern proteomic methodology and Materials Science. The main goal is to find clinically useful diagnostic and prognostic biomarkers for point-of-care use in the NICU. The basic working hypothesis is that harvesting of biomarkers directly in the injured brain by microdialysis will be instrumental in the translation and validation of brain-derived biomarkers of secondary injury mechanisms (e.g. neuroinflammation) shown to be of importance in our pre-clinical brain injury models. Modern proteomics methodology is a powerful tool to screen for entirely novel biomarkers of TBI. Materials Science technology is instrumental in optimising protein biomarker sampling performance and combined biosensor technology.

### ***Main results in 2016***

For main results in 2016 the reader is referred to the list of publications below.

### ***Significance***

The organisation of neurointensive care into a “laboratory-like” environment with powerful multimodality monitoring and computerised data collection provides a unique opportunity to monitor the acute brain injury process and the effect of treatment strategies, enabling the study of pathophysiological and neurochemical mechanisms of acute brain injury directly in the human brain. We hypothesise that this opportunity will be instrumental in the translation of promising basic science results to the NICU setting, a development that is likely to improve the outcome of patients with acute brain injury.

### ***Project 2: Experimental brain injury program – Neurotrauma***

**Participants:** Lars Hillered (Group leader), Per Enblad, Fredrik Clausen, Andreas Dahlin, Johanna Flygt, Sami Abu Hamdeh, Anders Lewén, Camilla Lööv, Amanda Norberg, Niklas Marklund, Inger Ståhl Myllyaho.

### ***Overall goal***

Uppsala Brain Injury Center (UBIC) – Experimental neurotrauma research is organised as a translational research network with focus on Traumatic Brain Injury (TBI) research. The basic objective of this multidisciplinary endeavour is to combat TBI with a broad spectrum of competencies ranging from molecule to man, i.e. from molecular genetics, animal models, TBI patients in the Neuro-ICU to rehabilitation and follow-up (<http://www.akademiska.se/neurotrauma/>). The ultimate goal of the research is to find new targets for therapeutic intervention to restore brain function following TBI that can be translated to the NICU setting.

### ***Methods***

The Division of Neurosurgery provides a well-established animal modelling facility, one of the major research platforms within the UBIC. To model the high degree of complexity of human TBI pathophysiology (e.g. focal contusions, epidural, subdural and intraparenchymal hemorrhages, diffuse axonal injury and mixed forms) a battery of animal models with different mechanical impact properties is required. We have established two focal contusion models of TBI (the Controlled Cortical Contusion Model and the Controlled Cortical Impact Model) and one mixed model (the lateral Fluid Percussion Injury Model) and lately a new model of diffuse axonal injury (the central Fluid Percussion Injury Model) for rats and mice. These models are widely used internationally, thus facilitating comparison of data between research groups.

In recent years, a long term strategy was adopted in close collaboration with Prof Bengt Meyerson, BMC, to establish a battery of methods for evaluation of the functional outcome of animals following TBI. Behavioural outcome measures are considered increasingly important in studies of neuroprotective drug effects, other therapeutic interventions and neurorepair strategies. The following methods have thus far been set up: the Morris Water Maze, the Rotarod, the Cylinder test, a four-grade Neuroscore testing neurological function and the Concentric Square Field Method testing a number of features of spontaneous behaviour of mice in a complex environment.

Other in-house methodology comprises cerebral microdialysis and biomarker analysis methods in our NICU lab, as well as basic molecular biology and morphology methods.

A number of additional methods including contemporary proteomics methodology, genetics and neuroimaging are available to us in our collaborative network activities (see above).

### ***Main lines of research***

The main conceptual lines of research within the UBIC comprise molecular studies of secondary brain injury mechanisms in animal models of TBI with focus on oxidative stress, neuroinflammation, diffuse traumatic axonal injury, endogenous brain repair and plasticity, as well as neuroprotection.

Interventional studies are ongoing in the following directions:

Neuroprotection: studies on neuroprotective drug candidates (e.g. anti-IL1 $\beta$  antibody, VEGF antibody) to block important secondary injury mechanisms such as injurious components of the inflammatory response (e.g. immune cell trafficking, blood-brain barrier perturbation) to reduce the total amount of brain damage and brain edema or targeting specific components (e.g. traumatic axonal injury).

Endogenous repair: studies on strategies to enhance axonal regeneration and plasticity following TBI.

### ***Main results in 2016***

For results in 2016 the reader is referred to the below list of publications. The main achievements are: i) continued characterization of our novel rodent model of diffuse axonal injury, including molecular and biomarker studies of early neuroinflammation after TBI to be translated to human TBI patients; ii) continued studies on the demonstrated link between TBI and Alzheimers disease; iii) the development of a refined microdialysis method allowing for improved sampling performance for protein biomarkers and proteomic studies, iiiii) Exploration of Proximity Extension Assay (PEA) technology for multiplexed protein biomarker sampling for biomarker screening, validation and temporal mapping of complex secondary injury mechanisms (e.g. inflammation) in animal TBI mmodels and human TBI patients.

### ***The group actively participated in the following international scientific meetings in 2015:***

Hillered L (2016) Microdialysis in Traumatic Brain Injury: Proteomics - methods and results (Invited plenary speaker). *The 2016 International Neurotrauma Society Symposium*, Cape Town, South Africa, February 1-4.

Hillered L and Enblad P (2016) Co-organisers of *8<sup>th</sup> International Symposium on Microdialysis*, Uppsala, Sweden, 25-27 May.

### **Publications 2014-2016**

Fischerström A, Nyholm L, Lewén A, Enblad P. Acute neurosurgery for traumatic brain injury by general surgeons in Swedish county hospitals: A regional study. *Acta Neurochir (Wien)*. 2014 Jan;156(1):177-85. [PMID: 24272412].

Marklund N, Farrokhnia N, Hanell A, Vanmechelen E, Enblad P, Zetterberg H, Blennow K, Hillered L (2014) Monitoring of  $\beta$ -amyloid dynamics after human traumatic brain injury. *J Neurotrauma* 31(1): 42-55 [IF: 4.3; PMID: 23829439].

Skoglund K, Hillered L, Purins K, Tsitsopoulos PP, Flygt J, Engquist H, Lewén A, Enblad P, Marklund N (2014) The neurological wake-up test does not alter cerebral energy metabolism and brain oxygenation in patients with severe traumatic brain injury. *Neurocrit Care* 20(3): 413-26 [IF: 3.0; PMID: 23934408].

Fridgeirdottir GA, Hillered L, Clausen F (2014) Escalated handling of young C57BL/6 mice results in altered Morris water maze performance. *Ups J Med Sci*, 119 (1): 1-9 [IF: 1.4; PMID: 24172203].

Wetterhall M, Bergquist J, Hillered L, Hjort K, Dahlin AP (2014) Identification of human cerebrospinal fluid proteins and their distribution an in vitro microdialysis sampling system. *Eur J Pharm Sci*, 57:34-40 [IF: 3.0; PMID: 24361471].

Purins K, Lewén A, Hillered L, Howells T, Enblad P (2014) Brain tissue oxygenation and cerebral metabolism in focal and diffuse traumatic brain injury. *Front Neurol*, May 1; 5:64. doi: 10.3389/fneur.2014.00064. [PMID: 24817863].

Nyberg C, Karlsson T, Hillered L, Ronne Engström E (2014) Metabolic pattern of the acute phase of subarachnoid hemorrhage in a novel porcine model: studies with cerebral microdialysis with high temporal resolution. *PLoS ONE* 9(6):1-7 [IF: 3.7; PMID: 24940881].

Rodriguez-Lorenzo A, Mani MR, Thor A, Gudjonsson O, Marklund N, Olerud C, Ekberg T (2014) Fibula osteo-adipofascial flap for reconstruction of a cervical spine and posterior pharyngeal wall defect. *Microsurgery* May;34(4):314-8. doi: 10.1002/micr.22217.

Rostami E, Engquist H, Johnson U, Howells T, Ronne-Engström E, Nilsson P, Hillered L, Lewén A, Enblad P (2014) Monitoring of cerebral blood flow and metabolism bedside in patients with subarachnoid hemorrhage - A Xenon-CT and microdialysis study. *Front Neurol* Jun 2;5:89 [PMID: 24917850].

Lööv C, Nadadhur A, Hillered L, Clausen F, Erlandsson A (2014) Extracellular ezrin - a novel biomarker for traumatic brain injury *J Neurotrauma* Aug 2 (E-Pub) [IF: 4.3; PMID: 25087457].

Dahlin AP, Purins K, Clausen F, Seedig A, Lorant T, Enblad P, Lewén A, Hillered L (2014) Refined microdialysis methodology for protein biomarker sampling in the neurointensive care setting. *Anal Chem* Sep 2; 86(17):8671-8679 [IF: 5.7; PMID: 25075428].

Clausen F, Lindh T, Salimi S, Erlandsson A (2014). Combination of growth factor treatment and scaffold deposition following traumatic brain injury has only a temporary effect on regeneration. *Brain Res* Aug 23. pii: S0006-8993(14)01118-4. doi:10.1016/j.brainres.2014.08.043.

Clausen F, Lindh T, Salimi S, Erlandsson A (2014). Combination of growth factor treatment and scaffold deposition following traumatic brain injury has only a temporary effect on regeneration. *Brain Res* Nov 7;1588:37-46. doi: 10.1016/j.brainres.2014.08.043. PMID: 25157904.

Israelsson C, Kylberg A, Bengtsson H, Hillered L, Ebendal T (2014) Interacting chemokine signals regulate dendritic cells in acute brain injury. *PLoS One* Aug 25;9(8):e104754. doi: 10.1371/journal.pone.0104754 [IF: 3.7; PMID: 25153123].

Israelsson C, Flygt J, Åstrand E, Kiwanuka O, Bengtsson H, Marklund N (2014) Altered expression of myelin-associated inhibitors and their receptors after traumatic brain injury in the mouse. *Restor Neurol Neurosci* 32(5):717-31. doi: 10.3233/RNN-140419.

Nyholm L, Steffansson E, Fröjd C, Enblad P (2014) Secondary insults related to nursing interventions in neurointensive care: a descriptive pilot study. *J Neurosci Nurs*. Oct;46(5):285-91.

von Seth M, Sjölin J, Larsson A, Eriksson M, Hillered L, Lipcsey M (2015) Effects of tigecycline and doxycycline on inflammation and hemodynamics in porcine endotoxemia: a prospective, randomized, and placebo-controlled trial. *Shock* 43(6):604-11[PMID: 25664982; IF: 2.7].

Tsitsopoulos PP, Marklund N (2015) A delayed spinocutaneous fistula after anterior cervical discectomy and fusion. *Spine J* Apr 1;15(4):783-4. doi: 10.1016/j.spinee.2014.11.008.

Lenell S, Nyholm L, Lewén A, Enblad P. Updated periodic evaluation of standardized neurointensive care shows that it is possible to maintain a high level of favorable outcome even with increasing mean age (2015) *Acta Neurochir* (Wien). Mar;157(3):417-25.

Güiza F, Depreitere B, Piper I, Citerio G, Chambers I, Jones PA, Lo TY, Enblad P, Nillson P, Feyen B, Jorens P, Maas A, Schuhmann MU, Donald R, Moss L, Van den Berghe G, Meyfroidt G. Visualizing the pressure and time burden of intracranial hypertension in adult and paediatric traumatic brain injury (2015) *Intensive Care Med*. Jun;41(6):1067-76. doi: 10.1007/s00134-015-3806-1. Epub 2015 Apr 18.

Blomquist E, Ronne Engström E, Borota L, Gál G, Nilsson K, Lewén A, Montelius A, Grusell E, Isacson U, Enblad P. Positive correlation between occlusion rate and nidus size of proton beam treated brain arteriovenous malformations (AVMs) (2015) *Acta Oncol*. 2016;55(1):105-12. doi: 10.3109/0284186X.2015.1043023. PubMed PMID: 25972265.

Merzo A, Lenell S, Nyholm L, Enblad P, Lewén A. Promising clinical outcome of elderly with TBI after modern neurointensive care. (2016) *Acta Neurochir* (Wien).;158(1):125-33.

Johnson U, Engquist H, Howells T, Nilsson P, Ronne-Engström E, Lewén A, Rostami E, Enblad P. Bedside Xenon-CT shows lower CBF in SAH patients with impaired CBF pressure autoregulation as defined by Pressure reactivity index (PRx) (2016) *Neurocrit Care*. Aug;25(1):47-55. doi: 10.1007/s12028-016-0240-3. PubMed PMID: 26842717.

Magnéli S, Howells T, Saiepour D, Nowinski D, Enblad P, Nilsson P (2016) Telemetric intracranial pressure monitoring: a noninvasive method to follow up children with complex craniosynostoses. A case report. *Childs Nerv Syst*. Jul;32(7):1311-5. doi: 10.1007/s00381-016-3023-4. PubMed PMID: 26861131.

Ekmark Lewén S, Flygt J, Fridgeirsdottir AG, Kiwanuka O, Hånell A, Meyerson B J, Mir A K, Gram H, Lewén A, Clausen F, Hillered L, Marklund N (2016) Diffuse axonal injury in mice induces complex behavioural alterations that are normalized by post-injury neutralization of interleukin-1 $\beta$ . *Eur J Neurosci* 43(8):1016-33 [PMID: 27091435; IF: 3.2].

Shariatgorji M, Nilsson A, Bonta M, Gan J, Marklund N, Clausen F, Källback P, Loden H, Limbeck A, Andrén PE (2016). Direct imaging of elemental distributions in tissue sections by laser ablation mass spectrometry. *Methods* Jul 15;104:86-92. PMID: 27136431.

Flygt J, Clausen F, Marklund N (2016). Diffuse traumatic brain injury in the mouse induces a transient proliferation of oligodendrocyte progenitor cells in injured white matter tracts. *Restor Neurol Neurosci* Oct 17. PMID: 27768001.

Nyberg C, Karlsson T, Hillered L, Stridsberg M, Ronne Engström E (2016) The Early Endocrine Stress Response in Experimental Subarachnoid Hemorrhage. *PLoS ONE* 11(3):e0151457 [PMID: 27007694; IF: 3.2].



von Seth M, Lipcsey M, Engström P, Larsson A, Hillered L, Maripuu E, Widström C, Sjölin J (2016) Rapid bolus administration does not increase the extravasation rate of albumin: A randomized controlled trial in the pig. *Shock* 2016 Oct 5 (in press) [PMID: 27749758; IF: 3.0].

Lindblom RPF, Tovedal T, Norlin B, Hillered L, Popova S, Alafuzoff I, Stefan Thelin S (2016) Mechanical reperfusion with leukocyte-filtered blood does not prevent injury following global cerebral ischaemia. *European Journal of Cardio-Thoracic Surgery* (in press) [PMID: 28007877; IF: 2.8].

Rostami E, Engquist H, Howells T, Ronne-Engstrom E, Nilsson P, Lewén A, Hillered L, Enblad P (2016) Early low cerebral blood flow and high cerebral lactate predict delayed cerebral ischemia in subarachnoid hemorrhage. *J Neurosurg* (in press).

Howells T, Johnson U, McKelvey T, Ronne-Engström E, Enblad P. The effects of ventricular drainage on the intracranial pressure signal and the pressure reactivity index. *J Clin Monit Comput*. 2016 Mar 17. [Epub ahead of print] PubMed PMID: 26987656.

Human Traumatic Brain Injury Results in Oligodendrocyte Death and Increases the Number of Oligodendrocyte Progenitor Cells. Flygt J, Gumucio A, Ingelsson M, Skoglund K, Holm J, Alafuzoff I, Marklund N. *J Neuropathol Exp Neurol*. 2016 Jun;75(6):503-15. doi: 10.1093/jnen/nlw025.

Targeting coagulation factor XII as a novel therapeutic option in brain trauma. Hopp S, Albert-Weissenberger C, Mencl S, Bieber M, Schuhmann MK, Stetter C, Nieswandt B, Schmidt PM, Monoranu CM, Alafuzoff I, Marklund N, Nolte MW, Sirén AL, Kleinschnitz C. *Ann Neurol*. 2016 Jun;79(6):970-82. doi: 10.1002/ana.24655.

Abu Hamdeh S, Marklund N, Lannsjö M, Howells T, Raininko R, Wikström J, Enblad P. Extended Anatomical Grading in Diffuse Axonal Injury Using MRI: Hemorrhagic Lesions in the Substantia Nigra and Mesencephalic Tegmentum Indicate Poor Long-Term Outcome. *J Neurotrauma*. 2017 Jan 15;34(2):341-352. doi: 10.1089/neu.2016.4426. PubMed PMID: 27356857.

Engquist H, Lewén A, Howells T, Johnson U, Ronne-Engström E, Nilsson P, Enblad P, Rostami E. Hemodynamic Disturbances in the Early Phase After Subarachnoid Hemorrhage: Regional Cerebral Blood Flow Studied by Bedside Xenon-enhanced CT. *J Neurosurg Anesthesiol*. 2016 Nov 30. [Epub ahead of print] PubMed PMID: 27906765.

Widén J, Eriksson BM, Ronne-Engström E, Enblad P, Westman G. Ventriculostomy-related infections in subarachnoid hemorrhage patients—a retrospective study of incidence, etiology, and antimicrobial therapy. *Acta Neurochir (Wien)*. 2016 Dec 7. [Epub ahead of print] PubMed PMID: 27928632.

Hedberg AL, Pauksens K, Enblad P, Söderberg J, Johansson B, Käyhty H, Sjölin J. Pneumococcal polysaccharide vaccination administered early after neurotrauma or neurosurgery. *Vaccine*. 2017 Jan 6. pii: S0264-410X(16)31299-3. doi: 10.1016/j.vaccine.2016.12.065. [Epub ahead of print] PubMed PMID: 28069358.

Nyholm L, Howells T, Enblad P. Predictive Factors That May Contribute to Secondary Insults With Nursing Interventions in Adults With Traumatic Brain Injury. *J Neurosci Nurs*. 2017 Feb;49(1):49-55. doi: 10.1097/JNN.0000000000000260. PubMed PMID: 28060220.

Astroglial activation and altered amyloid metabolism in human repetitive concussion Pashtun Shahim, Yelverton Tegner, Niklas Marklund, Kina Höglund, Erik Portelius, David L Brody, Kaj Blennow, and Henrik Zetterberg. 2017 *Neurology* In press

Intra- and inter-regional co-regulation of opioid genes: broken symmetry in spinal circuits". Malin Andersson, Vladimir Galatenko, Olga Kononenko, Hiroyuki Watanabe, Xing Wu Zhou, Anna Iatsyshyna, Irina Mityakina, Igor Bazov, Tatjana Yakovleva, Daniil Sarkisyan, Igor Ponomarev; Oleg Krishtal, Niklas Marklund, Alex Tonevitsky, DeAnna L. Adkins and Georgy Bakalkin 2017 *FASEB Journal* In Press

Cerebral amyloid angiopathy: a long-term consequence of traumatic brain injury? Marklund N. *Acta Neurochir* (Wien). 2017 Jan;159(1):21-23. doi: 10.1007/s00701-016-3005-z.

### **Reviews, book chapters, etc 2014-2016**

Rostami E, Engquist H, Enblad P (2014) Imaging of cerebral blood flow in patients with severe traumatic brain injury in the neurointensive care. *Front Neurol*. Jul 7;5:114.

Hånell A, Marklund N (2014) Structured evaluation of rodent behavioral tests used in drug discovery research. *Front Behav Neurosci* 22;8:252. doi: 10.3389/fnbeh.2014.00252. eCollection ( Review).

Hillered L, Dahlin AP, Clausen F, Chu J, Bergquist J, Hjort K, Enblad P, Lewén A (2014) Cerebral microdialysis for protein biomarker monitoring in the neurointensive care setting – a technical approach. *Front Neurol* 5:245. doi: 10.3389/fneur.2014.00245 [PMID: 25520696].

Hutchinson PJ, Jalloh I, Ungerstedt U, Helmy A, Carpenter KLH, Rostami E, Bellander B-M, Boutelle MG, Claassen J, Chen JW, Dahyot-Fizelier C, Enblad P, Gallagher C, Helbok R, Hillered L, et al (2015) Consensus statement from the 2014 International Microdialysis Forum. *Intens Care Med* 41(9):1517-28 [IF: 5.5; PMID: 26194024].

Scandinavian guidelines for initial management of minor and moderate head trauma in children. Astrand R, Rosenlund C, Undén J; Scandinavian Neurotrauma Committee (SNC).. *BMC Med*. 2016 Feb 18;14:33. doi: 10.1186/s12916-016-0574-x.

Rodent Models of Traumatic Brain Injury: Methods and Challenges. Marklund N. *Methods Mol Biol*. 2016;1462:29-46. doi: 10.1007/978-1-4939-3816-2\_3.

Clausen F, Hillered L, Marklund N (2016) The Fluid Percussion Injury rodent model in preclinical research on traumatic brain injury. In: (Ed: Risling M) Methods and challenges in experimental TBI (in press).

### **Agencies that support the work/ Funding**

Bissen Brainwalk fundation

The Swedish Research Council  
Vinnova Foundation  
Swedish Brain Foundation  
EU  
VR/ERA-NET Neuron  
Uppsala University Hospital (ALF funds)  
Berzeli Technology Centre for Neurodiagnostics  
Uppsala University Faculty of Medicine  
Selander Foundation

## Regenerative Neurobiology

**Group leader: Elena N. Kozlova, Assoc. Professor**

### Members of the group during 2016

Ali Inan El-Naggar, SOFOSKO student  
Carl Trolle, PhD  
Geeta Ravindran, PhD, postdoc  
Håkan Aldskogius, MD, PhD, professor emeritus  
Jan Hoeber, PhD student  
Niclas König, PhD  
Ninnie Abrahamsson, biomedical analyst  
Patrik Ivert, PhD student  
Ropafadzo Mzezewa, master student  
Svitlana Vasylovska, PhD, biomedical analyst  
Tanya Aggarwal, PhD, postdoc

### External Collaborations

*National:* Prof Adam Feller, Nanologica AB, Stockholm; Prof Outi Hovatta, Dept CLINTEC, Karolinska institutet; Profs Nils Welsh, and Per-Ola Carlsson, Dept Med Cell Biol, Uppsala Univ; Prof Erik Sundström, and Docent Elisabet Åkesson, Dept NEUROTEC, Karolinska institutet, Stockholm; Dr Igor Adameyko, Dept Pysiol Pharmacol, Karolinska institutet, Stockholm; Docent Nils Hailer and Dr. Nikos Schizas, Dept Surg Sci, Uppsala Univ.

*International:* Dr Christian Berens, Pathogenomics Res Group, Friedrich-Löffler-Institute, Jena, Germany; Prof Vladimir Berezin and Dr. Stanislava Pankratova, Panum Institute, Copenhagen Univ, Denmark; Prof Eugen Lukanidin, Danish Cancer Soc Res Ctr, Copenhagen, Denmark; Prof Su-Chun Zhang, Waisman Ctr, Univ Madison, WI, USA; Prof Kevin Eggan, Harvard Stem Cell Inst, Cambridge, MA, USA; Dr. Peter Shortland, Sch Sci and Health, Univ Western Sydney, Australia; Prof Emmanuel Hermans and Dr. Ronald Deumens, Dept Pharmacol, Cathol Univ Louvain, Brussels, Belgium; Prof Varda Shoshan-Barnatz and Dr. Adrian Israelson, Dept Life Sci and Nat Inst Biotechnol, Ben-Gurion Univ Negev, Beer-Sheva, Israel; Dr. Joep Saura, Biochem Molec Biol Univ, Sch Med, Univ Barcelona; Dr. Inez De Greef and Dr. Marie-José van Lierop, Treeway BV, Rotterdam, The Netherlands; Dr. PJ Anand, Alcyone Inc., Concord, MI, USA; Dr. Ivo Lieberam, MRC Ctr

Dev Neurobiol, King's Coll, London, UK; Drs Arsen Mikaelyan and Ekaterina Vorotelyak, Inst Dev Biol, Russian Acad Sci, Moscow, Russia.

**Our research has three long-term objectives:**

- Promote functional recovery after spinal root and spinal cord injury.
- Develop novel strategies using nanomaterial and cell based treatment of amyotrophic lateral sclerosis (ALS).
- Exploit the beneficial potential of neural crest stem cells for cell supportive and cell protective purposes with focus on endangered motor neurons in ALS, and on endogenous or transplanted insulin producing beta-cells.

***Transplantation of neural stem cells restores lost sensory functions after injury to dorsal roots***

Injured peripheral nerve fibres are able to regenerate, and thereby restore, lost nervous system functions. Nerve fibres in the brain and spinal cord are, however, unable to regenerate, and functional loss after injuries to these parts of the nervous system is often permanent. Furthermore, injury or disease of the nervous system can result in longstanding even chronic, pain conditions, so-called neuropathic pain. Our overall objective is to restore functions that are lost following spinal cord injury with a focus on sensory loss and dysfunction after plexus avulsion injuries.

Sensory information from peripheral tissues is conveyed to the spinal cord via sensory neurons located in paired segmental dorsal root ganglia just outside the spinal cord. These neurons send their information via dorsal roots into the spinal cord. In for example traffic or fall accidents these roots can be avulsed from the spinal cord. The injured axons are unable to re-enter the spinal cord, and as a result, the patient suffers permanent loss of sensation from the affected part of the body, most often the hand and arm, and often also intractable chronic pain. Our research aims to restore the sensory functions lost following these injuries.

We have shown that human neural progenitor cells implanted at the site of avulsed and re-attached dorsal roots support functional regeneration of sensory axons into the host spinal cord (Hoeber et al, 2015). This process appears to be the result of stem cell mediated growth permissive “gaps” in the glial boundary at the dorsal root-spinal cord interface. Our current research aims to determine the mechanisms underlying this ingrowth and optimize its outcome. In a long term perspective, these findings can help to develop novel treatment for patients who have suffered plexus avulsion injury, and possibly, also other injuries to the spinal cord.

***Nanomaterial and stem cell replacement for treatment of ALS***

We have developed a novel delivery system based on mesoporous silica nanoparticles for release of small peptide mimetics of bioactive/therapeutic molecules in the organism (Stem Cells Transl Med, 2013; Nanomedicine, 2014). The results of these studies can contribute to the development of a tunable, locally implantable delivery system for neuroregenerative purposes. We are currently employing this system for our research on spinal root and spinal cord injury as well as for delivery of novel neuroprotective agents in experimental models of amyotrophic lateral sclerosis (ALS), a lethal disorder characterized by progressive paralysis due to death of upper and lower motor neurons.

Our ALS research is carried on mouse and human neural cells harboring a mutation of superoxide dismutase (SOD)1, a commonly used model of human ALS. For early stage disease, our aim is to identify novel neuroprotective agents and deliver them *in vivo* using agent loaded nanoparticles. For late stage disease replacement of lost motor neurons their functional integration is the ultimate objective. For this purpose our aim is to generate human embryonic stem cell-derived motor neuron progenitors according to good manufacturing practice (GMP), implant them into the a model of spinal motor neuron degeneration together with nanoparticles loaded with motor neuron specific differentiation factors. To promote outgrowth of implanted motor neurons to denervated muscles nanoparticles loaded with neural regeneration stimulating factors are placed at strategic sites between spinal cord and muscle.

### ***Boundary cap neural crest stem cells for regenerative medicine***

We have shown that growth, survival and function of mouse and human insulin producing cells in the pancreas are promoted if the cells are cultured or transplanted together with murine boundary cap neural crest stem cells (bNCSC), a transient cell population residing at the junction between dorsal roots and spinal cord during embryonic development (Lau et al, 2015; Grapensparr et al, 2015). The beneficial effects of bNCSCs require direct cell-cell contact with beta-cells through cadherin-catenin connections (Ngamjariyawat et al, 2013; Wang et al, 2016). Our findings provide a basis for the development of stem cell-based strategies to improve outcome of islet or  $\beta$ -cell transplantation, and for increasing the endogenous  $\beta$ -cell mass in patients with diabetes type 1, who have lost large amounts of their insulin producing cells. Given the translational relevance of these results we intend to generate human bNCSC and explore their cell supportive and cell protective potential.

Recently bNCSCs were also shown *in vitro* to protect motor neurons subjected to excitotoxic challenge (Schizas et al, unpublished, as well as motor neurons harboring a an ALS-associated mutation in the gene for superoxide dismutase (SOD)1 (Aggarwal et al, accepted Neurotherapeutics). We aim to determine the mechanisms underlying these effects and translate them into *in vivo* models of motor neuron degeneration.

### **Publications 2014-2016**

1. Wang X, Xie B, Qi Y, Wallerman O, Vasylovska S, Andersson L, Kozlova EN, Welsh N (2016) Knock-down of ZBED6 in insulin-producing cells promotes N-cadherin junctions between beta-cells and neural crest stem cells *in vitro*. *Sci Rep.* 6:19006.
2. Grapensparr L, Vasylovska S, Li Z, Olerud J, Jansson L, Kozlova E, Carlsson PO (2015) Co-transplantation of human pancreatic islets with post-migratory neural crest stem cells increases  $\beta$ -cell proliferation and vascular and neural regrowth. *J Clin Endocrinol Metab.* 100:E583-590.
3. Hoeber J, Trolle C, König N, Du Z, Gallo A, Hermans E, Aldskogius H, Shortland P, Zhang SC, Deumens R, Kozlova EN (2015) Human embryonic stem cell-derived progenitors assist functional sensory axon Rregeneration after dorsal root avulsion injury. *Sci Rep.* 5:10666.
4. Lau J, Vasylovska S, Kozlova EN, Carlsson PO (2015) Surface coating of pancreatic islets with neural crest stem cells improves engraftment and function after intraportal transplantation. *Cell Transplant.* 24:2263-2272.

5. Latini F, Hjortberg M, Aldskogius H, Ryttefors M (2015) The use of a cerebral perfusion and immersion-fixation process for subsequent white matter dissection. *J Neurosci Meth.* 253:161-169.
6. Latini F, Hjortberg M, Aldskogius H, Ryttefors M (2015) The classical pathways of occipital lobe epileptic propagation revised in the light of white matter dissection. *Behav Neurol.* 2015:872645.
7. Kosykh A, Ngamjariyawat A, Vasylovska S, Konig N, Trolle C, Lau J, Mikaelyan A, Panchenko M, Carlsson PO, Vorotelyak E, Kozlova EN (2015) Neural crest stem cells from hair follicles and boundary cap have different effects on pancreatic islets in vitro. *Int J Neurosci.* 125:547-554.
8. Trolle C, Konig N, Abrahamsson N, Vasylovska S, Kozlova EN (2014) Boundary cap neural crest stem cells homotopically implanted to the injured dorsal root transitional zone give rise to different types of neurons and glia in adult rodents. *BMC Neurosci* 15:60.
9. Konig N, Trolle C, Kapuralin K, Adameyko I, Mitrecic D, Aldskogius H, Shortland PJ, Kozlova E (2014) Murine neural crest stem cells and embryonic stem cell-derived neuron precursors survive and differentiate after transplantation in a model of dorsal root avulsion. *J Tissue Eng Regen Med*, Apr 21 *J Tissue Eng Regen Med.* 2014 Apr 21. doi: 10.1002/term.1893.
10. Garcia-Bennett AE, König N, Abrahamsson N, Kozhevnikova M, Zhou C, Trolle C, Pankratova S, Berezin V, Kozlova EN (2014) In vitro generation of motor neuron precursors from mouse embryonic stem cells using mesoporous nanoparticles. *Nanomedicine (Lond)* 9:2457-2466.
11. Aggarwal T, Hoeber J, Ivert P, Vasylovska S, Kozlova EN (2017) Boundary cap neural crest stem cells promote survival of mutant SOD1 motor neurons. Accepted *Neurotherapeutics*.

### **Reviews 2014-2016**

1. Kozlova EN (2016) Stamceller kan återskapa förlorad känsel. *Neurologi i Sverige* 1:20-25.
2. Hoeber J (2015) Sensory regeneration in dorsal root avulsion. *Neural Regen Res* 10:1739-40.

### **Agencies that support the work/ Funding**

The Swedish Research Council (EuroNanoMed2)  
Stiftelsen Olle Engkvist Byggmästare

# Physiotherapy

**Group leaders: Pernilla Åsenlöf, PhD, PT, Professor**

## **Members of the group during 2016**

Elisabeth Anens, PhD, PT, post-doc  
Regina Bendrik, PT, PhD-student  
Annika Bring, PT, PhD  
Ingrid Demmelmaier, PT, PhD  
Christina Emilson, PT, PhD-student  
Margareta Emtner, PT, Senior Professor  
Ann Essner, PT, PhD-student  
Carina Hagman, PT, PhD-student  
Karin Hellström, PT, Associate Professor  
Sara Holm, PT, PhD  
Helena Igelström, PT, PhD  
Henrik Johansson, PT, PhD  
Per Lindberg, Clinical Psychologist, Professor (Psychology, Uppsala University)  
Hanna Ljungvall, Medical Social Worker, PhD-student  
Cathrin Martin, PT, Associate Professor  
Åsa Revenäs, PT, PhD  
Maria Sandborgh, PT, PhD (Mälardalen University)  
Sören Spörndly-Nees, PT, PhD-student  
Birgit Vahlberg, PhD, PT  
Susanna Tuvemo-Jonsson, PT, PhD-student  
Charlotte Urell, PT, PhD  
Hedvig Zetterberg, PT, PhD-student  
Lena Zetterberg, PT, PhD  
Ylva Åkerblom, PT, PhD-student

Physiotherapy research at Uppsala University is strongly linked to the clinic and hence characterised by patient-centred approaches and clinical intervention studies. Research is focused on physical activity, physical exercise, and activities training and their contribution to enhance health in various clinical populations. A significant feature of our research is the integration of behavioural medicine. The group does ground-breaking work in behavioural medicine interventions within the physiotherapy context, showing that physiotherapy interventions benefit from inclusion of health behaviour change strategies that are theoretically based and tailored to the individual patient. The understanding of how biological, psychological and social variables interact during development of chronic conditions as well as recovery is the basis for research. Research activities include issues related to adoption and maintenance of health-related behaviours (e.g. physical activity and sedentary behaviours, eating behaviours, and pain self-management behaviours) within a bio-psycho-social framework. Theoretical principles from learning psychology are integrated with empirical evidence on prognostic factors of each particular condition studied to create and evaluate tailored behavioural medicine interventions targeting relevant health behaviours. A comprehensive future goal is to find optimal matches of assessment strategies, treatments, self-management procedures and individual patient profiles/characteristics. The comprehensive research question is “Who benefits from which dose and content of physiotherapy treatment at which time?” Aspects unifying and differentiating conditions as

well as patient profiles regarding prerequisites and effects of health behavior interventions are expected. A particular target is physical activity interventions for persons with chronic conditions.

Current research includes studies on chronic pain, obstructive pulmonary disease (COPD), asthma, sleep apnoea, rheumatoid arthritis, cardio-vascular diseases, dysfunctional breathing, exercise induced breathing problems and asthma, stroke, Parkinsons' disease, Multiple sclerosis, Charcot-Marie-Tooth disease, cervical dystonia, myasthenia gravis, amyotrophic lateral sclerosis (ALS), and elderly people with increased fall risk.

Collaborators include researchers from the fields of physiotherapy, clinical psychology, clinical physiology, pulmonary medicine, psychiatry, pain and anaesthesiology, rheumatology, addiction medicine, cardiology, neurology, epidemiology, gerontology, nutrition, and surgical sciences.

### **Main projects 2016**

ALS/MNS and pain. (*L Zetterberg/P Åsenlöf*)

Physical activity and health related behaviour change in sleep disordered breathing and insomnia. (*H Igelström/P Åsenlöf*)

Integration of patients' innovations in a web-based intervention targeting physical activity in rheumatoid arthritis: tRAppen. (*Å Revenäs/P Åsenlöf*)

Chronic opioid treatment in chronic non-cancer pain: benefits and work ability versus risks and opioid use disorder (*P Åsenlöf*)

Ambulatory oxygen in patients with COPD who desaturate during exertion – A multicenter study in the Nordic countries (AMBOX-study). (*M Emtner*)

Muscle function, maintenance of physical activity, long term follow up of patients with COPD, and prevalence of pulmonary rehabilitation within primary care in Sweden. (*M Emtner*)

Identification, description and treatment of subjects with dysfunctional breathing problems and subjects with exercise-induced breathing problems. (*C Hagman/ M Emtner*)

Effects of individually-tailored physical and daily activities for patients with hip or knee osteoarthritis. (*M Emtner*)

Effects of individually-tailored physical and daily activities for residents in nursing home settings – A Nordic multi-centre study. (*K Hellström*)

Effects of fall-prevention intervention in community dwelling elderly people over 75 years: a CRT. (*K Hellström*)

Validation of outcome measures in canine physical rehabilitation and physiotherapy. (*A Essner/K Hellström*)



A survey of physical activity in persons with neurological diseases. (*E Anens*)

Exercise induced breathing problems among adolescents; the ANDAS 2016 study and the CELADY- study (*H Johansson*)

Physical activity intervention for patients with stroke. (*B Vahlberg*)

### **Publications 2014-2016**

Anens E, Emtner M, Zetterberg L, Hellström K. Physical activity in subjects with Multiple Sclerosis with focus on gender differences - A survey. *BMC Neurology* 2014, 14:47

Ahlström I, Hellström K, Emtner M, Anens E. Reliability of the Swedish version of the Exercise Self-Efficacy Scale (S-ESES): a test-retest study in adults with neurological disease. *Physiother Theory Pract* . 2014;24:1-6

Emtner M, Hallin R, Arnardottir HR, Janson C. Effect of physical training on fat-free mass in patients with chronic obstructive pulmonary disease (COPD). *Ups J Med Sci* 2014;28:1-7

Igelström H, Emtner M, Lindberg E, Åsenlöf P. Tailored behavioral medicine intervention for enhanced physical activity and healthy eating in patients with obstructive sleep apnea syndrome and overweight. *Sleep Breath* 2014; 18:655–668

Jonsson M, Urell C, Emtner M, Westerdahl E. Self-reported physical activity and lung function two months after cardiac surgery – a prospective cohort study  
*Journal of Cardiothoracic Surgery* 2014, 9:59

Johansson H, Norlander K, Hedenström H, Janson C, Nordang L, Nordvall L, Emtner M. Exercise-induced dyspnea is a problem in the general adolescent population. *Respiratory Medicine* 2014;108:852-858

Måhlin C, von Sydow H, Osmanovic A, Emtner M, Grönberg AM, Larsson S, Slinde F. Vitamin D status and dietary intake in a Swedish COPD population. *Clin Respir J* 2014;8:24-32

Pitta F, Mitchell S, Chatwin M, Clini E, Emtner M, Gosselink R, Grant K, Inal-Ince D, Lewko A, Oberwaldner B, Williams J, Troosters T. A Core Syllabus for Post-Graduate Training in Respiratory Physiotherapy. *Breathe* 2014;10:220-28

Rastad C, Martin C, & Åsenlöf P. Barriers, benefits and strategies for physical activity in patients with schizophrenia. *Physical Therapy* 2014;94(10):1467-79. doi: 10.2522/ptj.20120443.

Ristiniemi H, Perski A, Lyskow E, Emtner M. Hyperventilation and exhaustion syndrome. *Scandinavian Journal of Caring Sciences* 2014;28:657-64

Spörndly-Nees, S, Igelström, H, Martin, C, Lindberg, E, & Åsenlöf, P. Facilitators and barriers for eating behaviour changes in obstructive sleep apnoea and obesity – a qualitative content analysis. *Disability and Rehabilitation* 2014;36(1):74-81. doi: 10.3109/09638288.2013.782354.

Spörndly-Nees S, Åsenlöf P, Theorell-Haglöw J, Svensson M, Igelström H, & Lindberg E. (2013). Leisure-time physical activity predicts snoring in women: a prospective population-based cohort study over 10 years. *Sleep Medicine* 2014 Apr;15(4):415-21. doi: 10.1016/j.sleep.2013.09.020.

Westerdahl E, Urell C, Jonsson M, Bryngelsson IL, Hedenstrom H, Emtner M. Deep breathing exercises performed 2 months following cardiac surgery: a randomized controlled trial. *J Cardiopulm Rehabil Prev.* 2014;34(1):34-42. Epub 2013/11/28.

Arkkukangas M, Tuvemo Johnson S, Hellström K, Söderlund A, Eriksson E, Johansson A-C. Fall prevention through exercise with or without the support of Motivational Interviewing in older community-living people – a feasibility study of a randomized controlled trial. *Preventive Medicine Reports* On line 2015 02-03 [doi:10.1016/j.pmedr.2015.01.007](https://doi.org/10.1016/j.pmedr.2015.01.007)

Essner A, Sjöström R, Ahlgren E, Gustås P, Edge Hughes L, Zetterberg L, Hellström K. *Comparison of Polar RS800CX heart rate monitor and electrocardiogram for measuring inter-beat intervals in healthy dogs.* *Physiol. Behav.* 2015;138; 247-253 DOI: 10.1016/j.physbeh.2014.10.034

Essner A, Sjöström R, Gustås P, Edge-Hughes L, Zetterberg L, Hellström K. *Validity and reliability properties of canine short-term heart rate variability measures – A pilot study.* Accepted 2015-05-21. *Journal of Veterinary Behavior: Clinical Applications and Research*

Farkhooy A, Janson C, Arnardottir RH, Emtner M, Hedenström H, Malinowski A. Impaired carbon monoxide diffusing capacity is the strongest lung function predictor of changes in 12 minute -walking distance in COPD over a five-year follow-up. *COPD* 2015;12:240-8

Revenäs Å, Opava C, & Åsenlöf P. Experiences and innovations on support for physical activity in rheumatoid arthritis: a first step in the development of an internet service using participatory design. *BMC Medical Informatics and Decision Making* 2014;14:21. doi: 10.1186/1472-6947-14-21.

Anens E, Emtner M, Hellström K. An exploratory study of physical activity in persons with Charcot-Marie-Tooth disease. *Arch Phys Med Rehabil* 2015;96:260-8

Ahmadi Z, Lundström S, Janson C, Strang P, Currow DC, Emtner M, Ekström M. End of Life care in Oxygen-Dependent Chronic Obstructive Pulmonary Disease and Cancer – A national publication based study. *Eur Respir J* 2015;46(4):1190-3

Andersson M, Stridsman C, Rönmark E, Lindberg A, Emtner M. Physical activity and fatigue in chronic obstructive pulmonary disease – A population based study. *Respir Med* 2015;109:1048-57

Johansson H, Norlander K, Berglund S, Janson C, Malinowski A, Nordvall L, Nordang L, Emtner M. Prevalence of exercise-induced bronchoconstriction and exercise-induced laryngeal obstruction in a general adolescent population. *Thorax* 2015;70:57-63

Norlander K, Johansson H, Jansson C, Nordvall L, Nordang L. Surgical treatment is effective in severe cases of exercise-induced laryngeal obstruction: A follow-up study. *Acta Otolaryngol.* 2015;135(11):1152-9.

Olsson A, Engström M, Åsenlöf P, Skovdal K & Lampic C. Effects of tracking technology on daily life with dementia – three experimental single-case studies. Accepted in *Journal of Alzheimer's Disease and Other Dementias*, 2015;30(1):29-40. doi: 10.1177/1533317514531441. PMID 24771764

Troosters T, Pitta F, Oberwaldner B, Lewko A, Inal-Ince D, Grant K, Gosselink R, Burtin C, Emtner M, Clini E, Chatwin M, Mitchell S. Development of a syllabus for postgraduate respiratory physiotherapy education: the Respiratory Physiotherapy HERMES project. *Eur Respir J.* 2015;45:1221-1223.

Revenäs Å, Opava C, Martin C, Demmelmaier I, Keller C & Åsenlöf P (2015). Development of a Web-Based and Mobile App to Support Physical Activity in Individuals With Rheumatoid Arthritis: Results from the Second Step of a Co-Design Process. *JMIR Research Protocol* 2015;4(1):e22 doi:10.2196/resprot.3795.

Revenäs Å, Martin C, Opava H. C, Bruzewitz M, Keller C, Åsenlöf P. A Mobile Internet Service for Self-Management of physical activity in People with Rheumatoid Arthritis: Challenges in Advancing the Co-Design Process During the Requirements Specification Phase. *JMIR Research Protocol* 2015; 4(3):e111

Zetterberg H, Frykberg GE, Gäverth J, Lindberg PG. Neural and Nonneural Contributions to Wrist Rigidity in Parkinson's Disease: An Explorative Study Using the NeuroFlexor. *BioMed Research International.* 2015;Article ID:276182.

Zetterberg L, Urell C, Anens E. Exploring factors related to physical activity in cervical dystonia. *BMC neurology.* 2015;15:247. Epub 2015/12/02.

Arne M, Emtner M, Lisspers K, Wadell K, Stållberg B. Availability of pulmonary rehabilitation in primary care for patients with COPD: a cross-sectional study in Sweden *Eur Clin Respir J* 2016 Nov 28;3:31601

Bring A, Åsenlöf P & Söderlund A. What is the comparative effectiveness of current standard treatment, against individually tailored behavioural programme delivered either on the Internet or face-to-face for people with acute whiplash associated disorder? A randomised controlled trial. *Clinical Rehabilitation* 2016;30(5):441-453.

Demmelmaier I, Åsenlöf P, Bergman P, Nordgren B & Opava C. Pain rather than self-reported sedentary time explains variation in perceived health and activity limitation in persons with rheumatoid arthritis: a cross sectional study in Sweden. Accepted for publication in *Rheumatology International.*

Emilson C, Demmelmaier I, Bergman P, Lindberg P, Denison E & Åsenlöf P. (2016). A 10-year follow-up of tailored behavioural medicine treatment and exercise-based physiotherapy

in persistent musculoskeletal pain. Accepted for publication in *Clinical Rehabilitation*, 22<sup>nd</sup> February.

Emilson C, Åsenlöf P, Pettersson S, Bergman S, Sandborgh M, Martin C & Demmelmaier I. Physical therapists' assessments, analyses and use of behavior change techniques in initial consultations on musculoskeletal pain: direct observations in primary health care. *BMC* 17:316. DOI: 10.1186/s12891-016-1173-x

Essner A, Sjöström R, Zetterberg L, Hellström K, Gustås P, Högberg H, Test–retest reliability in a translated version of the Canine Brief Pain Inventory in canine osteoarthritis, *Acta Veterinaria Scandinavica*, 2016;58(Suppl 2):85:A10.

Essner A, Hielm-Björkman A, Högberg H, Validation of a Swedish version of the Helsinki Chronic Pain Index for the measure of chronic pain behaviors in canine osteoarthritis, *Acta Veterinaria Scandinavica*, 2016;58(Suppl 2):85:A11.

Essner A, Zetterberg L, Hellström K, Gustås P, Högberg H, Sjöström R, Validation of a translated version of the Canine Brief Pain Inventory for the measure of pain severity and functional movements in canine osteoarthritis, *J Small Anim Pract*, 2016;57(Suppl S2), p. 1–12.

Frändin K, Grönstedt H, Helbostad J, Bergland A, Andresen M, Puggaard L, Harms-Ringdahl K, Hellström K. *Long-term effects of individually tailored physical training and activity on physical function, wellbeing and cognition in Scandinavian nursing home residents – an RCT.* *Gerontology*. 2016 Mar 11. [Epub ahead of print PMID:26963569]

Hagman C, Janson C, Malinowski A, Hedenström H, Emtner M. Measuring breathing patterns and respiratory movements with the respiratory movement measuring instrument. *Clin Physiol Funct Imaging*. 2016;36:414-420

Holm S, Ljungman G, Åsenlöf P & Söderlund, A. Treating youth in pain: comparing tailored behavioural medicine treatment provided by physiotherapists with physical exercise. *European Journal of Pain* 2016;20(4):626-638. DOI: 10.1002/ejp.780

Johansson H, Norlander K, Alving K, Hedenstrom H, Janson C, Malinowski A, et al. Exercise test using dry air in random adolescents: Temporal profile and predictors of bronchoconstriction. *Respirology*. doi: 10.1111/resp.12682. Epub 2015 Nov 20 2016;21(2):289-96.

Johansson H, Norlander K, Janson C, Malinowski A, Nordang L, Emtner M. The relationship between exercise induced bronchial obstruction and health related quality of life in female and male adolescents from a general population. *BMC Pulm Med*. 2016;16(1):63.

Lövström L, Emtner M, Alving K, Nordvall L, Borres M, Janson C, Malinowski A. High level of physical activity is associated with poorer asthma control in young females, but not in males. *Respirology*. 2016 Jan;21(1):79-87

Pettersson S, Bring A, & Åsenlöf P. (2016). Stressful events and coping related to acute and sub-acute whiplash-associated disorders. Accepted for publication in *Disability and Rehabilitation*.

Revenäs Å, Opava CH, Ahlén H, Brucewitz M, Pettersson S & Åsenlöf P. A mobile internet service for self-management of physical activity in people with rheumatoid arthritis: Evaluation of a test version. *RMD Open* 2016;2:1. DOI: 10.1136/rmdopen-2015-000214.

Spörndly – Nees S, Åsenlöf P, Lindberg E. High or increasing levels of physical activity protect women from future insomnia. *Sleep Medicine* 2016.  
DOI: 10.1016/j.sleep.2016.03.017

Tuvemo Johnson S, Martin C, Anens E, Johansson A-C, Hellström K. Older adults' opinions on fall prevention in relation to physical activity level. *J Appl Gerontol.* 2016 Jan 14. pii: 0733464815624776. [Epub ahead of print]

Vahlberg B, Zetterberg L, Lindmark B, Hellström K, Cederholm T. "Functional performance, nutritional status and body composition in ambulant community-living individuals 1-3 years after suffering from a cerebral infarction or intracerebral bleeding" *BMC Geriatr.* 2016 Feb 19;16:48.

Vahlberg B, Lindmark B, Zetterberg K, Hellström K, Cederholm T. [Body composition and physical function after progressive resistance and balance training among older adults after stroke: an exploratory randomized controlled trial.](#) *Disabil Rehabil.* 2016 Jun 24:1-8. [Epub ahead of print] PMID:27341068

Vahlberg B, Cederholm T, Lindmark B, Zetterberg L, Hellström K. Short-term and long-term effects of a progressive resistance and balance exercise program in individuals with chronic stroke: a randomized controlled trial. *Disabil Rehabil.* 2016 Jul 14:1-8. [Epub ahead of print] PMID:27415645

Westerdahl E, Jonsson M, Emtner M. Pulmonary function and health-related quality of life 1-year follow up after cardiac surgery. *Journal of Cardiothoracic Surgery* 2016 **11**:99

Westerberg E, Molin CJ, Lindblad I, Emtner M, Rostedt Punga A. Physical exercise in Myasthenia Gravis is safe and improves neuromuscular parameters and physical performance-based measures: A pilot study. *Muscle & Nerve.* Accepted manuscript online: 9 December 2016

Urell C, Emtner M, Hedenstrom H, Westerdahl E. Respiratory muscle strength is not decreased in patients undergoing cardiac surgery. *J Cardiothorac Surg.* 2016;11(1):41. Epub 2016/04/03.(1)

## **Reviews and books**

Emtner M, Wadell K. Sjukgymnastik vid KOL. I KOL-Kroniskt Obstruktiv Lungsjukdom. Pages 547-565. Red K Larsson, Studentlitteratur, 2014, 740 pages. ISBN: 978-91-44-07817-5. Uppaga 3:1

Biquet G, Lindquist I, Martin C, Pettersson A. (2015). (red.) Att lära och utvecklas i sin profession. Lund: Studentlitteratur.

Emtner M, Wadell K. Fysisk träning vid Kroniskt Obstruktiv Lungsjukdom. In FYSS 2015. Red A Ståhle. [www.fyss.se](http://www.fyss.se)

Hellström K, Emtner M, Anens E. Fysisk aktivitetsnivå hos personer med MS med fokus på könskillnader. BestPractice 2015(11): 14-16.

Johansson H. Ansträngningsutlöst bronkobstruktion och ansträngningsutlöst laryngeal obstruktion bland ungdomar. BestPractice 2015 (10): 13-15.

Martin C. (2015). Bok-kapitel: Att stimulera lärande i undervisning. I: Biquet G, Lindquist I, Martin C, Pettersson A. Att lära och utvecklas i sin profession. Lund: Studentlitteratur.

Åsenlöf P. (2015). Bok-kapitel: Fysioterapeutens åtgärder vid smärtrehabilitering. Rehabiliteringsmedicin, teori och praktik. Lund: Studentlitteratur.

Emtner M, Wadell K. Effects of exercise training in patients with chronic obstructive pulmonary disease — a narrative review for FYSS (Swedish Physical Activity Exercise Prescription Book).  
Br J Sports Med 2016;50: 368-371

Emtner M. Vård vid astma och KOL. Socialstyrelsens nationella riktlinjer ur ett fysioterapeutiskt perspektiv. Fysioterapi 2016;8:30-36

Emtner M. Effekter av fysisk aktivitet vid astma. BestPractice 2016 25 juli

SBU (2016). Preventiva insatser vid akut smärta från rygg och nacke. Effekter av fysisk träning, manuell behandling och beteendepåverkande åtgärder. En systematisk litteraturöversikt. Stockholm: SBU.

Emilson C, Åsenlöf P. Långtidseffekter av beteendemedicinsk behandling vid smärta. BestPractice 2016 (28): 19-21.

Åsenlöf P et al. Preventiva insatser vid akut smärta från rygg och nacke. Presentation av en SBU-rapport. Fysioterapi 2016;5:34-42

### **Agencies that support the work/ Funding**

AFA

ALF

Agria Animal Insurance and the Swedish Kennel Club joint research fund

The Faculty of Medicine, Uppsala University

The Heart and Lung Foundation, Sweden

The Heart and Lung Patient Association, Sweden

The Stroke Research Fund

The Swedish Rheumatism Association

The Swedish Research Council

Ulla-Carin Lindquists stiftelse

Uppsala County Council Research Fund

Uppsala-Örebro Research Fund

## **Awards**

The Neuroscience Price for better learning: Annika Bring

## **Speech and Language Pathology**

**Group leader: Monica Blom Johansson, PhD**

### **Members of the group during 2016**

Per Alm, PhD, senior lecturer  
Monica Blom Johansson, PhD, senior lecturer  
Klaudia Ceder, research assistant  
Margareta Gonzalez Lind, PhD student  
Martina Hedenius, PhD, senior lecturer  
Margareta Jennische, PhD, associate professor  
Cecilia Nakeva Von Mentzer, PhD, Post doc  
Ingrid Sör, research assistant

The research of the group focuses on normal and pathological speech, language and swallowing, and its neural correlates across the life span. It aims to understand the neurological bases of language development; to explore language development and communication practices in and around individuals who use graphic systems as alternative communication forms; to understand the causal mechanisms of stuttering from a neuroscience perspective; to study what effects a disturbed breathing pattern has on the ability to swallow and on the ability to swallow safely, and to study psychosocial consequences of acquired language disorders.

### ***Project 1: REMEMBR (Reading, Memory, and Brain)***

**Participants:** Martina Hedenius (PI). Collaborators: Joanne Arciuli. Sven Bölte, Juha Kere, Janne von Koss Torkildsen, Martin Ingvar, Lars Nyberg, Jonas Persson.

This project explores the role of statistical/procedural learning and memory consolidation in language and reading development. It also investigates the compensatory potential of declarative memory in the case of statistical/procedural learning impairments. The research questions are addressed with both behavioral and brain imaging techniques, including (functional) Magnetic Resonance Imaging and Diffusion Tensor Imaging.

### ***Project 2: Aided language skills in children aged 5-15 years - a multi-site and cross-cultural investigation***

**Participants:** A multinational project involving about 20 countries. Margareta Jennische, and Annika Dahlgren Sandberg, Maria Larsson, Britt Amberntson (Göteborg), Stephen von Tetzchner (University of Oslo, Norway).

Augmentative and alternative communication (AAC) systems have gradually become more important as a supplement to, or a substitute for, spoken language, supporting the development of language and communication in children with little or no functional speech.

The acquisition of aided communication may provide insights into the nature of the underlying processes of language development in general. The use of aided communication is not simply a non-vocal expression of spoken language but has its own characteristics. The developmental path, from the use of pictograms and photographs via Blissymbols to orthographic script implies discontinuities in form not present in the acquisition of spoken language, and thus can help to elucidate the interaction between language meaning, language structure and language form.

The lack of crucial knowledge within the field of aided communication is the motivation for the present project. It is a joint international effort under the leadership of Professor Stephen van Tetzchner, University of Oslo. A large corpus of utterances produced with communication aids by children aged 5-15 years has been obtained and is actually being analysed to be published as a reference guide on aided communication development both for research and clinical use.

***Project 3: The nature of stuttering: Speech motor characteristics and neurobiological mechanisms***

**Participant:** Per Alm

The nature and the causal background of the speech fluency disorder stuttering has long been poorly understood. This project aims to clarify the nature of the speech motor disruptions and underlying causal mechanisms, to enable development of more effective methods of treatment. The speech motor disruptions are analyzed using multimodal recording including electromyography (EMG), electroglottography (EGG), and video. The analysis indicates that the disruptions are related to two basic types of speech motor failure. The cerebral speech motor preparation during the second before speech onset will be investigated using EEG (electroencephalography), with analysis of oscillatory patterns and event-related potentials. Based on the acquired results a pilot study for treatment of stuttering is planned, with a novel method for speech facilitation.

***Project 4: Aphasia and communication in everyday life as perceived by significant others***

**Participants:** Monica Blom Johansson, Marianne Carlsson, Per Östberg, Karin Sonnander

This project focuses the communicative rights of individuals with aphasia and their ability to be active participants in their social environment and in the community. In this last part of the project in particular, the significant others of individuals with aphasia are in focus including their own health and everyday life situation, how they could contribute to increase autonomy and social participation of individuals with aphasia and what support they may need themselves.

***Project 5: Language impairment or typical language development? Developing methods for linguistic assessment of bilingual children in Sweden***

**Participants:** Ute Bonnacker (Professor of general linguistics, Department of Linguistics and Philology, Uppsala University), Margareta Jennische, Eva-Kristina Salameh (PhD, Skåne University Hospital, Malmö)

This project aims to develop methods for the assessment of bilingual children for reliable diagnosis in both languages. Arabic and Turkish are in focus, as these languages are well



represented in Sweden and belong to two different language groups. Linguists and SLPs collaborate in studying the core linguistic features of typically developing bilingual children at age 4-7, with a focus on narratives. These data are then compared to samples from children with alleged LI, in order to identify clinical markers of LI in Arabic, Turkish and Swedish. The research group closely cooperates with the EU COST Action on bilingualism and LI.

***Project 6: Assessing Children's Speech Processing Ability, The Listen-Say Test***

**Participants:** Cecilia Nakeva von Mentzer, PhD, Mathias Hällgren, PhD Linköping University, Klaudia Ceder, research assistant, Martina Sundström, SLP, Karin Enqvist, SLP, Sofia Järlesäter, audiologist, Åsa Klingstedt, audiologist, and Fredrik Stillesjö, technical audiologist, Uppsala University Hospital, and David Moore, professor, Cincinnati Children's Hospital Medical Center, USA (in different constellations).

Impaired speech perception occurs in several groups of children enrolled at Speech Language Pathology and Audiological clinics. These may be children with Language Impairment (LI), attentional difficulties (ADHD), Hearing Impairment (HI) and children with Central Auditory Processing Disorders (CAPD). At present no standardized speech perception test in Swedish provides information about how children discriminate, identify and produce consonantal contrasts in words. It is therefore of great importance to develop diagnostic tools to obtain a reliable test procedure and enable differential diagnostics. The first data collection with the Listen-Say test indicates that the test appears to be sensitive for predicted perceptual difficulties of different consonant contrasts. The project consists of the following parts:

***6a) Assessing Swedish Normal-hearing Children's Speech Processing Ability, The Listen-Say Test*** with the aim to standardize and validate the Listen-Say test in Swedish – a speech perception test that gives information on how children discriminate and produce consonant contrasts in minimal word pairs. The findings indicate that the test appears to be sensitive for predicted perceptual difficulties of phonetic contrasts. Further test refinement is in process.

***6b) Assessing Swedish Deaf and Hard of Hearing (DHH) Children's Speech Processing Ability, The Listen-Say Test*** with the aim to evaluate speech perception ability of consonant contrasts in quiet and in 4T babble in DHH children.

***6c-e) Assessing Speech Processing Ability in 4-5 year old American Children with and without language impairment, the American-English version of the Listen-Say Test***

These projects aim to describe the development of an American 'Listen-Say'-test that uses monosyllabic minimal word pairs in a 3-interval, 2-alternative (XAB) adaptive level method to obtain discrimination thresholds for phonetic categories in noise; to evaluate how speech discrimination in 4-5 year old children with and without a diagnosed language impairment benefit from multisensory speech cues; and to give further insight about the link between speech perception and production in children with language impairment. The objective is to investigate how 4-5 year old children with and without a diagnosed language impairment produce the words that are used in experiment c and d.

***Project 7: Listening difficulties in children with language impairment, 2016-2018***

**Participants:** Cecilia Nakeva von Mentzer, Jennie Pihlgren, Elsa Erixon, Sofie Järlesäter (Teamet för hörselimplantat, Akademiska sjukhuset), Ingrid Sör, David R Moore, Cincinnati Children's Medical Hospital

The aim of this project is to investigate mechanisms involved in speech and auditory processing children with normal hearing between 7 to 12 years of age who have or have not been diagnosed with language impairment. The overall objective is to test the hypothesis that some children with language impairment have 'listening difficulties' (LiD) that are not detectable using conventional pure tone audiometry. The long-term goal with the planned research is to improve speech understanding in children with language impairment. The project consists of three parts:

***7a-b: Developmental trajectories in Swedish children who have been diagnosed with language impairment in their preschool years: listening and communication.***

**a)** This study aims to explore how Swedish Speech Language Pathologists (SLPs) assess and treat listening difficulties in children with language impairment and how cooperation between SLPs and audiologists is accomplished when difficulties are revealed.

**b)** This is a questionnaire based study that aims to disclose the developmental trajectories of school aged children who have been diagnosed with language impairment in their preschool years (the same children as in 7a). The ECLiPS is a scale consisting of 38 questions that incorporates 5 main subscales relevant to children referred because of listening difficulties. The ECLiPS thus provides the clinician with information regarding how much each of these impact on the child's daily interactions.

***c) The enhanced QuickSiN (Speech in Noise) test in American children.***

In this project a speech in noise test that captures some of the complexities of real world listening situations will be assessed in children between 6 -12 years of age with and without a diagnosed language impairment. Particular focus will be on evaluating speech understanding in four-talker babble, audiovisual and a spatial condition. Comparison to adult data will be made. Children's scores will be analyzed in relation to a kit of cognitive and auditory tests including high frequency audiometry.

***Project 8: Computer-assisted reading intervention in children with Down's syndrome***

**Participants:** Cecilia Nakeva von Mentzer, Margareta Jennische, Nelli Kalnak, Klaudia Ceder and Ingrid Sör

This project aims to investigate whether it is possible to support reading development in children with Down's syndrome (DS). Graphogame is an Internet based reading program with a phonics approach originally developed for children with dyslexia. It offers child friendly exercises for beginning readers and has recently proven successful for children with hearing loss. In the current study we will examine whether children with Down's syndrome may benefit from such an Internet-based reading intervention. In addition, the project aims to investigate how reading development in children with Down's syndrome (DS) may be supported by a phonics approach using Graphogame; GG - an Internet based reading program. GG was originally developed for children with dyslexia and offers child friendly exercises for beginning readers, i.e. grapheme-phoneme correspondence training, blending of phonemes into words and segmenting words in phonemes. GG has recently proven successful for children with hearing loss at 5-7 years of age.

***Project 9: Speech recognition in the elderly.***

**Participants:** Klaudia Ceder and Cecilia Nakeva von Mentzer

The aim of this project is to examine speech recognition in the elderly and to evaluate the influence of external and internal factors, as a noisy background and individual memory capacity. In the study, individuals with and without hearing impairment and individuals with and without subjectively experienced speech recognition difficulties will be compared by combining neurophysiological measurements (EEG, Mismatch negativity) and behavioral measurements of phonetic contrasts.

***Project 10: Swedish adaptation of the Comprehensive Aphasia Test (CAT) – an European CATs project***

**Participants:** Members of the Swedish adaptation group are Monica Blom Johansson, Klaudia Ceder, and Ingrid Sör; Ingrid Behrns and Francesca Longoni (University of Gothenburg); Per Östberg (KI).

The Collaboration of Aphasia Trialists (CATs) is an action of the European Collaboration in Science and Technology (COST). CATs consists of several working groups which work on aphasia-related research topics. One of them is developing/translating/adapting aphasia assessment tools comparable across different languages. An ongoing project is the adaptation of the Comprehensive Aphasia Test (CAT) to fourteen different languages, including Swedish. For each adaptation process, national interdisciplinary teams work accordingly with the previously agreed upon guidelines. To ensure comparability across the various languages, the adaptations are matched according to underlying linguistic variables such as word and sentence length, word frequency, imageability, morphological complexity, grammatical structure, and spelling regularity. Since some of the languages lack the necessary background data on variables such as imageability and frequency, studies are being conducted in order to establish these data. When the adaptation process is completed, each language version of the CAT will be standardized and normed.

***Project 11: Supporting Communicative Participation of Individuals with Aphasia***

**Participants:** Lise Randrup Jensen (PI) (Univ. of Copenhagen); Monica Blom Johansson; Elisabeth Ahlsén and Charlotta Saldert (University of Gothenburg); Jytte Isaksen (Denmark); Madeleine Cruise, Simon Horton and Carol Pound (UK); Nina Simmons-Mackie (US)

This network includes nine members and its purpose is mainly to study and/or develop good ways of evaluating Supported Conversation of Adults with Aphasia (SCA) with respect to underlying theories, participation and quality of life. The project also involves hosting the Nordic Aphasia Conference in Copenhagen 2017.

***Project 12: A PhD project within the area “Coordination of breathing and swallowing - Swallowing function in patients with Chronic Obstructive Pulmonary Disease”.***

**Participants:** Margareta Gonzalez Lindh, Monica Blom Johansson, Margareta Jennische, Hirsh Koyi

General aim: The focus of this thesis is to examine swallowing function and identify swallowing problems (oropharyngeal dysphagia) in patients with respiratory dysfunction due to chronic obstructive pulmonary disease (COPD) both in acute and stable phase, and in patients that have undergone a radiographic videofluoroscopic swallow study.

***a: Prevalence of swallowing dysfunction screened in Swedish cohort of COPD patients***

Chronic Obstructive Pulmonary Disease (COPD) is a common problem associated with morbidity and mortality. COPD may also affect the dynamics and coordination of functions such as swallowing. This project looked at prevalence of swallowing dysfunction, both subjective and screened with a swallowing test, in 51 patients with COPD in a stable phase.

***b: Prevalence of subjective swallowing dysfunction in patients with stable COPD. The TIE-study\* TIE= Tools Identifying Exacerbations***

Additional participants: Andrei Malinovski, Marieann Högman, Regina Bendrik, Björn Ställberg, Karin Lisspers

The Swedish TIE-study is a prospective multi-center study in primary and secondary care to identify the underlying etiology of exacerbations in COPD patients. The aim of this study is to investigate the prevalence of subjective swallowing dysfunction, i.e. oropharyngeal dysphagia (OPD) and to determine the relation to COPD disease stage (GOLD), gender, exacerbations and physical activity.

***c: Prevalence of swallowing dysfunction in exacerbations of chronic obstructive pulmonary disease***

The aim of this study is to determine whether patients presenting to the hospital with an acute exacerbation of chronic obstructive pulmonary disease (COPD) are more likely than controls to suffer from oropharyngeal swallow disorder.

***d: Videoradiographic Swallow Studies at Gävle hospital 2003-. Analysis of referral routines, type of dysphagia, underlying pathologies and recommendations.***

The aim of this study is to do a retrospective review of videofluoroscopic swallowing studies on patients with oropharyngeal dysphagia.

***Project 13: Speech- and oral sensorimotor interventions in evidence-based habilitation***

Participants: Anita McAllister (PI), Lotta Sjögreen (PI), Margareta Gonzalez Lindh, Madeleine Brodén, Corinna Krüssenberg, Irvina Ristic, Agneta Rubensson.

This network includes seven members and its purpose has been to search for and critically evaluate the evidence base for different kinds of interventions for speech and oral sensorimotor dysfunction including dysphagia in children and adults within the habilitation services in Sweden.

**Publications 2014-2016**

1. Nakeva von Mentzer, C., Lyxell, B., Sahlen, B., Dahlström, O., Lindgren, M., Ors, M., Kallioinen, P., & Uhlen, I. (2014). Computer-assisted reading intervention with a phonics approach for children using cochlear implants or hearing aids. *Scandinavian Journal of Psychology*, 55(5), 448-455.
2. Nakeva von Mentzer, C., Lyxell, B., Sahlen, B., Dahlström, O., Lindgren, M., Ors, M., Kallioinen, P., & Uhlén, I. (2014). The Phonics Approach in Swedish Children using Cochlear Implants or Hearing Aids: Inspecting Phonological Gain. *Journal of Communication Disorders, Deaf Studies & Hearing Aids* 2(3).

3. Nakeva Von Mentzer, C., Lyxell, B., Sahlen, B., Dahlstrom, O., Lindgren, M., Ors, M., Kallioinen, P., Engstrom, E., & Uhlen, I. (2014). Segmental and suprasegmental properties in nonword repetition - An explorative study of the associations with nonword decoding in children with normal hearing and children with bilateral cochlear implants. *Clinical Linguistics & Phonetics*, 1-20
4. Jennische, M. & Zetterlund, M. (2015) Interpretation and Construction of Meaning of Bliss-words in Children. *Augmentative and Alternative Communication*, 31(2): 97–107. DOI: 10.3109/07434618.2015.1036117
5. Kallioinen, P., Olofsson, J., Nakeva von Mentzer, C., Lindgren, M., Ors, M., Sahlen, B. S., . . . Uhlen, I (2016). Semantic Processing in Deaf and Hard-of-Hearing Children: Large N400 Mismatch Effects in Brain Responses, Despite Poor Semantic Ability. (1664-1078 (Linking). doi: D - NLM: PMC4978721 OTO - NOTNLM
6. Eliasson, A. C., Holmström, L., Aarne, P., Nakeva von Mentzer, C., Weiland, A. L., Sjostrand, L., Forssberg, H., Tedroff, K & Löwing, K. I (2016). Efficacy of the small step program in a randomised controlled trial for infants below age 12 months with clinical signs of CP; a study protocol
7. Gonzalez Lindh M, Blom Johansson M, Jennische M, Koyi H. (2016). Prevalence of swallowing dysfunction screened in a Swedish cohort of COPD patients. *International Journal of Chronic Obstructive Pulmonary Disease*. Accepted.

## Reviews 2014-2016

1. Alm P. (2014). Stuttering in relation to anxiety, temperament, and personality: Review and analysis with focus on causality. *Journal of Fluency Disorders*, 40, 5-21.
2. Hedenius, M. (2015). Dyslexi - ett komplext samspel mellan arv, miljö och samhällets krav. *Barnläkaren*, nr 5.

## Agencies that support the work/ Funding

Stiftelsen Sunnerdahls Handikappfond (Project 1)  
 Jerringfonden (Project 1)  
 Stiftelsen Promobilia (Project 1)  
 Kungliga Vetenskapsakademien (Project 1)  
 Akademiska sjukhuset ALF-anslag (Project 1)  
 Faculty of Medicine at Uppsala University (Project 3)  
 Strokefonden (Project 4)  
 The Swedish Research Council, Humanities and social science (Project 5)  
 Tysta skolan (Project 6)  
 Svenska Dyslexistiftelsen (Project 7)  
 FORTE: Swedish Research Council for Health and Working Health Care (Project 6 and 7)  
 Stiftelsen Sävstaholm (Projekt 8)  
 Disciplinary Domain of Medicine and Pharmacy, Uppsala University (Project 9)  
 Afasifonden (Project 10)

## ***Uppsala University Behavioral Facility***

Uppsala University Behavioral Facility (UUBF) was established in 2011 through strategic funding from the Faculty of Medicine and Pharmacy. UUBF functions as a non-profit core facility that administers and organizes experimental behavioral testing of mice, rats and fish with the aim to optimize access to well validated tests for research groups at Uppsala University as well as for external researchers, and promote the further development of high quality behavioural tests. Services offered include experimental design, statistical processing and interpretation of results, rental of equipment including advanced recording equipment, and full performance of experiments. During the last years the number of users has increased, and reached approximately 60 users distributed over a number of research groups. A recent survey shows that the services offered are appreciated. Based on requests in the survey, we strive to provide annual courses on behavioral research covering several different aspects of behavioral neuroscience.

E-mail: [uubf@farmbio.uu.se](mailto:uubf@farmbio.uu.se). Homepage: <http://www.farmbio.uu.se/Plattformar/uubf/>

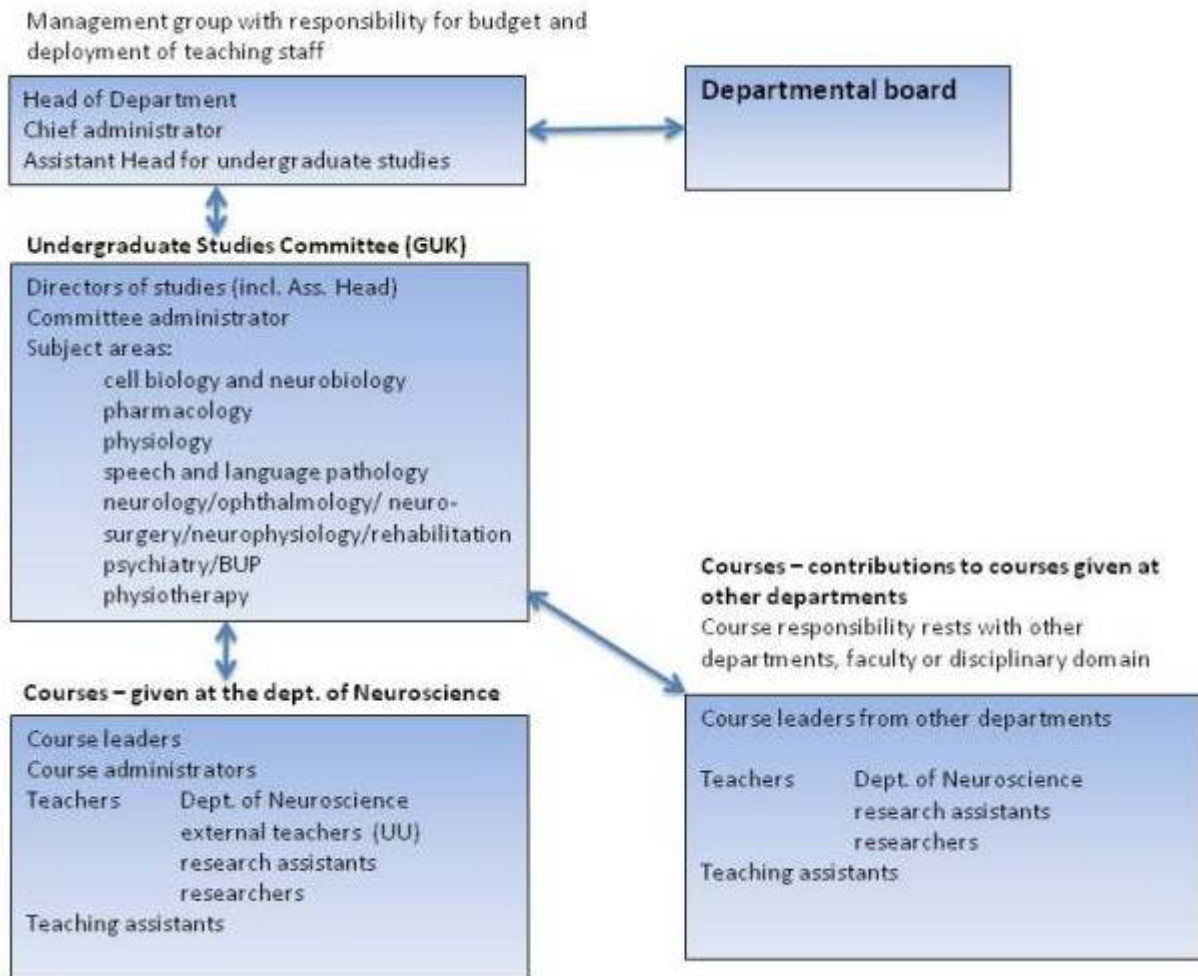
## UNDERGRADUATE STUDIES 2016



*Annika Bring, senior lecturer and researcher in Physiotherapy, was the winner of Neuroscience award for better teaching 2016  
From left: Finn Hallböök, Head of Department, Annika Bring and Anne-Marie Landtblom, Assistant Head of Department for Undergraduate studies*

## **Organization of Undergraduate studies at the Department**

The organisational structure of the Department's educational efforts at basic and advanced levels was revised in 2011/12. The tasks of the directors of studies (studierektor), course leaders, teachers and course administrators were more clearly defined in order to promote a more efficient leadership within all levels of undergraduate teaching at the department. This revision was initiated and performed by the committee for undergraduate studies (Grundutbildningskommittén, GUK).



Our leadership organisation for undergraduate studies is described in the figure above. The main organ for pedagogical leadership is the committee for undergraduate studies (GUK). The committee is made up of the directors of studies for the main subject areas, clinical neuroscience (neurology, neurophysiology, neurosurgery, ophthalmology and rehabilitation medicine), cell- and neurobiology, pharmacology, physiology, physiotherapy. Psychiatry (including child and adolescent psychiatry), speech and language pathology, and one administrator. Each sector covers several courses, and a course may fall under more than one director of studies depending on the content of its syllabus.



### **Roles of director of studies, course leader and course administrator**

- Director of studies:
  - Strategy, development and planning of the educational offering, cases of cheating and resolution of disputes, introduction of new teachers.
- Course leader (block co-ordinator)
  - Scheduling, planning and implementation of courses, course information, student contact, examination and grading.
- Course administrator
  - Study documentation, educational and course information (Selma, student portal), administration of current and prospective courses.

### **Undergraduate studies committee (GUK)**

The membership of the Undergraduate studies is composed of the directors of studies for the seven major subject areas. For 2016 these were:

- Cell biology and neurobiology (C&N)  
Dan Larhammar
- Pharmacology (FA)  
Madeleine Le Grevès
- Physiology (FY)  
Olle Nylander
- Speech and language pathology (LOG)  
Monica Blom-Johansson
- Neurology/opthalm./n-surgery/n-physiol./rehab. (NEUR)  
Ann-Marie Landtblom
- Psychiatry/Child and adolescent psychiatry/ nursing pr. (PSYK)  
Mia Ramklint  
(Lisa Ekselius - Nursing and medium-length healthcare pr.)
- Physiotherapy (PT)  
Lena Zetterberg

The group is chaired by Anne-Marie Landtblom and assisted by the committee's administrator, Neil Ormerod. The committee meets regularly, at least twice per semester.

### **Activities and achievements of the Undergraduate studies committee**

A half-day teaching conference was held at the Psychiatry building on 25th August, with themes of cheating (deceptive conduct) and pedagogical perspectives on health. Teachers from the department presented several cases of cheating and how these were handled. Guest speakers Karin Appelgren and Cilla Häggkvist from the university's Student Affairs and Academic Registry Division spoke and answered questions from an enthusiastic audience on ethical and legal aspects of the issue of cheating. The department's Anne-Marie Landtblom gave a presentation of ideas arising from a Norwegian concept of "health pedagogics".

Mia Ramklint, psychiatry, achieved the title Excellent teacher. The unit for psychiatry was given the Symbiosis prize for best course module in the medicine programme. The pedagogic prize of our department, the Neuro prize for better learning, was awarded to Annika Bring, from the unit for physiotherapy. Physiotherapy Education Days were held in Uppsala with the title "The physiotherapist of tomorrow".

Topics of discussion have been, amongst others, standardized methods for evaluation of individual student reports, IPL and health pedagogics from a salutogenic perspective.

## List of Courses given by the Dept of Neuroscience

Programme/ Course	Course code/ course part	Course Leader	Course administrator
<b>Within the faculty of medicine</b>			
<b>Medicine</b>			
KNEP Communication and the Nervous System	3NR113	Klas Kullander	Stefan Pettersson/ Eva Lena Wahlberg Neil Ormerod/ Eva Lena Wahlberg
NHoI, Neurobiology, Homeostas and Intervention Clinical Clerkship	3NR137 3NR012	Madeleine Le Grevès	Wahlberg
Clinical Medicine V/ Clinical Medicine IV	3NR008/3NR014	Mia Ramklint	Gunneli Ekberg
	<i>Neurology</i>	Ann-Marie Landtblom	Sari Thunberg
	<i>Psychiatry</i>	Mia Ramklint	A.-C. Fält
	<i>Ophthalmology</i>	Gerd Holmström	Gunneli Ekberg
Child and Adolescent Psychiatry	3BP001	Mia Ramklint	A.-C. Fält
Communication skills	3PS053/54	Mia Ramklint	A.-C. Fält
<b>Biomedicine</b>			
Molecular Cell Biology	3MU123	Finn Hallböök	Karin Nygren
VBE - Tissue Biology with Embryology	3MU122	Finn Hallböök/ Sonya Stenfelt	Neil Ormerod
Neurobiology	3MU132	Malin Lagerström	Neil Ormerod
Pharmacology with medicinal chemistry	3MU150	Dan Larhammar	Neil Ormerod
Comparative medicine	3MU143	Madeleine Le Grevès	Neil Ormerod
<b>Master's programme in biomedicine</b>			
Advanced Neurobiology	3NR600,	Bryndis Birnir / Zhe Jin	Karin Nygren
Drug Target Identification and Evaluation	3NR380	Helgi Schiöth	Karin Nygren
Master's Degree Project in Biomedicine	3MU230	Lina Thorvaldsson (examinator)	Karin Nygren
Laboratory Project in Biomedicine	3MU015/3MU130	Helgi Schiöth (examinator)	Karin Nygren
Research training in biomedicine and laboratory animal science	3NR730	Madeleine Le Grevès	Karin Nygren
<b>Nursing</b>			
Nursing and medical science within psychiatric care	3PS040	Caisa Öster	A-C Fält
<b>Specialist nursing</b>			
Psychiatry	3PS300	Caisa Öster	A-C Fält
Nursing in Psychiatry/Mental Health I	3PS301	Caisa Öster	A-C Fält
Nursing in Psychiatry/Mental Health II	3PS302	Kristina Haglund	A-C Fält
Advanced Nursing Study within Psychiatric Care	3PS303	Caisa Öster/Kristina Haglund	A-C Fält
Degree Project in Psychiatric Care	3PS304	Caisa Öster	A-C Fält
<b>Speech and language pathology</b>			
Basic Concepts of Anatomy, Physiology and Pathophysiology	3LG020	Elena Kozlova	Anki Gustafsson/ Stefan Pettersson
Professional Logopedics I	3LG110	Nadina Laurent	Anki Gustafsson/ Stefan Pettersson
Professional Logopedics II	3LG111	Sofia Ögefäldt	Anki Gustafsson/ Stefan Pettersson
Nervous System Disorders in Adults	3LG024	Per Alm	Anki Gustafsson/ Stefan Pettersson
Child Logopedics 1	3LG210	Maria Krüger-Vahlquist	Anki Gustafsson/ Stefan Pettersson
Speech Impairment: Stuttering. Head and Neck Cancer	3LG404	Per Alm/Sofia Ögefäldt	Anki Gustafsson/ Stefan Pettersson
Clinical Child Logopedics 1	3LG610	Maria Krüger-Vahlquist	Anki Gustafsson/ Stefan Pettersson
Speech Pathology in Congenital Nervous System Disorders	3LG214	Monica Blom Johansson	Anki Gustafsson/ Stefan Pettersson

Voice Pathology	3LG215	Sofia Ögeföldt	Anki Gustafsson/ Stefan Pettersson
Speech Pathology in Acquired Nervous System Disorders	3LG216	Monica Blom Johansson	Anki Gustafsson/ Stefan Pettersson
Speech Pathology in Language and Reading Disorders in School-Aged Children	3LG217	Cecilia Nakeva von Mentzer	
Clinical Voice Pathology,	3LG613	Maria Krüger-Vahlquist	Anki Gustafsson/ Stefan Pettersson
Professional Logopedics III	3LG112	Nadina Laurent	Anki Gustafsson/ Stefan Pettersson
Clinical Course: Stuttering	3LG615	Maria Krüger-Vahlquist	Anki Gustafsson/ Stefan Pettersson
Clinical Speech Pathology in Acquired Nervous System Disorders in Adults	3LG620	Maria Krüger-Vahlquist	Anki Gustafsson/ Stefan Pettersson
Clinical Speech Pathology in Congenital Nervous System Disorders	3LG619	Maria Krüger-Vahlquist	Anki Gustafsson/ Stefan Pettersson
Clinical Speech Pathology in Language and Reading Disorders	3LG621	Maria Krüger-Vahlquist	Anki Gustafsson/ Stefan Pettersson
Professional Logopedics IV	3LG113	Nadina Laurent	Anki Gustafsson/ Stefan Pettersson
Master's Thesis in Speech and Language Pathology	3LG503	Per Alm, Monica Blom Johansson	Nadina Laurent
Advanced Clinical Logopedics (elective)	3LG616	Monica Blom Johansson	Anki Gustafsson/ Stefan Pettersson
Advanced Theoretical Speech and Language Pathology	3LG617	Monica Blom Johansson	Anki Gustafsson/ Stefan Pettersson
<b>Physiotherapy</b>			
Physiotherapy I	3PT011	Ann Sundbom/Pernilla Åsenlöf	Stefan Pettersson
Physiology and Anatomy I	3PT012	Svante Winberg	Stefan Pettersson
Physiotherapy I: Health Behaviour and Research	3PT013	Charlotte Urell	Stefan Pettersson
Anatomy II	3PT021	Ann Månsson	Stefan Pettersson
Physiotherapy II	3PT022	Helena Igelström/Ewa Wenngren	Stefan Pettersson
Anatomy II: Muscles and Joints	3PT023	Ann Månsson	Stefan Pettersson
Physiotherapy II: Movement, Biomechanics and Functional Anatomy	3PT024	Ewa Wenngren	Stefan Pettersson
Physiotherapy III: Acute and Subacute Conditions	3PT031	Johanna Holmbäck	Stefan Pettersson
Neuroanatomy and Physiology Related to Pain and Stress	3PT032	Camilla Ekwall	Stefan Pettersson
Psychiatry	3PS034	Mimmie Willebrand	A-C Fält
Physiotherapy in Neurological Disorders, Theory and Practice	3SG036	Camilla Ekwall	Stefan Pettersson
Phys. in Pain and Musculoskeletal Dysf., Theory and Clinic	3SG096	Christina Emilsson	Stefan Pettersson
Basic Physiology Related to Pain and Stress	3SG037	Cecilia Norrbrink	Stefan Pettersson
Neurology	3SG069	Dag Nyholm	Stefan Pettersson
Paediatrics and Physiotherapy in Paediatrics	3SG086	Eva Gäve	Stefan Pettersson
Physiotherapy in Patient Care, Theory and Practice	3SG027	Johanna Holmbäck	Stefan Pettersson
Clinical Education in Physiotherapy, Elective	3SG029	Camilla Ekwall	Stefan Pettersson
Research Methodology II	3SG087	Sara Holm	Stefan Pettersson
Rehabilitation ...in patients with Non-communicable diseases	3SG081	Margareta Emtner	Stefan Pettersson
Research Methodology III/Research plan	3SG091	Mikael Andersson	Stefan Pettersson
Health and Health Promotion	3SG072	Sören Spörndly-Nees	Stefan Pettersson
Physiotherapy and Geriatric Care	3SG068	Marie Sandström	Stefan Pettersson
Research Methodology IV/Bachelor's Thesis	3SG090	Karin Hellström	Stefan Pettersson
Physiotherapy for Adults with Neurological Disorders	3SG093	Lena Zetterberg	Stefan Pettersson
Degree Thesis in Physiotherapy, Advanced Level	3SG094	Cathrin Martin	Stefan Pettersson
Clinical Course in Physiotherapy for Exchange Students	3SG074		Stefan Pettersson

#### Within the faculty of pharmacy

#### Pharmacy (bachelor's programme)

Physiology	3FF112	Olof Nylander	Stefan Pettersson/ Eva Lena Wahlberg
------------	--------	---------------	--------------------------------------

#### Within the disciplinary domain of science and technology

<b>Biology/Molecular biology</b>			
Neurobiology	1BG207	Malin Lagerström	Neil Ormerod
<b>Civil engineer chemistry/technology</b>			
Physiology and Molecular Cell Biology	3FF158	Olof Nylander	Stefan Pettersson/ Eva Lena Wahlberg
<b>Elective courses</b>			
<b>Within the faculty of medicine</b>			
Psychotraumatology	3PS038	Kerstin Bergh Johannesson	A-C Fält
Medical history	3NR501	Eva Ahlsten	Stefan Pettersson Eva Lena Wahlberg
Exploring the Brain I	3NR201	Klas Kullander	Stefan Pettersson
Exploring the Brain II	3NR202	Klas Kullander	A-C Fält
Psychiatry	3PS050	Caisa Öster	Sari Thunberg
Advanced Course in Neuroscience Care	3NR009	Niklas Marklund	Anki Gustafsson
Research Methods	3LG501	<i>Therese Glatz (Psychology)</i>	Anki Gustafsson
Evaluation of Scientific Reports	3LG517	<i>Ebba Elwin (Psychology)</i>	Anki Gustafsson
Clinical Supervision	3LG927	Maria Krüger-Vahlquist	Anki Gustafsson
Paediatric Swallowing and Feeding	3LG935	Margareta Gonzalez Lindh	Anki Gustafsson
Sports Medicine and Sports Rehabilitation	3SG007	Charlotte de Belder Tesséus	Stefan Pettersson
Behavioural Medicine: Theory and Practice within Health Care	3SG089	Annika Bring	Stefan Pettersson
Advanced Physiotherapy: Theory and Method	3SG085	Cathrin Martin	Stefan Pettersson
<b>Laboratory courses</b>			
Advanced Course in Developmental Genetics	Several		Karin Nygren
Advanced Course in Neuropharmacology	Several		Karin Nygren
Elective Course in Neuroscience	Several		Karin Nygren

## ***Programmes at the Dept of Neuroscience***

### **Programme in Biomedicine**

The bachelor's programme in Biomedicine (Kandidatprogrammet i Biomedicin) has approximately 43 students per year with a total of 128 over its three years.

The Biomedicine Programme teaches the biology of the human body from the smallest molecule to the functions of the whole organism, and the complex brain in health and in disease. Five courses in the Bachelor's programme were given from our department: Cell and Molecular Biology (new 2015) (course leader Finn Hallböök/Henrik Ring, 15 hp), Tissue Biology with Embryology (revised) (course leader Finn Hallböök/Sonya Stenfelt, 15 hp), Neurobiology (new 2014) (course leader Malin Lagerström 10 hp), Pharmacology and medicinal chemistry (new 2015) (course leader Dan Larhammar and Ulrika Rosenström/ (dept of Medicinal chemistry) and the course on Experimental animal welfare (new 2014). The department contributes significantly to the course in physiology (Olle Nylander/Markus Sjöblom, 16,5 hp).

#### **Assurance of quality**

The educational quality of the programme is continuously assessed: Course- and programme syllabus, course evaluations, communication skills, mentor support, professional identity and exam project reports are regularly reviewed. Course evaluations are used as a basis for revising courses. These course evaluations are summarised by two student representatives. Good points, bad points and suggestions for improvements are presented, and a discussion with the course leader follows. The results of evaluation are further discussed in the programme committee. In the mentor system senior students may act as mentors and are reimbursed for tutoring students studying for re-exams. To strengthen their professional identity and employability, students pay visits to different companies. The form of examination for the degree project was revised, following advice from the Pedagogic Unit, in order to ensure that it meets the criteria for the Swedish Higher Education Authority's evaluation.

#### **Development of teaching and learning**

“Professional training” with practice in oral presentation, discussion techniques, giving feedback, writing short reports as well as scientific papers. These training progresses throughout the different courses during subjects covered in the curriculum. The seminars are given by invited experts and cover extra-curricular topics. The overall aim of the project is to increase the employability and general proficiency of the students.

#### **Internationalization**

The programme has exchange agreements with universities in several countries, for instance Denmark, Portugal and UK as well as a pharmaceutical company in England for exam projects. America and Australia are the most popular countries and most students choose universities in English-speaking countries.

#### **Broader recruitment**

Students are very much engaged in activities related to PR for the programme, such as recruiting new students and making the programme known among future employers and

students. There is an “Ambassador” project in which biomedical students visit different schools to give a presentation of the program. They also participate in educational fairs.

## **The Master Programme in Biomedicine**

The Department hosts the international Master Programme in Biomedicine, which started in 2010. The programme is intended as an extension of the Bachelors Programme in Biomedicine. Lina Thorvaldson, from the Department of Medical Cell Biology, is programme coordinator and Karin Nygren is the administrator for the programme. The courses in the first year are given by several different departments in the medical and pharmaceutical faculties. During the second year, the students can choose freely from other courses, and are able to specialize in their field of interest. They also complete a master's thesis in their chosen specialty. The most popular option for the second year is the Clinical Drug Development course. It is also common for students to do independent laboratory projects during this period or to do a 45 credit thesis, starting already in the middle of the third semester.

There is also an option of ending the programme after a year, when students may take a one-year master's degree that fulfils the requirements for Swedish post-graduate studies.

The Master in Biomedicine is dimensioned for 30 students. The number of admitted students has varied slightly, but the most variation has been in the number of fee-paying students (between one and thirteen). Twenty-nine each year in 2012, 2013 and 2014. In 2015, only 17 non-paying students were accepted, partly because of an increase in the number of accepted fee-paying students. In 2016, the number rose to 21 non-paying students. Between two and five students each year choose to finish with a one-year master. Among the students who study two years, almost all finish the programme on time and we have very few students who drop out (one or two each year).

Of the students that have graduated from the programme, many have begun post-graduate studies or have been employed within life science or drug development.

The courses in the programme are also listed as independent courses taught in English and students that are not enrolled in the master programme may be registered for these courses. Our department contributes with two courses; Advanced Neuroscience (15 credits) given by the Physiology unit and Preparation for Research with Focus on New Drug Targets (15 credits) given by the Functional Pharmacology unit. Other courses in the first year are Homeostasis and Endocrine Disorders with a Focus on Major Diseases (15 credits) from the Department of Medical Cell Biology, and Drug Discovery and Development (7.5 credits) and Computational Medicinal Chemistry (7.5 credits) from the Department of Medicinal Chemistry. The students also have the option to study Immunology (15 credits), given by the Biology Education Centre, instead of the two 7,5 credit courses. The Department of Neuroscience also coordinates the Master Thesis projects.

The theme of the programme is: “From the ailing body and the ailing brain to the discovery and development of new drugs”. The programme provides in-depth knowledge of some of our major diseases, as well as the healthy and in diseased brain. Students follow the process of developing new drugs, from finding new targets to developing the final product. The focus of the programme is placed on research-oriented questions for application in academic research and in the pharmaceutical and biotechnological industries. The curriculum includes scheduled lectures, laboratory practicals, seminars, problem-oriented group assignments, demonstrations and study visits.

### **Assurance of quality**

Between 2013 and 2015, the master programme was evaluated by the Swedish Higher Education Authority. and a substantial work was done under 2014 and 2015 to address the comments made in the evaluation and improve the programme. A programme council, with a responsibility for the continuous quality control of the programme, has been formed. Several changes have been made in the courses of the programme in the form of new lectures, seminars, laboratory practicals and assignments, and all course syllabi have been revised. There have also been new lectures added to the common seminar series for all the master programme at the Medical Faculty, and the structure of this seminar will be revised during 2016 to introduce a flipped-classroom pedagogy and group discussions on ethical topics. The organization of the examination of the Master thesis projects has been revised so that there now are four subject experts examining the student theses apart from the examiner. The instructions and criteria for the projects have been revised so that no reports should be passed unless they fulfil the stricter criteria. The importance of ethical aspects and considerations and the societal benefits of each project must be discussed as separate subjects.

Continuous quality work will proceed with meetings with the programme council and regular meetings with students in the programme, as well as course evaluations. The master programs are coordinated by the central master program committee at the Medical Faculty and our program is represented by Lina Thorvaldsson.

### **Development of teaching and learning**

Our teachers are recruited from the teaching staff and researchers from each participating department. They are expected to follow the university policy on professional development and participate in relevant pedagogical training. Lectures in project planning and leadership, design methods, presentation techniques and research ethics are integrated in the courses during the first semester.

Students from other universities have often not taken any course in laboratory animal science, which can cause problems for those wishing to do master thesis projects that include animal research. As a solution to this, we have developed a course of 15 credits that combines the laboratory animal science course with a laboratory project. This course is offered as an alternative during the third semester, and will provide the students with an opportunity to gain the Felasa certificate that allows them to perform animal experimentation.

From the autumn of 2016, the students also have the opportunity to do the same laboratory animal science course as a part of their master thesis, if they choose to do a longer thesis of 45 credits. The option to do a thesis of 45 credits was implemented for the first time in 2016, and 9 out of the 27 students doing their thesis this academic year have chosen to do a longer thesis.

### **Internationalization**

The proportion of students with an international background decreased with the introduction of the tuition fees in 2011, but has increased steadily since then although with some variation between the years. Two thirds of students registered in 2010 came from an international background. With the introduction of tuition fees in 2011, this dropped to one third, was back at two thirds 2015 and dropped to one fourth in 2016. Six tuition-fee paying students were accepted in 2016. Among the 27 new students admitted in the autumn of 2015, 12 had an international background (they came from Bangladesh, Greece, Iraq, Germany, Japan, Mexico, Indonesia, France, Egypt, Great Britain and China). The proportion of non-paying students from EU countries have also increased over the years, possibly as a result of the

increased awareness of European students that studies in Sweden are free and of high quality.

## **The Speech and Language Pathology Programme**

The ninth class (LK13) of speech and language pathologist (21 students) graduated in January and 40 new students were admitted to the program in the spring semester (36 females and 4 males). We were sad to see Anki Gustafsson, who had administered the programme and its courses since its inception, leave the department for a new position at SLU. We wish Anki well in all her future endeavours.

In addition to regular courses, a course at advanced level in ‘Evidence-based swallowing rehabilitation: diagnostics, prevention and treatment’ 7.5 hp were given during 2016. In addition to the course, an open lecture was held by Professor Maggie-Lee Huckaby, New Zealand, in “Biofeedback in Strength and Skill Training Protocol and Software, with 80 participants.

### **Development of teaching and learning**

The National meeting for education in speech and language pathology in 2016 was hosted in Linköping with participants, teachers and students from all Speech and language pathology programmes in Sweden. The meeting discussed common problems and possible collaborations.

Regarding general and subject-based professional development in teaching and learning, our teachers have attended courses and conferences in accordance with their individual development plans.

Clinical training is an important and significant part of the programme. One of our teachers is responsible for the recruitment of a sufficient number of high-quality supervisors. The high quality of the students’ internships is maintained by close contact between these supervisors and university teachers. A meeting is held every year for clinical supervisors. This year seminars about Multi-lingual research and Motivational Interviewing were held. About 80 clinical teachers attended the meeting.

During the spring 2016, the programme celebrated the European speech-language pathology day with a seminar with invited speakers giving talks about dyspraxia organized by the students.

The students were given the opportunity to participate in the National Conference in Speech-language pathology in Jönköping. Six students participated as did five of our teachers.

### **Internationalization**

The program participates in STUREN, the Stuttering Research and Education Network, involving representatives from all Nordic countries, also including Belgium. Martina Hedenius is external sensor at the SLP program at Bergen University, Norway.

Nine students have been doing their elective course on advanced level, 7.5 hp or part of their master thesis abroad (Great Britain or the USA).



### **Broadened recruitment**

One student participated at the SACO educational fair in Stockholm. Speech and language pathology is a relatively unknown to the general public.

## **The Medicine Programme**

A revision of the programmes curriculum was introduced during 2013 - 2014 that mainly dealt with the clinical semesters (7-11). The Department played a major role in the discussions and preparations for the new and revised curriculum and continues to contribute to the development of the programme through representatives in the programme committee. The curriculum is divided into three stages, each of them run by a study council of teachers and students, and headed by two teachers - one from a basic science department and the other from a clinical science department.

Stage 1 encompasses semesters 1-4 and has its emphasis on basic sciences in an integrative perspective with the relevant clinical sciences. Teachers from the clinical science departments regularly participate as lecturers and in classes. Stage II encompasses semesters 5 – ca 2/3 of semester 8 and has its emphasis on integrated teaching between clinical medicine and surgery. Throughout this period periods of two to several weeks are scheduled for integrated preclinical-clinical teaching. Stage III encompasses the final part of the curriculum, i.e. semesters 8 through 11. This stage includes a 30 ECTS independent project work in accordance with the Bologna process and the rest is dedicated to clinical courses alternating with short periods of preclinical-clinical integration.

The Department's specific educational activities and teaching within the curriculum is described in more detail below, in the sections dealing with the teaching of each unit. In brief, the Department is responsible for an introductory neuroscience course (*Communication, Nerves and Psyche*), has major roles in the courses *Energy and Metabolism, Circulation and respiration* in semester 1, *Growth and Development, Homeostasis and Endocrinology*, semester 2, is responsible for *Neurobiology, Homeostasis and Intervention*, semester 3, and has an overall administrative and pedagogical responsibility for *Clinical Medicine IV*, semester 8. The Department's teaching commitments include integrated preclinical-clinical neuroscience, neurology, neurosurgery, clinical neurophysiology, rehabilitation medicine, psychiatry and ophthalmology.

The Department further participates in the program with teaching in endocrinology and neuroendocrine mechanisms in gender biology, as well as a clinical course in child and adolescent psychiatry. The Department also make significant contributions to exercises in group dynamics and discussion skills, several other courses through lectures and as tutors in problem based learning sessions, laboratory classes, and the independent thesis projects.

## **The Physiotherapy Programme**

In the spring of 2016 the Physiotherapy programme started its fourth semester following the 2014 curriculum (UP 14). Fifty students were admitted to the programme. Thirty-six students graduated in the spring and 35 students in the autumn of 2016, all having followed the curriculum of 2005.

Twenty-eight students were registered to write the thesis of 15 credits on the one-year Master's Programme.

### **Development of teaching and learning**

Throughout 2016 the process of creating a new curriculum, with the aim of implementing and integrating a behavioural medicine profile in the programme, continued. All teachers were involved in some way, e.g. creating new course plans or planning new assignments.

The working process of the development of UP 14 was based on “co-participation” between academic staff and clinical representatives in the implementation phase. A project manager together with a project team and a steering group, selected from the teachers and staff at the unit, assured the progress of the work in three phases: Phase 1 entailed a period of “planning and professional development”; Phase 2 “development of curriculum”; and, Phase 3 “implementation of the new curriculum”.

In spring 2016 “Phase 3” continued with the fourth semester of the new curriculum.

The second, third and fourth courses in the spring semester of 2016 were given for the first time. The main course: “Physiotherapy IVa- Rehabilitation and practice (18 c)” was launched, with main focus in rehabilitation for individuals with different forms of disabilities (mainly from neurology disorders) as well as integrating knowledge of behavioural medicine with expertise in physical activity. Course evaluations showed a positive response.

In the fall of 2016 the main course in physiotherapy “Physiotherapy V-Musculoskeletal Disabilities and Mental illness, including Clinical Practice (22.5 c)” was completed. The increased knowledge on effects of physiotherapy in mental illness was urgent to incorporate in UP 14 and we are satisfied that the mission was accomplished as a part of this course.

The teachers in the fourth and fifth semester of UP 14 also implemented a range of new pedagogical elements in their courses, with an increase in activity-promoting forms of teaching, which encourage students to take greater responsibility for their own learning such as case-seminars.

In parallel with the start of the fourth and fifth semester of UP 14, preparations for the sixth and last semester with start in the spring of 2017, continued. The main preparations focused on developing a new department at the University Hospital (Akademiska sjukhuset) for clinical education together with representatives from the nurse- and medical programs in order to enhance increased inter professional learning for the programs included.

The programme's teaching staffs was, as usual, invited to attend the educational courses, seminars and workshops offered by the Division for Development of Teaching and Learning. A majority of the programme's teacher attended the yearly “Teachers' Learning Day” at the Department of Neuroscience, which had the theme “Cheating in teaching”.

In order to be an active part in the pedagogical work at the faculty the physiotherapy program put on one our teachers, lecturer Henrik Johansson in the “The pedagogic council at the disciplinary domain of medicine and pharmacy”. The council is a link between teaching, learning and pedagogic research. The teachers at the program were encouraged to participate in the pedagogical activities arranged by the council.

The staff and teachers at the programme hosted in November of 2016 the “Teachers national education days”. A conference for teachers and representatives of students from the Physiotherapy programs in Sweden. The conference theme was “The future physiotherapy

program” and included lecturers, seminars, discussions and reflections over the challenges for our physiotherapy programs in the future. Conference evaluations showed a very positive response.

Regular staff meetings with focus on pedagogical issues such as “definitions of concepts used in the programme”, “how integrate new knowledge from research into teaching and in the clinic”, “exams performed on-line” “how increase the knowledge of reflection in the programme” as well as “the red thread and progression throughout the courses” were accomplished during 2016.

In order to disseminate and expand knowledge of behavioural medicine and methods of integrating behavioural medicine with our education in physiotherapy, the programme provided extensive opportunities for professional development and training, in the form of seminars and face-to face discussions with course leaders. These efforts were led by Professor Pernilla Åsenlöf and senior lecturer Annika Bring, project manager for UP 14.

### **Assurance of quality**

Efforts towards the assurance of quality in the physiotherapy programme continued during 2016, including theoretical and clinical activities among the staff, evaluation of clinical training, course evaluations, as well as self-evaluations. The results were compiled and formed the basis of an analysis of the programme in terms of strengths, weaknesses and need for change.

The staff also accomplished a document “Goals and strategies” for the programme for three to five years ahead. The document gives guidelines for the staff to work for and accomplish.

### **Clinical training**

Finding trainee posts for clinical practice for our students was accomplished.

Lecturer and senior lecturers with clinical affiliation at the program constantly motivate and inspire clinical physiotherapists, as well as inform about supervising, with the objective of securing trainee posts.

Annual meetings for clinical supervisors formed part of our on-going efforts to maintain a high level of quality in the trainee posts during 2016.

We feel that the general teaching quality in the clinics has been guaranteed during the year.

### **Internationalisation**

The programme committee for the physiotherapy programme had decided to give our internationalisation efforts a lower priority during 2016, due to the demands of implementing the new curriculum.

It was decided in the programme committee that the physiotherapy course “Physiotherapy IV b – Physical activity to national non-communicable diseases and research methodology II (6.0 c) can be performed in English in case of foreign students at the programme.

In 2016 the programme became a member of the “European Network of Physiotherapy in “Higher Education”. The aim of the Network is to bring together and enhance collaboration between European Institutes and physiotherapy educational institutions in the European region.

Senior lecturer Annika Bring presented a poster by UP 14 at the 2016 International Congress of Behavioral Medicine with the title “A new core curriculum for integration of behavioural medicine and physiotherapy in graduate studies: Planning, implementation, and expected outcomes”.

One student did an elective clinical practice course during the 6<sup>th</sup> semester in Mexico.

### **Broader recruitment**

The programme has about 40% male students. We aim to recruit more students with immigrant backgrounds in order to reflect the patients physiotherapists meet in clinic. Our study adviser and director of studies are continuously engaged in information activities, such as those directed to high-school students.

### **Prizes and awards**

Linda Sjölander from the hospital in Hudiksvall and Marlene Södergård Thorén from Linköping were awarded with the programme's annual award for excellent clinical teaching.

Senior lecturer Annika Bring was awarded the department of Neurosciences annual award for "Better learning".

## **The Specialist Nursing Programme**

The Specialist Nursing programme admits a total of 150 students per year, of which 16 students were in the Programme in Psychiatric Care, based at the Dept. of Neuroscience, in the spring of 2016 and, 9 students were admitted in the autumn semester. In the one-year programme in Psychiatric Care efforts have been made over several years to attract a greater number of students. The application rate is somewhat dependent on the labour market, for example as regards the opportunities for nurses to take paid leave.

The programme provides in-depth knowledge of psychiatry and mental health as a medical science, but is primarily concerned with psychiatry and mental health as caring sciences. The focus of the programme is placed on the diversified knowledge base necessary for a specialized nurse in a modern health-care environment, with incorporation of the international research field.

### **Assurance of quality**

The evaluation of the programme is on going with course evaluations, evaluations of clinical training and evaluation of different parts of education. Changes to the programme are made in collaboration with teachers, students and staff at the unit and results of evaluation are further discussed in the programme committee. In 2016 the programme had been authorised after adjusting criteria for examination procedures according to the parameters laid down by Swedish Higher Education Authority (the Swedish National Agency for Higher Education).

### **Development of teaching and learning**

During the autumn semester we have introduced more problem based learning in the programme. This was useful for the students learning both assessed by themselves and was also reflected in the examinations. Clinical examinations (OSCE's) of professional competence at an advanced level have been used in the programme for several years. Main focus is on assessment of communication skills, as this is one of the most central competences in psychiatric nursing and we continuously develop performances and assessments with help of student and teachers evaluation.

### **Clinical training**

Trainee posts for clinical practice for the students have been arranged in collaboration with, five clinical psychiatric specialist nurses employed as head clinical supervisors at the

University Hospital, Department of Psychiatric Care. They are responsible for the quality of clinical practice, and they make practical arrangements in order to help students to attain their learning objectives. Information, education and motivation for the clinical supervisors are a recurrent part of quality assurance in clinical practice. We arrange meetings for the supervisors in Uppsala every semester, presenting information on the curriculum, syllabus and learning outcomes for the students and arranging different lecturers. One of our aims is to only have clinical specialist nurses at an advanced level as supervisors.

#### **Broader recruitment**

All teachers are continuously engaged in information activities directed to nurses at a basic level in clinical practice.

## **The Nursing Programme**

The Nursing programme admits a total of 230 students per year and the moment "*Psykiatri*" 7.5 hp" provides knowledge of psychiatry and mental health in medical as well as caring sciences. The focus is placed on the knowledge base necessary for a nurse at a basic level in a modern health-care environment, with incorporation of the international research field.

#### **Assurance of quality**

The evaluation of the programme is on going with course evaluations, evaluations of clinical training and evaluation of different parts of education. Changes to the moment are made in collaboration with teachers, students and staff at the unit. The results of evaluation are further discussed in the programme committee. The course leader works together with the teachers in the nursing programme in order to develop pedagogical strategies and to adjust the course to the overall design of the nursing programme.

#### **Development of teaching and learning**

During 2016 the previous course has been remodelled to fit in as a moment in three courses in semester one, four and six in the nursing programme. In addition we have been developing a new eligible course in semester five which started in December 2016. The course evaluation showed, that the students highly evaluated the course and assessed the course content to be of great value for their forthcoming professional life. It is a challenge to acquaint students with psychiatry and psychiatric care in the short time available and much work has been on improving student- and teacher-guides.

#### **Clinical training**

Students undertake one week of clinical practice during the course. The teachers' work together with five clinical psychiatric specialist nurses employed as head clinical supervisors at the University Hospital Department of Psychiatric Care. They are responsible for the quality of clinical practice, and they make practical arrangements in order to help students to attain their learning objectives. Information, education and motivation for the clinical supervisors are a recurrent part of quality assurance in clinical practice. We arrange meetings for the supervisors in Uppsala every semester, presenting information on the curriculum, syllabus and learning outcomes for the students and arranging different lecturers. One of our aims is to only have clinical specialist nurses at an advanced level as supervisors.

#### **Broader recruitment**

Teachers are engaged in information activities arranged by the Nursing Programme.

## ***Elective courses***

The Department offered a wide range of elective courses in 2016, touching on topics ranging from advanced neuropharmacology to Medical history. English was the language of instruction for some of these courses, including the advanced level courses in neuroscience and drug targeting.

Both the physiotherapy and speech and language pathology units gave a number of elective courses aimed at students wishing to further their professional development. The most popular of these was offered by the unit for physiotherapy in Sports Medicine and Sports Rehabilitation.

The Department's courses in psychiatry and aimed at professionals working in related disciplines, such as social work, continued to attract a great deal of interest.

The Department also offered individually-tailored laboratory-based courses. These courses are valuable for students who wish to develop expertise in scientific research and laboratory techniques.

## ***Teaching by Units in the Department***

### **Developmental Genetics**

In 2016 the following lecturers and PhD students have participated in the teaching of neurobiology for biomedical, biology and pharmacy students:

***Lecturers:*** Klas Kullander, Malin Lagerström, Elín Magnúsdóttir, Jon Jakobsson, Fabio Freitag, Sharn Perry, Sanja Mikulovic, Samer Simwani, Fabio Caixeta, Henrik Boije.

***Supervisors of practicals and seminars:*** Fabio Freitag, Marina Franck, Elín Magnúsdóttir, Tianle Gao, Henrik Boije, Samer Simwani, Ana Del Pozo Cano and Sharn Perry.

Staff at the Unit have had course leader responsibility for the following courses:

***Communication and the Nervous System (KNEP), 5 hp, the Medicine Programme:*** Approximately 120 students each term learn about the fundamental organisation of the nervous system. The course consists of lectures, demonstrations, lab practicals, and case-based seminars, with a written examination at the end. Klas Kullander is course leader.

***Neurobiology, 10 hp, the Biomedicine Programme:*** This course is scheduled once per year (second period of fall semester) as an integrated part of the Biomedicine programme. 35-45 students attend the course on each occasion. The course is given in Swedish and English. Malin Lagerström was the course leader. The course consists of lectures, demonstrations, lab practicals, written exam, and seminars.

***Neurobiology, 15 hp, Biology Programme of the Faculty of Science and Technology:*** The course is given once per year (first period of the spring semester) and attracts 20-40 students. The course is given in English and approximately one third of the students are usually

exchange students. Malin Lagerström was the course leader of the course with assistance from Jörgen Jonsson. The course consists of lectures, demonstrations, practicals, oral and written exams and seminars.

***Elective course: Exploring the brain I and II, 7.5 hp***

Klas Kullander, with assistance from Sharn Perry and Jörgen Jönsson, was responsible for these popular evening courses, which offer an introduction to issues in neuroscience to interested members of the general public.

Several lectures are given in other courses such as, Cell and Molecular Biology (Biomedicine programme) and Pain pharmacology for Physiotherapy students.

Lectures are also given at the Advanced Neurobiology master's course.

## **Developmental Neuroscience**

The undergraduate teaching by staff at the unit for Developmental Neuroscience for 2016 took place mainly within the courses: Cell and Molecular Biology (CMB) in the Biomedicine programme, 2nd semester (10 weeks 100%, 50 students); Tissue biology with Embryology (VBE) in the Biomedicine programme, 3rd semester (10 weeks 100%, 30 students); Growth and degeneration (ToD, T2) Medicine programme 2nd semester, medical embryology section (2,5 weeks 100% 115 students).

Henrik Ring was course leader for the CMB course, Sonya Stenfelt was course leader for the VBE course and Finn Hallböök was responsible for the human embryology block within the ToD course.

The CMB course is one of the most fundamental courses within the Biomedicine programme and provides knowledge of the basic structures and cell biology-related mechanisms in a eukaryote cell. During the previous year we have introduced more student based learning activities such as cases (problem-based learning) that trigger the students to a more active search for knowledge related to cell- and molecular biology.

The biomedicine VBE course is given in collaboration with Dept's IMBIM and Med Cell Biology. Within the Tissue biology course, embryonic development is used as a primer for understanding the establishment of specialized tissues in the vertebrate embryo.

The embryology block within the ToD-course in the Medicine programme spans 2.5 weeks and covers human embryology and basic mechanisms of developmental biology. The course is given twice a year with approximately 110 students per semester. The course is part of the revised medicine programme and hosts one case-based seminar. In addition to the lectures in embryology, supervision responsibility for 3 seminars and six case-based seminar groups per semester.

Several lectures are given in other courses such as Laboratory Animal Science, Neurobiology for both the Biomedicine programme and the Medicine programme, and the Masters course in Neurobiology.

**Assurance of quality:**

Biomedicine programme courses are subject to a web-based student course evaluation. In addition to the formal and anonymous evaluations, we have scheduled an informal discussion at the end of the course where the structural and pedagogic organization is brought up. These discussions are very useful and informative.

## Functional Pharmacology

**Medicine programme:** In the Medicine programme we are responsible for the course Neurobiology, Homeostasis and Intervention (T3, 20.5 hp). Madeleine Le Grevès is course leader and director of studies in pharmacology. This course is given twice a year with around 90 students each time. Personnel at the unit give lectures in pain and analgesia as well as vascular pharmacology, lead PBL cases and seminars, and organize examinations.

In addition we participate in the course Homeostasis and Endocrine Regulation (T2, 8.5 hp) where we have PBL cases and seminars. We are also responsible for the pre-clinical parts of the course Integration VII (4.5 hp, T8, Madeleine Le Grevès is course leader).

**Biomedicine:** In the Master's programme in Biomedicine we are responsible for the course Drug Target Identification and Evaluation in Neuroscience (15hp) with Helgi Schiöth as the course leader. This course is run entirely within the unit with a few invited lecturers.

In the Biomedicine programme, Madeleine Le Grevès leads course in Comparative Medicine (5 hp), which is given in the autumn semester. The course provides theoretical knowledge and practical skills in laboratory animal science, covering topics such as: legislation concerning the use of laboratory animals, laboratory animal ethics, biology and welfare of laboratory animals, experimental techniques, planning, execution and publication of animal experiments and alternatives. Handling and common invasive techniques of rats and mice is mandatory.

We also participate with lectures on G Protein Coupled Receptors, transporters, synaptic transmission, neurotransmitters and cardio vascular pharmacology in other courses in the program.

**Other programmes:** We also participate in lectures (electrophysiology, ion channels, pain and analgesia) and lab practical at a Neurobiology course.

We participate in the programme in pharmacy with lectures in neurophysiology (for the course in physiology).

Schiöth is Director of PhD studies at the BMC node at the department.

## Medical History

Our aim is to disseminate knowledge of medical history within the Faculty of Medicine and Pharmacy by lectures and seminars for medical students, by initiating research projects within medical history, and by offering elective courses in medical history. Eva Ahlsten teaches every half year, medical and pharmacological history to medical students, term three. Besides that, every half year all medical students, during their third term are shown the exhibitions on a guided tour of the Medical History Museum. The guides are Henry Johansson, Bertil



Karlmark, Lars Orelund and Mats Westman. Every half year, nursing students, during their first term, are given a guided tour of the museum. The guides are Eva Ahlsten, Urban Josefsson, and Bertil Karlmark. Pharmacy students visit the museum twice a year to learn ex tempore-making by a pharmacist, Anders Uppfeldt or Barbro Samuelsson.

### ***Elective course in Medical history, 7.5 hp***

The sixth course in Medical History was performed during spring 2016. Eva Ahlsten has led the course since 2013. Teachers came from a wide-range of professional backgrounds, including physicians, a psychologist, a mid-wife, senior researchers and academic teachers. The lectures were given at the Medical History Museum in Uppsala. Every lecture was followed by a short visit to the exhibition rooms where the students were shown those exhibition cases and apparatuses that are connected to the subject of the given lecture. The subjects of the course, besides an introduction of common medical history, were psychiatric history, pharmacological history, epidemics and vaccinations, the history of surgery, midwifery, the history of alleviation of one's pain and the history of resuscitation, the history of paediatrics, the history of insulin, the Bible's views of the sick and poorly. Fourteen students attended the course.

## **Pharmacology**

The unit for Pharmacology's major teaching commitments are in the programmes of Medicine and Biomedicine, and primarily concern pharmacology, neurobiology and endocrinology.

In the *Medicine Programme*, our main teaching is in the courses Homeostasis and Endocrinology (T2, 8.5 hp) and Neurobiology, Homeostasis and Intervention (T3, 19.5 hp). Our teaching includes lectures, seminars, laboratory practicals, and examinations. The unit is responsible for an integration course on T9 (1.5 hp), spanning the fields of endocrinology, neurobiology, and gender aspects. All of these courses are run once every semester.

In the Biomedicine programme share responsibility with the department of medical chemistry for the course "Pharmacology with medicinal chemistry", 12 hp.

Numerous lectures are given in other courses (including other faculties and universities) at undergraduate and graduate level, particularly lectures concerning the distinction between science and pseudoscience but also various aspects of neurobiology and pharmacology.

Exam and degree projects and advanced level courses are supervised for students in biomedicine, medicine, biology, pharmacy and engineering as well as international exchange students.

## **Physiology**

During the past year the following lecturers and Ph.D. students have participated in the teaching of physiology for medical, biomedical, civil engineering and pharmacy students:

Lecturers: Bryndis Birnir, Zhe Jin, Olof Nylander, Markus Sjöblom and Svante Winberg, Sergiy Korol.

Ph.D. Students: Arianna Cocco, Laura Vossen, Johanna Axling, Amol Bhandage, Olga Dyakova.

In the **Medicine Programme** we teach biophysics, cardiovascular, endocrine, gastrointestinal and neural physiology. We also participate as case supervisors in different courses. Ph.D. students participate as supervisors in the laboratory course for medical students. We have responsibility for the following subjects: Membrane potential (T1), ergometry test on bicycle (T1), refraction (T3), nystagmus (T3), neurological examination (T3), temperature regulation (T3), and electrophysiology (T3).

In the **Biomedicine Programme** we teach transport proteins and transport mechanisms over the cell membrane, the autonomic nervous system (including the enteric nervous system), cardiovascular and gastrointestinal physiology. We have responsibility for the following student laboratory subject: Ergometry test on bicycle and temperature regulation. Bryndis Birnir is the course leader for “Advanced neurobiology” 15 credits included in the Master of Medical Science programme.

In the **Physiotherapy Programme** Svante Winberg is the course leader responsible for teaching a course in physiology, in which both Olof Nylander and Markus Sjöblom participate extensively. Laboratory subjects: Blood pressure and ECG, ergometry test on bicycle and spirometry.

For **Pharmacy students**, 180 + 130 per year, We teach sensory and basic neural physiology, respiratory, endocrine and gastrointestinal physiology. We have responsibility for the laboratory classes: Spirometry. Bachelor of Science program in pharmacy (7.5 hp): We teach sensory and basic neural physiology, cardiovascular, respiratory and endocrine physiology. We have responsibility for the following student laboratory subjects: Blood pressure and ECG, dissection of swine heart and spirometry.

**Other Programmes:** Physiology for civil engineers (6 hp), 15 students per year, we teach sensory and basic neural physiology, cardiovascular, respiratory, endocrine and gastrointestinal physiology.

## Neuroanatomy

**Medicine programme** (230 students per year): The unit participates with lectures in functional neuroanatomy in Communication, Nerves and Psyche (T1, 5 hp), Neurobiology, Homeostasis and Intervention (T3, 19,5 hp) and Clinical Medicine V (T8, 25,5 hp). The unit also participates as PBL tutors in Neurobiology, Homeostasis and Intervention (T3, 19,5 hp) and Clinical Medicine V (T8, 25,5 hp).

**Speech and Language Pathology programme** (35 students per year): The unit is responsible for an integrated course in Anatomy and Physiology (T1, 6 hp). The focus of the course is in neuroscience, and the unit is responsible for lectures and for demonstrations in human brain anatomy.

**Biomedicine programme** (50 students per year): The unit participates with lectures in neurohistology in Tissue Biology and Embryology (T3) and neuroplasticity in Neurobiology (T3).

**Physiotherapy programme** (80 students per year): The unit participates with lectures, group teaching and examination in neuroanatomy during their first year course in Basic Anatomy.

**Additional teaching:** The unit gives lectures on functional neuroanatomy in the independent course Neurobiology (ca 20 students per year, 15 hp) at the Faculty of Science and Technology. The unit also gives lectures in Regenerative Neurobiology and Neuroplasticity in the master program course Advanced Neurobiology with Diseases of the Brain (ca 30 students, 15 hp).

## **Clinical Neuroscience Units**

### **(Neurology, Neurosurgery, Neurophysiology and Rehabilitation Medicine)**

An introduction in the clinical neurosciences is given during preclinical training, integrated with basic sciences such as neurobiology and neuroanatomy. The main course in clinical neurosciences takes place at semester 8 during clinical training. The course in clinical neurosciences consists of lectures, case discussions, seminars, practical training and individual supervision of students. The core curriculum in clinical neurosciences for medical students is based on national guidelines, which are defined by the Swedish network for teachers in neurology.

#### ***Undergraduate education with course leader responsibilities***

##### ***1) Clinical neuroscience for Medical students, 190 students per year***

The course in clinical neurosciences is part of Clinical Medicine IV (comprising 28.5 hp), which is an integrated course in clinical neurosciences, ophthalmology, psychiatry and otorhinolaryngology. Mia Ramklint (psychiatry) has been the responsible teacher for Clinical Medicine IV during 2016.

**Course leaders:** Anja Smits/Anne-Marie Landtblom (neurology); Per Enblad (neurosurgery), Kristin Elf (neurophysiology) and Ulrika Holmström (rehabilitation medicine).

**Block leader** for neurology/neurosurgery/neurophysiology/rehabilitation medicine: Anja Smits/Anne-Marie Landtblom

##### ***2) Neurology for students in Physiotherapy, 40-50 students per year***

Dag Nyholm has been course leader for a two week- course (3 hp) in neurology for physiotherapists during 2016.

#### ***Undergraduate education with no course leader responsibility***

Neurology is involved in undergraduate teaching at several other courses/programmes, such as: *Medicine programme (T3, T6, T9, 180 students per year)*, lectures on “Muddy Points”, “Neurological Examination”, “Acute Neurology” for residents (AT-läkare) are given by Shala Berntsson, Eva Kumlien, *Speech and Language Pathology programme (30 students per year)*, lectures in neurology have been given by Anne-Marie Landtblom and Anja Smits (3 hp); *Biomedicine programme*, Johan Zelano lectured in neurology; *Nursing programme*, Jon Forsman, Paul de Roos and Johan Virhammar lectured neurology.

## Ophthalmology

**Medicine programme:** Anatomy and physiology of eye and vision, Neurobiology, homeostasis and intervention:

Ophthalmology teaches 4 lectures in ocular anatomy and physiology of vision.

Ophthalmology, undergraduate course:

Ophthalmology is taught in an integrated course, Clinical medicine IV, covering ophthalmology, ear-nose-throat, psychiatry, and neurology, neurosurgery and neurophysiology.

Teaching in ophthalmology includes lectures, seminars and clinical training/practice. Clinical training is organized at the ophthalmology clinic at the Uppsala university hospital and additionally at ophthalmology clinics in regional hospitals around Uppsala, to assure a good clinical exposure for the students. During the clinical training, students participate in a 1.5 week clinical rotation. The rotation including auscultation with a consulting senior ophthalmologist, auscultation in vitreoretinal surgery, auscultation in cataract surgery and auscultation with a nurse/optometrist and student consultation under the supervision of a qualified specialist in ophthalmology, on hands training in refraction and removal of a foreign body and case lectures. There are also three multidisciplinary seminars taught together with specialists from departments of ear-nose-throat, psychiatry and neurology. At the end of the course, there is a practical and a theoretical examination, respectively.

Elective course, Emergency neurology:

Ophthalmology contributes with lectures and clinical training.

Elective course, Emergency medicine

Ophthalmology contributes with clinical training.

Elective course, Clinical practice, professional attitude physician

Ophthalmology contributes with clinical training.

The Biomedicine Programme

Ophthalmology is taught during half a day. The teaching includes lectures.

Additional teaching

Ophthalmology also contributes with lectures on specific topics in the specialist nursing programmes, the orthoptist education and the master's programme at the Department of Neuroscience.

International teaching

Undergraduate programme, College of Optometry, University of Houston, Houston, Texas, USA Structure, function and pathology of the lens, Per Söderberg. Annual lectures.

Undergraduate- and Masters- and Graduate program, Dept. of Biomedical Engineering, University of Miami, Miami, Florida, USA, Laser Safety.

Assurance of quality

For each course in the Medicine and Biomedicine Programmes, clinical and the theoretical training are separately evaluated by the students in writing.

## **Psychiatry**

### **(Psychiatry and Child and Adolescent Psychiatry)**

**Medicine programme:** The unit of psychiatry has course leader responsibility for teaching psychiatry and child and adolescent psychiatry. We also teach the subjects communication skills and medical psychology as part of the course *Professional Skills and Communication*, which is spread across the whole programme. Within this course we give lectures and provide practical training in semesters 1, 3, 4 and 8. Finally, we give solitary lectures at different courses, such as about neurotrauma at the introductory neuroscience course *Communication, Nerves and Psyche*, at semester 1, and about neuropsychological development, at the course *Growth and Development and Homeostasis and Endocrinology* at semester 2, and about emergency psychiatry during *Emergency Medicine II*, at semester 11.

**Nursing programme:** The unit for Psychiatry is responsible for the mandatory course “Nursing and Medical Science within Psychiatric Care” at semester 1, 4 and 6.

**Specialist Nursing programme in psychiatric care:** The unit for psychiatry is responsible for the specialization in Psychiatric care within the specialist-nursing programme, 60 credits.

**Physiotherapy programme:** One week is allocated to psychiatry, consisting in lectures.

**Biomedicine programme:** As part of the course *Diseases – Clinical Survey* we teach psychiatry once a year.

**Speech and Language Pathology Programme:** As part of the course *Nervous System Disorders in Adults* we teach psychiatry once a year

**Freestanding courses:** We have a distance-learning course in *Psychiatry*, 15 credits, that is very popular, with more than 200 applicants each year.

### **Assurance of quality**

Our teaching is conducted in accordance with the Uppsala University pedagogic programme. We use pedagogic methods that aim to activate the students, both Problem Based Learning (PBL), case-methodology and seminars for reflection; and our teachers are educated in working with these methods. A lot of effort has been put into strengthening of the constructive alignment between goals, teaching methods and examinations. We use students' evaluations as a basis for revising and developing our courses and pedagogical methods.

### **Development of teaching and learning**

During the 2016 further efforts were made to improve teaching and learning  
These efforts included:

- Pedagogic education of teachers and clinical tutors.
- Producing web-based educational materials, with lectures and interactive learning tasks, as a complement to other teaching and as a web-based course.
- Working with examination forms. In the medicine programme, a clinical examination, based on a psychiatric consultation role-play with an actor, has been implemented. We have developed two Objective Structured Clinical Examinations' (OSCE), in the Specialist Nursing programme.

-We have developed three Inter Professional Learning (IPL) tasks for students from the medicine, the nursing and the specialist nursing programmes.

**Clinical training**

Medical and nursing students had their clinical training at the University hospital, Division of psychiatry.

**Awards gained**

The unit was awarded the Symbiosis prize for best teaching unit participating in the programme in medicine.

The end