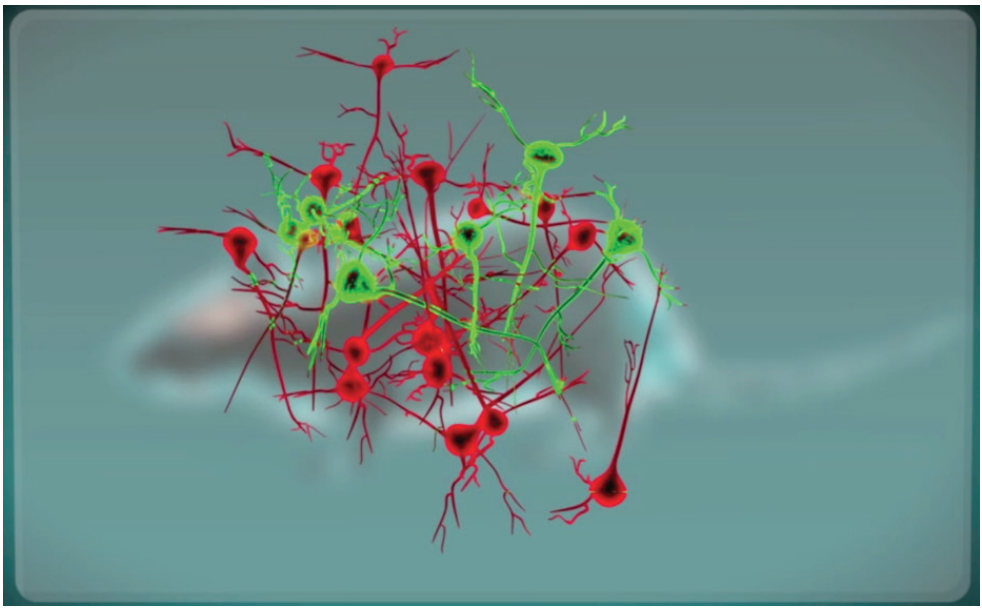
UPPSALA
UNIVERSITET

Department of Neuroscience

# ANNUAL REPORT 2012



# Annual Report

# 2012

# Department of Neuroscience

# Uppsala University

*Cover Picture: Neurons organized in networks control all functions of the brain.*
*Photo: Michael Norbäck, Developmental Genetics*

Box 593
SE- 751 24 Uppsala
www.neuro.uu.se
Editor: Cecilia Yates (cecilia.yates@neuro.uu.se)

# INTRODUCTION

The activities of the Department of Neuroscience at Uppsala University Faculty of Medicine continue to cover a broad range of basic and clinical research as well as education on the nervous system. During year 2012 the Department had around 150 employees, including PhD students, and a large number of postdoctoral fellows. Over one-third of the staff is of foreign origin, adding to the Department's international profile. Moreover, the clinical research groups engage numerous clinicians; these are employed by the University Hospital, but have part-time teaching and research responsibilities within the Neuroscience Department. The pre-clinical research groups are concentrated within the facilities of Uppsala University Biomedical Center, while clinical research groups are spread out in different buildings in the main University Hospital campus. As part of efforts to concentrate the Department's activities, the unit for Physiotherapy and the unit for Speech Physiology and Pathology moved to the Biomedical Center and have spent their second full year of activity there in 2012. The research groups in psychiatry, while housed in an older building on the hospital grounds, have been eagerly awaiting relocation to the new modern House of Psychiatry, which was erected nearby during 2012 and is soon to be inaugurated.

The organizational growth of the Department has been associated with a strong expansion in educational commitments and research activities. In particular, the formation of a committee for our extensive undergraduate education within the Department was a focus for 2011. This committe has now been firmly established with the creation of a position of a Assistant Head of Department with special responsibilities for the organization of undergraduate teaching at the basic and advanced levels in 2012. Reasons of administrative efficiency were important for the faculty reorganization in 1998. However, the prime purpose of forming a joint Department, from a large number of preclinical and clinical neuroscience-oriented Departments, was to strengthen neuroscience research in Uppsala. This has been a challenging task, given the different backgrounds and traditions in administration, teaching and research. A major task, until recently, has, therefore, been to consolidate the Department's organization, as well as to find synergies in teaching and areas for cooperative research. In 2012 we have witnessed continued progress along these lines.

The restructured website launched a few years ago has also continued to support research groups and individuals, and has been used for continuously updating relevant intradepartmental information also during 2012. Thus, efforts to improve external communication have resulted in a significantly better visibility of the Department in the scientific community and among the public at large. Daily updates regarding the Department's activities in various areas have continued to be presented on the Department's website during 2012. These updates are often based on internet searches, mainly in national media websites, of material published elsewhere on the activities of the Department's scientists and teachers in the community. This news service has become a popular means for increasing in-house information on the external activities of the Department.

## Research

In order to concentrate research competencies and resources the Department has identified a restricted number of research themes as areas worth pursuing further. These areas have had a proven record of success, and are considered promising in terms of cross-fertilization between the basic and clinical disciplines of neuroscience. These thematic areas were evaluated during 2011 by an international Quality and Renewal committee and the outcome has guided

reallocation of resources during the fiscal year 2012. Important factors considered in the Department's decision to identify areas of common interest and significance were: i) to build upon already existing strong and promising research areas, ii) to build workable bridges between preclinical and clinical research; and iii) to create opportunities for innovation by bringing together research groups from a wide range of disciplines. These thematic areas were actively discussed, and partially redefined, during 2012. The conceptual focus on these areas, when combined with pro-active measures by the Department, has continued to strengthen scientific impact, increasing national and international recognition, attracting young promising scientists, as well as increasing success rates in the competition for major national and international funding.

## Department Retreat

In August 2012 the Department again arranged a two-day retreat for group leaders and key administrators. The event took place in Grisslehamn, a scenic coastal village on the Baltic Sea, an hour´s drive from Uppsala. This was the fifth retreat in this series since year 2007 and offered the participants the opportunity to engage in intense discussion of the Department´s profile, achievements, economy, research themes, teaching and administrative services. Particular attention this year was given to success factors and strategies facilitating creative interaction among team member, a topic that prompted lively discussion.

## Undergraduate and Graduate Education

The teaching responsibilities of the Department have increased substantially over the last few years. The Department of Neuroscience received the largest budget for teaching within the Faculty of Medicine during 2012. The Department's courses for medical students in 2012 have been fully adapted to the new medical curriculum. Education in neuroscience is introduced from the start of the new curriculum, largely as case-oriented and student-activating teaching in groups of 8-10 students, with emphasis placed on integrating basic and clinical sciences. In general, the new curriculum has been beneficial for capturing the student's interest for neuroscience early in their studies. However, it has also presented a challenge to the Department's teaching capacity. The Department has now changed course syllabuses to adapt to the new program for all semesters, including the clinical courses. The third class of medical students participating in the revised five and a half year course of studies graduated in June 2012.

The Department has continued to have extensive responsibilities within the Physiotherapy and Speech Pathology and therapy programmes during 2012. The fourth group of logopedic students finished their course of education in 2012. The Department has considerable commitments within the Biomedicine, Nursing, and Pharmacy programmes, and plays an active role in the efforts of the faculty to modernize the contents, and improve the teaching methods, of these programmes. In addition, the Department hosts an international Masters Programme in Biomedicine which was given for the third time in the autumn of 2012. This Masters programme has been developed by the Department in collaboration with other departments within the medical and pharmaceutical faculties. Furthermore, the Department has also been involved in the Masters programme in Public Health since its inception.

Finally, we are pleased to announce that 22 students received their doctoral degrees at the Department during 2012. Of these, 12 was males and 10 females, 15 students were from the clinical research areas and 7 students were from the preclinical research area.

## Conclusions

The year 2012 has been a fruitful period due to the work of the qualified and dedicated staff of the Department. Our continuing efforts to increase cross-collaboration in thematic research areas, and to facilitate teaching and administration have been particularly rewarding. We are very pleased to note that the positive appraisal of our scientific performance within the University-wide Quality and Renewal 11 evaluation (KoF11) has successfully guided action in research in 2012, and will certainly continue to inspire Departmental activities in the coming years.

Uppsala, January 12th 2013

Ted Ebendal, PhD
Professor
Head of Department

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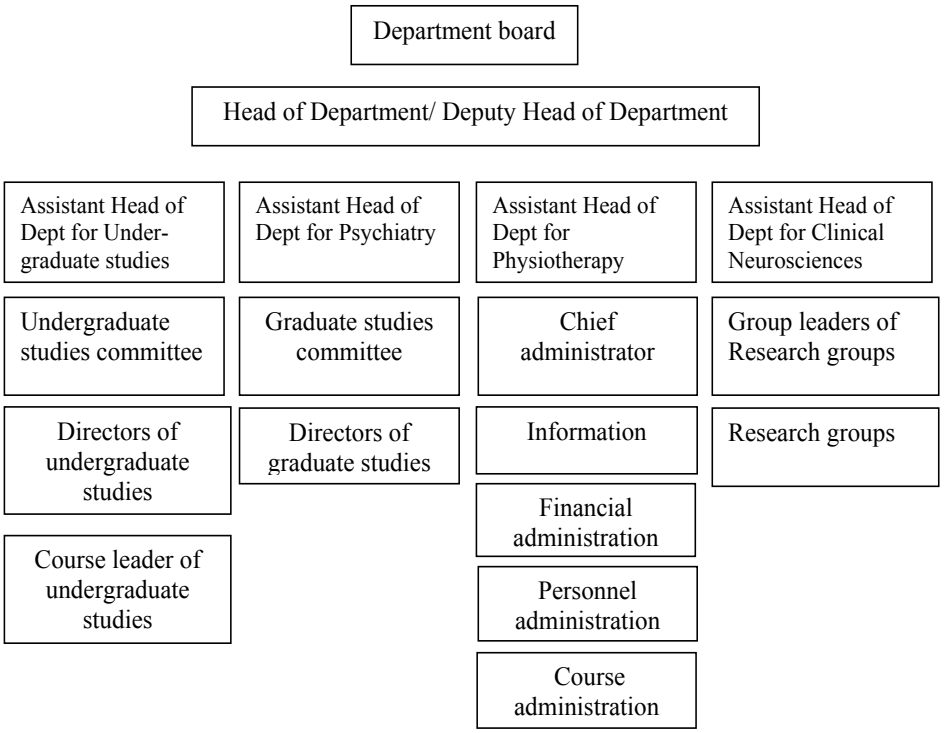
## ORGANIZATION




**Head of Department**
Ted Ebendal

**Deputy Head of Department**
Lisa Ekselius

**Department board**
Per Enblad, teacher representative
Lars Hillered, teacher representative
Pernilla Åsenlöf, teacher representative
Håkan Askmark, teacher representative
Cecilia Yates, representative for technical/administrative personnel
Daniel Ocampa Daza, graduate student representative (to 120930)
Charlotte Urell, graduate student representative (from 121001)
Mattias Schedwin student representative (to 120930)
Tina Sandström student representative (to 120930)
Sandra Hammarström student representative (from 121001)
Anna Brunell student representative (from 121001)
Eva Kumlien, teacher representative, deputy
Bryndis Birnir, teacher representative, deputy
Karin Nordström, teacher representative, deputy
Finn Hallböök, teacher representative, deputy

Sari Thunberg, representative for technical/administrative personnel, deputy
Johan Lindqvist, graduate student representative, deputy (to 120930)
Maria Blixt, graduate student representative, deputy (from 121001)
Mia Jukovic, student representative, deputy (from 121001)
Dicle Cetinkaya, student representative, deputy (from 121001)
Douglas Anderson Åhlfeldt, student representative, deputy (from 121001)

**Assistant Head of Department for Undergraduate studies**
Finn Hallböök

**Assistant Head of Department for Psychiatry**
Lisa Ekselius

**Assistant Head of Department for Clinical Neurosciences**
Lars Hillered

**Assistant Head of Department for Physiotherapy**
Cathrin Martin

**Chief administrator**
Lena Karlsson

**Director of graduate studies**
Bryndis Birnir
Lars Larsson

**Section Director**
Margareta Jennische

**Director of undergraduate studies**
Anja Smits
Finn Hallböök
Lena Zetterberg
Lisa Ekselius
Markus Sjöblom
Mia Ramklint
Olof Nylander
Robert Fredriksson

**Administration**
Anders Nilsson
Anki Gustafsson
Berit Hård- Wallenqvist
Cecilia Edling
Cecilia Yates
Elin Tögenmark
Else-Marie Andersson
Gun Schönnings
Gunneli Ekberg
Inger Hedlund
Annika Jordell Kylberg
Karin Nygren
Lena Bohlin
Mariana Hooli
Mona Persson
Neil Ormerod
Petra Millbert
Pia Fredlund
Sari Thunberg
Stefan Pettersson

**Undergraduate studies committee**
Finn Hallböök (Head of committee)
Anja Smits (to 121001)
Gabriella Persdotter-Hedlund (to 120921)
Lena Zetterberg
Mia Ramklint
Monica Blom Johansson (from 121001)

Neil Ormerod
Olof Nylander
Robert Fredriksson

**Graduate studies committee**
Lars Larsson (Head of committee)
Bryndis Birnir
Annika Bring
Helgi Schiöth
Karin Edebol Eeg Olofsson
Neil Ormerod
Niklas Marklund

**Equality committee**
Lena Karlsson (Head of committee)
Ellen Grut
Gabriella Persdotter-Hedlund (to 120921)
Nadina Laurent(from 121009)
Niclas König(from 121009)

**Health and Safety Committee**
Lena Karlsson (Head of committee)
Annika Jordell-Kylberg
Cecilia Edling
Fredrik Clausen
Markus Sjöblom
Markus Sjöblom
Martin Larhammar
Sari Thunberg
Siv Strömberg
Susanna Tuvemo-Johnson

## ADDRESS LIST DEPARTMENT OF NEUROSCIENCE

| | |
|---|---|
| Aare Reddy,Sudhakar | sudhakar.aare@neuro.uu.se |
| Abalo, Xesus | xesus.abalo@neuro.uu.se |
| Abelson, Klas | klas.abelson@neuro.uu.se |
| Abrahamsson, Ninnie | ninnie.abrahamsson@neuro.uu.se |
| Abu Hamdeh, Adel | adel.abuhamdeh@neuro.uu.se |
| Abu Hamdeh, Sami | sami.abu.hamdeh@akademiska.se |
| Agartz, Ingrid | ingrid.agartz@neuro.uu.se |
| Ahlqvist, Kerstin | kerstin.ahlqvist@neuro.uu.se |
| Ahmad, Abdulbaghi | abdulbaghi.ahmad@neuro.uu.se |
| Aldskogius, Håkan | hakan.aldskogius@neuro.uu.se |
| Alm, Per | per.alm@neuro.uu.se |
| Alsiö, Johan | johan.alsio@neuro.uu.se |
| Andersson, Birgit | birgit.andersson@neuro.uu.se |
| Andersson, Else-Marie | else-marie.andersson@neuro.uu.se |
| Andersson, Mikael | mikael.andersson@neuro.uu.se |
| Anens, Elisabeth | elisabeth.anens@neuro.uu.se |
| Aquilonius, Sten-Magnus | sten-magnus.aquilonius@neuro.uu.se |
| Aresh, Bejan | bejan.aresh@neuro.uu.se |
| Arinell, Hans | hans.arinell@neuro.uu.se |
| Arnberg, Filip | filip.arnberg@neuro.uu.se |
| Arvidsson, Emma | emma.arvidsson@neuro.uu.se |
| Askmark, Håkan | hakan.askmark@neuro.uu.se |
| Babateen, Omar | omar.babateen@neuro.uu.se |
| Bagchi, Sonchita | sonchita.bagchi@neuro.uu.se |
| Banduseela, Varuna | varuna.banduseela@neuro.uu.se |
| Benedict, Christian | christian.benedict@neuro.uu.se |
| Bergdahl, Lena | lena.bergdahl@neuro.uu.se |

| | |
|---|---|
| Bergh Johannesson, Kerstin | kerstin.bergh.johannesson@akademiska.se |
| Bergqvist, Christina | christina.bergqvist@neuro.uu.se |
| Berntsson, Shala | shala.berntsson@neuro.uu.se |
| Bhandage, Amol | amol.bhandage@neuro.uu.se |
| Birnir, Bryndis | bryndis.birnir@neuro.uu.se |
| Blixt, Maria | maria.blixt@neuro.uu.se |
| Blom Johansson, Monica | monica.blom.johansson@neuro.uu.se |
| Blunder, Martina | martina.blunder@neuro.uu.se |
| Boden, Robert | robert.boden@neuro.uu.se |
| Bohlin, Lena | lena.bohlin@neuro.uu.se |
| Bohman, Hannes | hannes.bohman@neuro.uu.se |
| Braun, Madelen | madelen.braun@neuro.uu.se |
| Bring, Annika | annika.bring@neuro.uu.se |
| Broman. Jan-Erik | Jan-Erik.Broman@neuro.uu.se |
| Brooks, Samantha | samantha.brooks@neuro.uu.se |
| Burman, Joachim | Joachim.burman@neuro.uu.se |
| Bylund, Ann | ann.bylund@neuro.uu.se |
| Bäckström, Josefin | josefin.backstrom@neuro.uu.se |
| Carlsson, Ingrid | ingrid.carlsson@neuro.uu.se |
| Carri, Nestor | nestor.carri@neuro.uu.se |
| Cedernaes, Jonathan | jonathan.cedernaes@neuro.uu.se |
| Cesarini, Kristina | kristina.cesarinni@neuro.uu.se |
| Clausen, Fredrik | fredrik.clausen@neuro.uu.se |
| Comasco, Erika | erika.comasco@neuro.uu.se |
| Corpeno, Rebeca | rebeca.corpeno@neuro.uu.se |
| Dahlbom, Josefin | josefin.dahlbom@neuro.uu.se |
| Danfors, Torsten | torsten.danfors@neuro.uu.se |
| Danielsson, Katarina | katarina.danielsson@neuro.uu.se |
| De Haan, Roel | |
| Demmelmaier, Ingrid | ingrid.demmelmaier@neuro.uu.se |
| Djupsjö, Anders | anders.djupsjo@neuro.uu.se |
| Ebendal, Ted | ted.ebendal@neuro.uu.se |
| Edling, Cecilia | cecilia.edling@neuro.uu.se |
| Edvinsson, Dan | Dan.Edvinsson@neuro.uu.se |
| Ekberg, Gunneli | gunneli.ekberg@neuro.uu.se |
| Ekbrink, Helena | helena.ekbrink@neuro.uu.se |
| Ekmark-Lewèn, Sara | sara.ekmark-lewen@neuro.uu.se |
| Ekselius, Lisa | Lisa.Ekselius@neuro.uu.se |
| Ekwall, Camilla | camilla.ekwall@neuro.uu.se |
| Elmgren Frykberg,Gunilla | gunilla.elmgren.frykberg@neuro.uu.se |
| Emilson, Christina | christina.emilson@neuro.uu.se |
| Emtner, Margareta | margareta.emtner@neuro.uu.se |
| Enblad, Per | per.enblad@neuro.uu.se |
| Ericson, Hans | hans.eriksson@neuro.uu.se |
| Eriksson, Anders | anders.eriksson@neuro.uu.se |
| Eriksson, Gunilla | gunilla.eriksson@neuro.uu.se |
| Eriksson, Sara-Lisa | |
| Erlandsson, Anna | anna.erlandsson@neuro.uu.se |
| Fagius, Jan | jan.fagius@neuro.uu.se |
| Feresiadou, Amalia | amalia.fereseiadou@neuro.uu.se |

| | |
|---|---|
| Fernandez, Manuel | Manuel.Fernandez@neuro.uu.se |
| Flemström, Gunnar | gunnar.flemstrom@neuro.uu.se |
| Flygt, Johanna | johanna.flygt@neuro.uu.se |
| Folke, Fredrik | fredrik.folke@neuro.uu.se |
| Fredlund, Pia | pia.fredlund@neuro.uu.se |
| Fredriksson, Anders | anders.fredriksson@neuro.uu.se |
| Fredriksson, Robert | robert.fredriksson@neuro.uu.se |
| Färdig, Rickard | rickard.fardig@neuro.uu.se |
| Galos, Peter | peter.galos@neuro.uu.se |
| Gezelius, Henrik | henrik.gezelius@neuro.uu.se |
| Goergen, Philip | philip.goergen@neuro.uu.se |
| Gudjonsson, Olafur | olafur.gudjonsson@neuro.uu.se |
| Gupta Löfving, Sandra | |
| Gustafson, Ann-Marie | ann-marie.gustafson@neuro.uu.se |
| Gustafsson, Ann-Cathrine | anki.gustafsson@neuro.uu.se |
| Gåve, Eva | eva.gave@neuro.uu.se |
| Götürk, Camilla | |
| Haglund, Kristina | Kristina.Haglund@neuro.uu.se |
| Halawa, Imad | imad.halawa@neuro.uu.se |
| Hallböök, Finn | finn.hallbook@neuro.uu.se |
| Hallman, Jarmila | jarmila.hallman@neuro.uu.se |
| Hartzell, Monica | monica.hartzell@akademiska.se |
| Harun-Or-Rashid, Mohammad | mohammad.harun.or.rashid@neuro.uu.se |
| Hedenius, Martina | martina.hedenius@neuro.uu.se |
| Hedlund, Inger | inger.hedlund@neuro.uu.se |
| Hedström, Yvette | yvette.hedstrom@neuro.uu.se |
| Hellsten, Sofie | sofie.hellsten@neuro.uu.se |
| Hellström, Karin | karin.hellstrom@neuro.uu.se |
| Hesselager, Göran | goran.hesselager@neuro.uu.se |
| Hillered, Lars | lars.hillered@neuro.uu.se |
| Hogenkamp, Pleunie | pleunie.hogenkamp@neuro.uu.se |
| Holm, Sara | sara.holm@neuro.uu.se |
| Holmbäck, Johanna | johanna.holmback@neuro.uu.se |
| Holtz, Anders | anders.holtz@neuro.uu.se |
| Hooli Mariana | mariana.hooli@neuro.uu.se |
| Howells, Tim | tim.howells@neuro.uu.se |
| Hulter Åsberg, Kerstin | kerstin.hulter.asberg@neuro.uu.se |
| Hultqvist, Greta | greta.hultqvist@neuro.uu.se |
| Hutchinson, Ashley | ashley.hutchinson@neuro.uu.se |
| Hård-Wallenqvist, Berit | berit.hard-wallenqvist@neuro.uu.se |
| Hägerbaum, Birgitta | birgitta.hagerbaum@neuro.uu.se |
| Hägglund, Maria | maria.hagglund@neuro.uu.se |
| Höglund, Anna-Stina | anna-stina.hoglund@neuro.uu.se |
| Hörberg, Niklas | niklas.horberg@neuro.uu.se |
| Igelström, Helena | helena.igelstrom@neuro.uu.se |
| Isaksson, Johan | johan.isaksson@neuro.uu.se |
| Israelsson, Charlotte | charlotte.israelsson@neuro.uu.se |
| Jacobsson, Karl-Gustav | karl-gustav.jacobsson@neuro.uu.se |
| Jakobsson Larsson, Birgitta | birgitta.jakobsson.larsson@neuro.uu.se |
| Jarrin, Miguel | miguel.jarrin@neuro.uu.se |

| | |
|---|---|
| Jennische, Margareta | margareta.jennische@neuro.uu.se |
| Jin, Yang | yang.jin@neuro.uu.se |
| Jin, Zhe | zhe.jin@neuro.uu.se |
| Johansson-Niemelä, Birgitta | Birgitta.Johansson.Niemela@akademiska.se |
| Johansson, Anders | anders.johansson@neuro.uu.se |
| Johansson, Henrik | henrik.johansson@neuro.uu.se |
| Johnson, Ulf | ulf.johnson@neuro.uu.se |
| Jonsson, Jörgen | jorgen.jonsson@neuro.uu.se |
| Jonsson, Ulf | ulf.jonsson@neuro.uu.se |
| Jordell-Kylberg Annika | annika.jordell-kylberg@neuro.uu.se |
| Junemar Silvemark, Annika | annika.silvemark@neuro.uu.se |
| Jüris, Linda | linda.juris@neuro.uu.se, |
| Jägare, Annika | annika.jagare@neuro.uu.se |
| Kalicharan, Patra | kalicharan.patra@neuro.uu.se |
| Karamanis, Georgios | Georgios.Karamanis@neuro.uu.se |
| Karlsson, Lena | lena.karlsson@neuro.uu.se |
| Khalifa, Najah | najah.khalifa@neuro.uu.se |
| Kilimann, Manfred | manfred.kilimann@neuro.uu.se |
| Klockars, Anica | anica.klockars@neuro.uu.se |
| Knorring von, Lars | lars.von_knorring@neuro.uu.se |
| Korol, Sergiy | sergiy.korol@neuro.uu.se |
| Kouros, Ioannis | ioannis.kouros@neuro.uu.se |
| Kozhevnikova, Mariya | mariya.kozhevnikova@neuro.uu.se |
| Kozlova-Aldskogius, Elena | elena.kozlova@neuro.uu.se |
| Krishnan, Arunkumar | arunkumar.krishnan@neuro.uu.se |
| Krüger-Vahlquist, Maria | maria.kruger.vahlquist@neuro.uu.se |
| Kullander, Klas | klas.kullander@neuro.uu.se |
| Kumlien, Eva | eva.kumlien@neuro.uu.se |
| König, Niclas | niclas.konig@neuro.uu.se |
| Lagerström, Malin | malin.lagerstrom@neuro.uu.se |
| Lagman, David | david.lagman@neuro.uu.se |
| Lannsjö, Marianne | marianne.lannsjo@neuro.uu.se |
| Lapshyna, Kateryna | kateryna.lapshyna@neuro.uu.se |
| Larhammar, Dan | dan.larhammar@neuro.uu.se |
| Larhammar, Martin | martin.larhammar@neuro.uu.se |
| Larsson, Lars | lars.larsson@neuro.uu.se |
| Laurell, Katarina | katarina.laurell@neuro.uu.se |
| Laurent, Nadina | nadina.laurent@neuro.uu.se |
| Le Greves, Madeleine | madeleine.legreves@neuro.uu.se |
| Leao, Katarina | katarina.leao@neuro.uu.se |
| Leao, Richardson | richardson.leao@neuro.uu.se |
| Lee, Yu-Jen | frank.lee@neuro.uu.se |
| Lewén, Anders | anders.lewen@neuro.uu.se |
| Li, Meishan | meishan.li@neuro.uu.se |
| Lind, Signe | signe.lind@neuro.uu.se |
| Lindblad, Frank | frank.lindblad@neuro.uu.se |
| Lindmark, Birgitta | birgitta.lindmark@neuro.uu.se |
| Lindqvist, Johan | johan.lindqvist@neuro.uu.se |
| Lindström Leif | Leif.Lindstrom@neuro.uu.se |
| Llano Diez, Monica | monica.llano.diez@neuro.uu.se |

| | |
|---|---|
| Lundberg, Per Olov | po.lundberg@neuro.uu.se |
| Lundell, Ingrid | ingrid.lundell@neuro.uu.se |
| Lundin, Lars-Gustav | LG.Lundin@neuro.uu.se |
| Lundin, Tom | Tom.Lundin@neuro.uu.se |
| Lundström, Erik | erik.lundstrom@neuro.uu.se |
| Lööv, Camilla | camilla.loov@neuro.uu.se |
| Mackenzie, Åsa | asa.mackenzie@neuro.uu.se |
| Makris, Georgios | georgios.makris@neuro.uu.se |
| Marklund, Niklas | niklas.marklund@neuro.uu.se |
| Markström, Agneta | Agneta.Markstrom@akademiska.se |
| Martin, Cathrin | cathrin.martin@neuro.uu.se |
| Mattsson, Peter | peter.mattsson@neuro.uu.se |
| Melberg, Atle | atle.melberg@neuro.uu.se |
| Memic, Fatima | fatima.memic@neuro.uu.se |
| Mendu, Suresh | suresh.mendu@neuro.uu.se |
| Meyerson, Bengt | bengt.meyerson@neuro.uu.se |
| Michel, Per-Olof | per-olof.michel@neuro.uu.se |
| Mikulovic, Sanja | sanja.mikulovic@neuro.uu.se |
| Milesson Fors, Björn | bjorn.milesson.fors@neuro.uu.se |
| Millbert, Petra | petra.millbert@neuro.uu.se |
| Mohell, Nina | nina.mohell@aprea.com |
| Månsson, Ann | ann.mansson@neuro.uu.se |
| Nagaraja, Chetan | chetan.nagaraja@neuro.uu.se |
| Nehlin Gordh, Christina | christina.nehlin.gordh@neuro.uu.se |
| Ngamjariyawat, Anongnad | anongnad.ngamjariyawat@neuro.uu.se |
| Nilsson Linus | |
| Nilsson, Anders | anders.nilsson@neuro.uu.se |
| Nilsson, Emil | emil.nilsson@neuro.uu.se |
| Nilsson, Gunno | gunno.nilsson@medcellbiol.uu.se |
| Nilsson, Pelle | pelle.nilsson@neuro.uu.se |
| Nordenankar, Karin | karin.nordenankar@neuro.uu.se |
| Nordenstam, Carin | carin.nordenstam@neuro.uu.se |
| Nordström, Karin | karin.nordstrom@neuro.uu.se |
| Noroozy, Siamak | siamak.noroozy@neuro.uu.se |
| Nousia, Katherina | katherina.nousia@neuro.uu.se |
| Nyberg, Christoffer | christoffer.nyberg@neuro.uu.se |
| Nyberg, Gunnar | gunnar.nyberg@neuro.uu.se |
| Nygren, Ingela | ingela.nygren@neuro.uu.se |
| Nygren, Karin | karin.nygren@neuro.uu.se |
| Nyholm, Dag | dag.nyholm@neuro.uu.se |
| Nyholm, Lena | lena.nyholm@neuro.uu.se |
| Nylander, Olof | olof.nylander@neuro.uu.se |
| Ocampo Daza, Daniel | daniel.ocampo-daza@neuro.uu.se |
| Ochala, Julien | julien.ochala@neuro.uu.se |
| Ogilvie, Hannah | hannah.ogilvie@neuro.uu.se |
| Olander, Hedvig | hedvig.olander@neuro.uu.se |
| Olsén, Hanna | hanna.olsen@neuro.uu.se |
| Olsson, Gunilla | gunilla.olsson@neuro.uu.se |
| Oreland, Lars | lars.oreland@neuro.uu.se |
| Ormerod, Neil | neil.ormerod@neuro.uu.se |

| | |
|---|---|
| Papadopoulos, Fotios | fotis.papadopoulos@neuro.uu.se |
| Perland, Emelie | emelie.perland@neuro.uu.se |
| Perry, Sharn | sharn.perry@neuro.uu.se |
| Persdotter-Hedlund, Gabriella | gabriella.persdotter@neuro.uu.se |
| Persson, Mona | mona.persson@neuro.uu.se |
| Pettersson, Hanna | hanna.pettersson@neuro.uu.se |
| Pettersson, Stefan | stefan.pettersson@neuro.uu.se |
| Pettersson, Susanne | susanne.pettersson@neuro.uu.se |
| Peuckert, Christiane | c.peuckert@neuro.uu.se |
| Pruner, Jasna | jasna.pruner@neuro.uu.se |
| Purins, Karlis | karlis.purins@neuro.uu.se |
| Päären, Aivar | aivar.paaren@neuro.uu.se |
| Qaisar, Rizwan | rizwan.qaisar@neuro.uu.se |
| Ramirez, Adriana | adriana.ramirez@neuro.uu.se |
| Ramklint, Mia | mia.ramklint@neuro.uu.se |
| Rask-Andersen, Mathias | mathias.rask-andersen@neuro.uu.se |
| Rastad, Cecilia | cecilia.rastad@neuro.uu.se |
| Reis, Amilcar | amilcar.reis@neuro.uu.se |
| Renaud, Guillaume | guillaume.renaud@neuro.uu.se |
| Restrepo, Ernesto | ernesto.restrepo@neuro.uu.se |
| Ring, Henrik | henrik.ring@neuro.uu.se |
| Rogoz, Katarzyna | katarzyna.rogoz@neuro.uu.se |
| Ronne-Engström, Elisabeth | elisabeth.ronne.engstrom@neuro.uu.se |
| Roshanbin, Sahar | sahar.roshanbin@neuro.uu.se |
| Rosling, Agneta | agneta.rosling@neuro.uu.se |
| Rostami, Elham | elham.rostami@neuro.uu.se |
| Ruchkin, Vladislav | vladislav.ruchkin@ltdalarna.se |
| Rystedt, Alma | alma.rydstedt@neuro.uu.se |
| Ryttlefors, Mats | mats.ryttlefors@neuro.uu.se |
| Salci, Konstantin | konstantin.salci@neuro.uu.se |
| Sandström, Marie | marie.sandstrom@neuro.uu.se |
| Schiöth, Helgi | helgi.schioth@neuro.uu.se |
| Schweizer, Nadine | nadine.schweizer@neuro.uu.se |
| Schönnings, Gun | gun.schonnings@neuro.uu.se |
| Sedin, John | john.sedin@neuro.uu.se |
| Sergiy, Korol | sergiy.korol@neuro.uu.se |
| Shirazi Fard, Shahrzad | shahrzad.shirazifard@neuro.uu.se |
| Sjöblom, Markus | markus.sjoblom@neuro.uu.se |
| Skoglund, Karin | karin.skoglund@neuro.uu.se |
| Sköld, Mattias | mattias.skold@neuro.uu.se |
| Smith, Casey | casey.smith@neuro.uu.se |
| Smits, Anja | anja.smits@neuro.uu.se |
| Sommansson, Anna | anna.sommansson@neuro.uu.se |
| Sperber, Göran | goran.sperber@neuro.uu.se |
| Spörndly-Nees, Sören | soren.sporndly-nees@neuro.uu.se |
| Stefano, Johann | |
| Stjärne, Ludvig | ludvig.stjarne@neuro.uu.se |
| Strömberg, Siv | siv.stromberg@neuro.uu.se |
| Ståhl-Myllyaho, Inger | inger.stahl-myllyaho@neuro.uu.se |
| Sudhakar, Aare | sudhakar.aare@neuro.uu.se |

| | |
|---|---|
| Sundblom, Jimmy | jimmy.sundblom@neuro.uu.se |
| Sundbom, Ann | ann.sundbom@neuro.uu.se |
| Sundbom, Renée | renee.sundbom@neuro.uu.se |
| Sundelin Wahlsten, Viveka | viveka.sundelin@neuro.uu.se |
| Swartling, Malin | malin.swartling@neuro.uu.se |
| Swartz, Jackie | jackie.swartz@neuro.uu.se |
| Sveen, Josefin | josefin.sveen@neuro.uu.se |
| Szmidt, Malgorzata | malgorzata.szmidt @neuro.uu.se |
| Sällman-Almén, Markus | markus.sallman-almen@neuro.uu.se |
| Tahib, Nezar | nezar.tahib@neuro.uu.se |
| Taylor, Hanna | hanna.taylor@neuro.uu.se |
| Thunberg, Sari | sari.thunberg@neuro.uu.se |
| Thurfjell, Barbro | barbro.thurfjell@neuro.uu.se |
| Thörnqvist, Per-Ove | per-ove.thornqvist@neuro.uu.se |
| Titova, Olga | olga.titova@neuro.uu.se |
| Todkar, Aniruddha | aniruddha.todkar@neuro.uu.se |
| Trolle, Carl | carl.trolle@neuro.uu.se |
| Tuvemo Johnson, Susanna | susanna.tuvemo.johnson@neuro.uu.se |
| Tögenmark, Elin | elin.togenmark@neuro.uu.se |
| Urell, Charlotte | charlotte.urell@neuro.uu.se |
| Vahlberg, Birgit | birgit.vahlberg@neuro.uu.se |
| Wallmark, Svante | svante.wallmark@neuro.uu.se |
| Vasylovska, Svitlana | svitlana.vasylovska@neuro.uu.se |
| Wenngren, Ewa | ewa.wenngren@neuro.uu.se |
| Wesslén, Nils | nils.wessle@neuro.uu.se |
| Widmark, Jenny | jenny.widmark@neuro.uu.se |
| Willebrand, Mimmie | mimmie.willebrand@neuro.uu.se |
| Williams, Michael | michael.williams@neuro.uu.se |
| Winberg, Svante | svante.winberg@neuro.uu.se |
| Virhammar, Johan | johan.virhammar@neuro.uu.se |
| Wistrand, Per | per.wistrand@neuro.uu.se |
| Wolf, Martina | martina.wolf@akademiska.se |
| Von Knorring, Anne-Liis | anne-liis.von_knorring@neuro.uu.se |
| Von Mentzer, Cecilia | cecilia.vonMentzer@neuro.uu.se |
| Wootz, Hanna | hanna.wootz@neuro.uu.se |
| Västermark, Åke | ake.vastermark@neuro.uu.se |
| Xavier, Miguel | miguel.xavier@neuro.uu.se |
| Xu, Bo | bo.xu@neuro.uu.se |
| Yamskova, Olga | olga.yamskova@neuro.uu.se |
| Yates, Cecilia | cecilia.yates@neuro.uu.se |
| Zelano, Johan | johan.zelano@neuro.uu.se |
| Zetterberg, Lena | lena.zetterberg@neuro.uu.se |
| Zetterling, Maria | maria.zetterling@neuro.uu.se |
| Zhang, Xiao | xiao.zhang@neuro.uu.se |
| Åsenlöf, Pernilla | pernilla.asenlof@neuro.uu.se |
| Öckerman, Anders | anders.ockerman@neuro.uu.se |
| Ögefeldt, Sofia | sofia.ogefeldt@neuro.uu.se |
| Östberg, Per | per.ostberg@neuro.uu.se |
| Öster, Caisa | Caisa.Oster@neuro.uu.se |

## DISSERTATIONS 2012

**Aare Sudhakar, Reddy**: Clinical Neurophysiology, *"Intensive care unit muscle wasting. Skeletal muscle phenotype and underlying molecular mechanisms".*

**Arnberg, Filip**: Psychiatry,*"Long-term posttraumatic stress in survivors from disasters and major accidents".*

**Banduseela, Varuna**: Clinical Neurophysiology, *"Molecular and cellular networks in critical illness associated muscle weakness. Skeletal muscle proteostasis in the intensive care unit".*

**Bohman, Hannes**: Child and Adolescent Psychiatry, *"Adolescents with depression followed up. Prognostic significance of somatic symptoms and their need of inpatient".*

**Bring, Annika**: Physiotherapy, *"A behavioural medicine perspective on acute whiplash associated disorders - daily coping, prognostic factors and tailored treatment.*

**Danfors, Torsten**: Neurology, *"11Cmolecular imaging in focal epilepsy".*

**Färdig, Rickard**: Psychiatry, *"Evaluation of the illness management and recovery program for schizophrenia and schizoaffective disorder".*

**Ghaderi Berntsson, Shala**: Neurology, *"Towards novel biomarkers for low-grade glioma".*

**Lannsjö, Marianne:** Neurosurgery, *"Mild traumatic brain injury - studies on outcome and prognostic factors".*

**Llano Diez, Monica:** Clinical Neurophysiology, *"Mechanisms underlying intensive care unit muscle wasting".*

**Memic, Fatima**: Developmental Genetics, *"Crossing the midline - locomotor neuronal circuitry formation".*

**Mendu Suresh Kumar**: Physiology, *role of GABA and GABA-A channels in T lymphocytes and stem cells.*

**Nehlin Gordh, Christina**: Psychiatry, *"Alcohol use and secondary prevention in psychiatric care".*

**Nordenankar, Karin**: Developmental Genetics, *"Functional analysis of the vesicular glutamate transporter 2 in specific neuronal circuits of the brain."*

**Qaisar, Rizwan**: Clinical Neurophysiology, *"Myonuclear organization and regulation of muscle contraction in single muscle fibres. Effects of ageing, gender, species, endocrine factors and muscle size".*

**Ring, Henrik**: Developmental Neuroscience, *"Characterization of retinal progenitor cells".*

**Rogoz, Katarzyna**: Developmental Genetics, *"Signalling mechanisms in the neuronal networks of pain and itch".*

**Rystedt, Alma**: Neurology, *"Botulinumtoxin - formulation, concentration and treatment".*

**Sällman Almén, Markus**: Functional Pharmacology, *"The membrane proteome: evolution, characteristics and classification".*

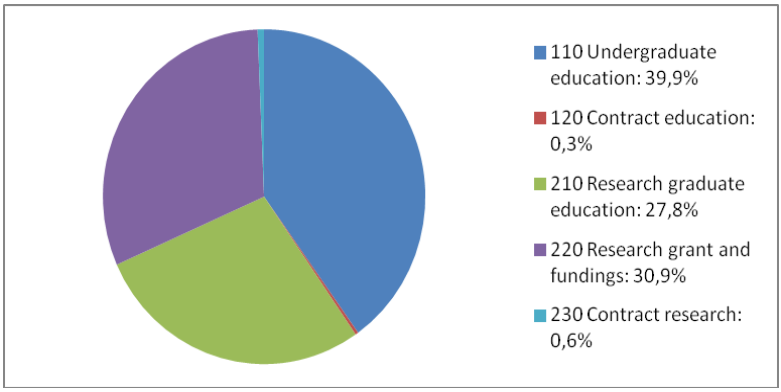
**Skoglund, Karin**: Neurosurgery, *"The neurological wake-up test in neurocritical care".*

**Sundblom, Jimmy**: Neurology, *"Autosomal dominant leukodystrophy with autonomic symptoms and rippling muscle disease. Translational studies of two neurogenetic disease".*

**Västermark, Åke**: Functional Pharmacology, *"Evolution of membrane bound proteins and their ligands: the melanocortin (MC) receptor inverse agonists AgRP2, ASIP2, drug/metabolite transporters, and SPNS1".*

## Finance 2012

Total revenues 2012: 148 769 037 SEK




Research grants and funds: 45 969 632 SEK:

| | |
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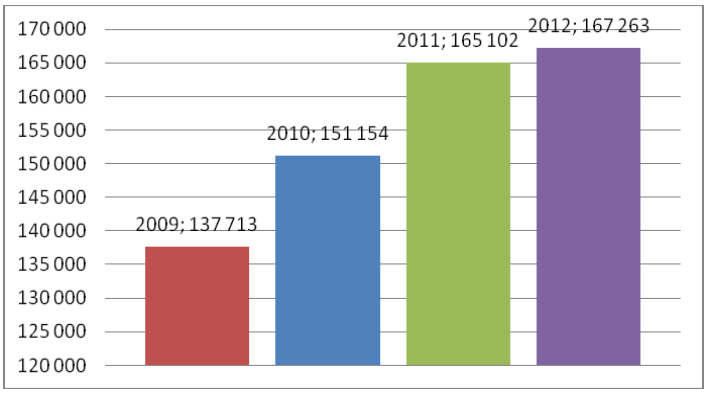
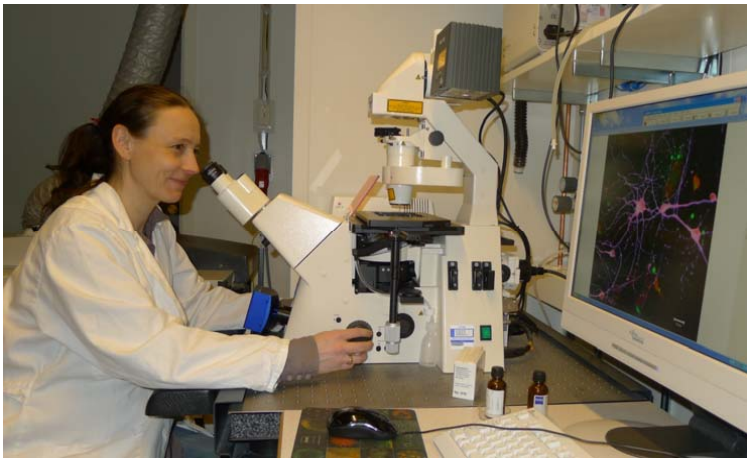
| 44,9% | The Swedish Research Council |
| 22,2% | Other private fundings |
| 5,5% | Swedish Brain Foundation |
| 5,4% | Uppsala Akademiförvaltning |
| 5,3% | EU:s seventh framework programme |
| 4,2% | National Board of Health and Welfare |
| 3,8% | FORMAS |
| 2,8% | Göran Gustafssons stiftelse |
| 1,8% | FAS |
| 4,2% | Others |

Costs´ development 2009-2012 (THOUSAND SEK)



# SCIENTIFIC REPORTS



*Christiane Peuckert, researcher in Developmental Genetics*

# *Clinical Neurology & Psychiatry*

## Clinical Neurology

**Group leader: Anja Smits, Professor**

**Members of the group during 2012**

Imad Halawa, MD
Birgitta Jakobsson-Larsson, PhD student
Eva Kumlien, Associate Professor
Katarina Laurell, MD PhD
Per Olov Lundberg, Professor em
Erik Lundström, MD PhD
Peter Mattsson, Associate Professor
Atle Melberg, Associate Professor
Ingela Nygren, MD PhD
Dag Nyholm, Associate Professor
Alma Rystedt, PhD
Jimmy Sundblom, MD, PhD
Johan Virhammar, PhD student
Sten-Magnus Aquilonius, Professor em
Håkan Askmark, Adjunct Professor
Shala Berntsson, MD, PhD
Joachim Burman, PhD student
Torsten Danfors, MD, PhD
Jan Fagius, Associate Professor
Svante Wallmark, PhD student
Johan Zelano, MD PhD

Neurological disorders are among the greatest threats to public health (World Health Organization 2012). There are still several gaps in our understanding of disorders of the nervous system, but we know enough about their nature and treatment to be able to shape effective strategies to combat some of the most prevalent among them. As such, research at the neurology unit of the Dept of Neuroscience is strongly patient-oriented and our scientific questions arise from daily clinical practice. Patients with common neurological disorders such as epilepsy, movement disorders, stroke and multiple sclerosis (MS) provide powerful resources for clinical studies, while more rare diseases like hereditary neurological disorders and low-grade gliomas are studied in collaboration with other centres.

The variety in research projects at the unit is a prerequisite for further development of neurology as a strong clinical specialty with patient-oriented research. There is an evident risk, on the other hand, that separate research projects are too small to be competitive, and the unit has therefore systematically intensified collaborations within the department and focused on translational research. Some of these projects have been very successful and are summarized here.

***Clinical and interventional studies***

- In collaboration with the PET Centre, the role of 123I-FP-CIT SPECT, 18F-FDG-PET and 11C-PE2I PET is studied in Parkinson's disease and related disorders, while other tracers such as 11C-flumazenil and GR205171 (Neurokinin-1 receptor antagonist) are studied in focal epilepsy. PET with the tracer 11C-methionine is used for the differential diagnosis of low-grade gliomas, in combination with physiological MRI techniques such as perfusion and diffusion MRI, and in the follow up of these patients to detect early tumour progression.
- A multicentre trial has been planned and will soon be initiated to compare the efficacy of intestinal levodopa/carbidopa gel infusion versus deep brain stimulation in a randomized design, sponsored from the Swedish Research Council.

- 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 recent doctoral thesis.
- Normal pressure hydrocephalus (NPH) is a gait disorder caused by disturbed CSF circulation. A retrospective study of infusion techniques and CSF dynamic tests has been published and further prospective studies to evaluate new MRI parameters with higher diagnostic sensitivity in these patients are ongoing.
- Clinical comparative studies on quality of life and on the specific needs of hospital care in patients with motor neuron disease and in patients who suffered from subarachnoid haemorrhages.
- In 2004, a patient with "malignant" MS was successfully treated with hematopoietic stem cell transplantation (HSCT); since then more than 20 patients have been treated with mostly favourable effects on neurological function. The unit participates in an international prospective two-armed trial comparing HSCT with natalizumab in patients with aggressive MS.
- In addition, five patients with chronic inflammatory demyelinating polyneuropathy (CIDP) resistant to conventional treatment have been successfully treated with HSCT. In collaboration with the Karolinska University Hospital, Sahlgrenska University Hospital and Norrlands University Hospital, clinical data of a total of 11 CIDP patients treated with HSCT in Sweden (the largest published series so far) are analyzed and will shortly be presented.
- Epidemiological studies on the efficiency, safety, and sociodemographic distribution among recently adopted treatment options in epilepsy have been conducted. Our recent publications indicating suboptimal use of anti-epileptic drugs due to sociodemographic disparities in prescription patterns, and of epilepsy surgery due to suboptimal referral patterns, have attracted a general interest. These publications have contributed to a national debate between the Swedish Neurological Society, patient organizations and leading politicians, on how to deal with the shortage of neurologists in Sweden and the diversity and inequality of neurological services between different parts of the country.

***Translational studies***

Translational projects include phenotypic characterization of patients with hereditary neuromuscular disorders, the role of inflammatory markers in patients with MS, epileptogenic mechanisms in a mouse model for focal epilepsy and pharmacokinetic-pharmacodynamic modelling in patients with Parkinson's disease. 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 tissues from patients with ALS, Parkinson's disease, gliomas and other neurological disorders.

***Summary of recent developments***

The neurology unit has developed successfully over the past five years. Through strong focus on collaborative and translational projects, we have been able to contribute to high-quality studies with a number of publications in high-impact journals. During 2012, four PhD students have defended their doctoral thesis and one student has given half-time seminar. Several new PhD projects have been initiated, three with focus on translational research. The unit is an active partner in various national studies and collaborations (MS, Parkinson's disease, Huntington disease, NPH, epilepsy, neuro-oncology, stroke), as well as in international trials and networks (neurogenetics, stroke, neuro-oncology). As a consequence, neurology has received steadily increasing research funding, including external grants from major research foundations and governmental funding ("ALF"). Scientific achievements have

gone hand-in-hand with other initiatives, such as the organization of national teaching courses, scientific meetings and representations in the Swedish Neurological Society, the Scandinavian Reference Group for Treatment of Parkinson's disease and the European Federation of Neurological Sciences (EFNS).

**Publications 2010-2012**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* *contributed equally*

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**Agencies that support the work/ Funding**

Ulla-Carin Lindquist stipendium
Citizens United for Research in Epilepsy
Epilepsifonden
Hanna Eklunds Foundation
Lions Foundation
Swedish Society for Medical Research
Parkinsonfonden
Uppsala County Council (ALF)
Lions Cancerfond
Margaretahemmet Foundation
Radiumhemmets Jubileum Foundation
Regional Research Council Uppsala/Örebro
Selanderska Stiftelsen

Svenska Epilepsiförbundet
Utvecklingsfonden, Uppsala University Hospital
NHR
H Larssons Foundation, M, Å och H Ländells Foundation
M Sjöströms Foundation
G och M Lundbergs stiftelse för Neurologisk forskning
Major Gösta Linds minnesfond
Swedish Research Council

### Awards

Pedagogical Award from the Medical Student Association (Atle Melberg)

## Clinical Neurophysiology

### *Neuromuscular*

**Group leaders:**
**Lars Larsson, Professor, MD, PhD**
**Julien Ochala, Docent, PhD**

### Members of the Basic and Clinical Muscle biology group during 2012:

Lars Larsson,(Professor, MD, PhD) Barry Dworkin (Visting Professor, PhD), Julien Ochala (Docent, PhD, Swedish Research Council supported Researcher), Meishan Li (MD, PhD), Niccola Cacciani (MD, PhD), Rizwan Qaisar (MD, PhD), Humberto Gonzales (MD, PhD student), Sudhakar Aare (PhD student), Varuna Banduseela (PhD student), Rebeca Corpeno (PhD student), Monica Llano Diez (PhD student), Johan Lindqvist (PhD student), Hannah Ogilvie (PhD student), Guillaume Renaud (PhD student),. Yvette Hedström /Sr. Res. Tech), Ann-Marie Gustafsson (Sr Res Tech), Maria Wilén (Sr. Res. Tech), Hazem Aqqad (grad. student), Rutger Norbert (international undergrad student), Ayse Malcı (international undergrad student).

### International collaborations

18 European groups within a Fp7 EU-project (Myoage), 25 European groups within an EU COST project (CM1001). Prof. Caroline Byron (Copenhagen, Denmark), Profs Lea Sistonen and Leif Eriksson (Turku, Finland), Profs. Vuokko Kovanen, Sarianna Sippilä and Harri Suominen (Jyväskylä, Finland), Profs. Laszlo Vigh and Peter Literti Nagy (Budapest, Hungary), Prof Bertrand Friguet, Dr. Norma Romero and Prof. Mario Pende (Paris, France), Dr. Isabelle Penisson-Besnier (Angers, France), Mathias Gautel, (London, UK), Ass. Prof. Gonzalo Blanco (University of York, UK), Prof. Wolfgang Linke (Munster, Germany), Prof. Bernhard Brenner (Hannover, Germany), Prof. Simone Spuler (Charite University, Germany), Prof. Antonio Musaro (Rome, Italy), Profs. Marco Sandri, Luisa Gorza and Stefano Schiaffino (Padova, Italy), Profs Naoto Yagi and Hiroyuki Iwamoto (Spring-8, Japan), Prof. Paul Gregorevic (Melbourne, Australia), Prof. Edna Hardeman (Sidney, Australia), Ass. Prof. Kristen Nowak (Perth, Australia), Prof. J.-P. Jin (Detroit, USA), Prof. P.O. Hasselgren (Boston, USA), Prof. Rick Moss (Madison, USA), Prof. Gerald McClearn and Roger

McCarter (State College, USA), Prof. Karyn Esser (Lexington, USA), Prof. Velia Fowler (San Diego, USA), Prof. Denis Guttridge (Columbus, Ohio).

The aims of our research focusing on neuromuscular muscle wasting disorders in the ***Basic and Clinical Muscle biology*** are to:

- Determine underlying mechanisms
- Develop and improve diagnostic methods and monitoring techniques
- Implement and evaluate specific therapeutic intervention strategies

***Basic and Clinical Muscle Biology***

Our research within *basic and clinical muscle biology* focuses on the mechanisms underlying the muscle wasting and impaired muscle function that is associated with critical illness and aging, at the gene, protein, muscle cell and muscle levels. A significant part of the research efforts are also devoted to detailed studies of regulation of muscle contraction at the motor protein and muscle cell levels in patients with mutations of sarcomeric proteins, such as myosin, myosin associated and regulatory proteins (troponin and tropomyosin). Methods have been developed for detailed studies of:

1. Regulation of muscle contraction at the cell and motor protein levels, i.e., contractile measurements in the short muscle cell segments obtained with the percutaneous muscle biopsy technique and studies of myosin function after extraction of myosin from a short muscle cell segment, i.e., methods to measure catalytic properties (motility speed) and force generation capacity.
2. Quantitative and qualitative analyses of myofibrillar protein expression in single muscle fibre segments, including cell biological, biochemical, structural (mass spectrometry) and biophysical (X-ray diffraction) methods.
3. Imaging techniques for 3D analysis and reconstruction of myonuclei organization in single muscle fibre segments using a novel algorithm
4. Experimental models for detailed mechanistic studies of muscle wasting in critically ill intensive care units, involving large (porcine) and small (rodent) animal models where animals are mechanically ventilated, pharmacologically ventilated and monitored for long durations (several weeks). These models are used in parallel with clinical studies in intensive care unit patients using methods unique for our group in combination with clinical electrophysiological methods.

The different methods for studies of regulation of contraction and myofibrillar protein synthesis/degradation have been developed for studies of small muscle samples and can be used independently of mammalian species. This gives us unique opportunities for combined mechanistic experimental and clinical studies focusing on important clinical problems. Some of these methods are presently being used in routine clinical diagnostics. The combined expertise and methods available in this group for detailed studies of skeletal muscle in health and disease from patients and in experimental animal models is unique, second to none and not available in any other research group. The research is conducted in collaboration with excellent research groups at UU, in Europe, Australia, Japan and the US. The research group consists of group leaders Professor/Docent, Adjunct Professor, MDs with a PhD degree, post-docs (PhDs), PhD students, fulltime senior research technicians and graduate/undergraduate students.

**Publications 2010-2012**

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**Agencies that support the work/ Funding**

ALF (Uppsala University hospital)
Ass. Francaise contre les Myophaties
European Union (MYOAGE, Fp7 CT-223756)
European Union (COST CM1001)
Harald och Greta Jeanssons Foundation
King Gustaf V and Queen Victoria Foundation
STINT
Swedish Research Council (8651, LL)

Swedish Research Council (21493, JO)
Swedish Research Council (21492; 4-year forskarassistent, JO)
Apotekare Hedbergs Foundation
Tore Nilsons Foundation for medical research
Tureus Foundation
Uppsala University

## *Neuromuscular Synapse and Advanced Electrophysiological*

**Group leaders:**
**Anna Rostedt Punga, MD, PhD** (Neuromuscular synapse and myasthenia gravis)
**Erik Stålberg, Professor em.** (Development of advanced electrophysiological methods)

**Members of the group during 2012:**

**Neuromuscular synapse and myasthenia gravis:**
Anna Rostedt Punga, Linnea Haggård, Mayank Chauhan

**Collaborators:**

Prof Markus Rüegg, Basel, Switzerland, Prof Elisabeth Chroni, Patras, Greece
Prof Sonia Berrih-Aknin, INSERM, Paris, France

**The Development of Advanced Electrophysiological Methods:** Erik Stålberg, Arne Sandberg. From other countries: J Navallas, Spain; S Nandedkar, USA; L Puuksa, Estonia; DB Sanders USA; J Kouyoumdjian Brazil; M Sonoo, Japan.

**The general aims of the neuromuscular group are:**

1. Elucidation of the pathogenic mechanisms underlying neuromuscular disorders, with focus on myasthenia gravis (MG).

2. 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.

***Project 1) 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. We work both with the animal model of experimental autoimmune myasthenia gravis (EAMG) and in the clinical setting with MG patients.

During the past year we have found a loss of neural nitric oxide synthase (nNOS) from the muscle membrane in MG. Since nNOS localization to the sarcolemma is crucial for sustained muscle contraction, the observed nNOS loss can contribute to the chronic muscle fatigue in MG. Instead, we found increased nNOS in the cytoplasm, which increases the intracellular levels of NO and in turn induces atrophy signals, through up-regulation of the atrogenes MuRF-1 and atrogenin-1. This process may contribute to the secondary muscle atrophy observed in MG Additionally, we saw in a pilot study of Swedish MG patients, that they have a deficit in active vitamin D [25(OH) D]. Since 25(OH) D has important functions in regulating the regulatory T-cells and the autoimmune response, as well as directly acting through muscle receptors, it is very important to control vitamin D levels in MG patients to supplement low values.

***2) Development of Advanced Electrophysiological Methods***

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, but more reference material is needed. 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 preliminary results are currently being processed. Also, a needle manufacturer has also 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.
Our method of Scanning EMG has resulted in a PhD thesis in Spain for one of the participants (Navallas). The results are now use for simulation studies in muscle.
The method for direct muscle stimulation is being evaluated in critical illness (together with Prof Larssons group).
Surface EMG is being evaluated as an alternative to invasive needle EMG examinations.
New algorithms for analysis of surface EMG particularly in paediatric praxis are being established, for example in children with spinal muscle atrophy (SMA).
Abnormalities in the neurographic parameters F-waves are studied in relation to various diseases.

**International collaborations**

Anna Rostedt Punga acts as joint workpackage leader together with Prof Markus Rüegg, Basel, Switzerland, in the “Fight-MG” European research network about Myasthenia Gravis, currently until 2013 on pathophysiology at the neuromuscular junction.
The group of Prof Sonia Berrih-Aknin, INSERM, Paris, France is working together with “Neuromuscular synapse and myasthenia” in finding new biomarkers in MG.
Prof Erik Stålberg is involved in collaborations with J Navallas, Spain, S Nandedkar, USA and M Sonoo, Japan in developing new motor unit analysis techniques.
Both groups are involved in collaboration with DB Sanders USA and J Kouyoumdjian Brazil to improve the method of single-fiber EMG.

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**Agents that support the work/ Funding**

The Swedish Society of Medicine
Lars Hiertas memorial Foundation
The Erik, Karin and Gösta Selanders Foundation
EU FP7 project # 242210 "Fight-MG" (in collaboration with prof Markus Rüegg, Basel)

**Awards**

"Eberhardt Pfleiderer Preis" from the German Myasthenia Gravis foundation (Anna Rostedt Punga)
Honorary member of IFCN (Erik Stålberg)

## *Central and Somatosensory Nervous System*

**Members of the group during 2012**

Roland Flink, Karin Eedebol Eeg-Olofsson, Hans Axelsson, Tomas Winkler, Åsa Amandusson, Bernard Aoun, Roland Schmidt

***Research 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 preliminary report on the clinical use of equivalent current dipole analysis and surgical strategy and outcome in epilepsy surgery patients was presented at the IFCN congress in Kobe in 2010, *Clinical utility of EEG dipole analysis in the preoperative evaluation of epilepsy surgery patients*.

Another part of the project concerns epidemiological data describe patients subjected to surgical treatment of epilepsy. The National Registry of Surgical Treatment of Epilepsy is administrated at the department of Clinical Neurophysiology, Neuroscience Center, Academic Hospital.

***Project 2: Pediatric neurophysiology***

Project leader: Karin Edebol Eeg Olofsson

"Reference values for F wave parameters in healthy 3–20 year old subjects" was printed in the January 2011 issue *of Clinical Neurophysiology*. Authors were L. Puksa, K. Edebol Eeg-Olofsson, E. Stålberg and B. Falck.

*"Association between sociodemographic status and antiepileptic drug prescriptions in children with epilepsy"* was E-published in Oct., and printed i Dec 2012, in *Epilepsia*. Authors were P Mattsson, T Tomson, K Edebol Eeg-Olofsson, L Brännström and G Ringbäck Weitoft.

A manuscript entitled *"Neonatal EEG recordings during 2002-2007 in five Swedish counties"* will be submitted in 2013. Author Karin Edebol Eeg-Olofsson.
A manuscript entitled "Low-frequent Repetitive Transcranial Magnetic Stimulation (rTMS) in adolescents with Tourette syndrome and additional psychiatric conditions: results from a pilot study" will be submitted during 2013. Collabrative work between the Departments of Clinical Neurophysiology and Child and Adolescent Psychiatry. Authors: Karin Edebol Eeg-Olofsson and Najah Khalifa.

A study on the efficacy and safety of lidocaine for treatment of neonatal seizures has been performed in 30 infants analysing the continous EEG recording with respect to clinical and subclinical epileptic seizures. The manuscript is currently being reviewed in Acta Pediatrica. (Lundqvist, Ågren, Hellström-Westas, Flink, Wikström).

***Project 3: Neurophysiologic studies in the evaluation of traumatic brain injury***

**Project leader:** Tomas Winkler

1. Experimental spinal cord injury
Acute traumatic spinal cord injuries induce both immediate loss of conduction and progressive destruction of the spinal cord. Blocking one of several different neuroactive substances and transmittors within the spinal cord before injury will inhibit both the conduction loss and the secondary injury. We try to find if the secondary injury can be affected by blocking any of these substances after injury.

2. Blocking of myelinassociated axonal growth inhibitor factors within CNS.
In CNS axonal growth after injury is inhibited by factors associated to the myelin (NOGO system). If NOGO is blocked axonal regrowth after injury could be possible. We are testing the effect of antibodies against NOGO on axonal growth in CNS.

***Project 4: Navigated transcranial magnetic stimulation in the evaluation and treatment of patients with epilepsy***

**Project leader:** Åsa Amandusson

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 recently initiated several studies focusing primarily on different aspects of cortical excitability in healthy subjects and patients with epilepsy. During 2012 we have developed a standardized semi-automatic method for ppTMS measurement and completed a methodological study comparing different ways of performing ppTMS. We have also completed a study in which

cortical excitability during trigeminal nerve stimulation (a newly introduced therapeutic neurostimulation for epilepsy) was studied in healthy subjects.

***Project 5: Neurophysiologic methods in intraoperative monitoring (IOM)***

**Project leader:** Hans Axelson

The ION project can be divided in two parts: a) optimize the method for intraoperative neurophysiology (ION) in patients undergoing intraspinal or spine surgery. This also includes analysing data from the last five years of ION to obtain reliability measures for the methods. b) preoperative and intraoperative mapping of eloquent cortical areas. Direct electrical stimulation of cerebral cortex is a well-known method for mapping the eloquent cortical areas of motor cortex and speech areas. The 'traditional' 50-60 Hz frequency continuous stimulation used can trigger epileptic seizures during the procedure setting the patient at risk. A different method using high frequency stimulation in intermittent bursts of stimuli is a new way to perform this potentially dangerous procedure.

***Project 6: Pain and Itch in Human Disease***

**Project leader: Roland Schmidt**

***Background:*** About 1.5% of the Swedish population suffers from neuropathic pain. This is difficult to treat and it is estimated that as many as half of all patients receive inadequate pain relief. 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). Extensive experiments on rodent models have been found to be partially misleading since the pain systems in man and rodent are fundamentally different also in the peripheral nerve system.

***Questions, methods and goals:*** The technique of microneurography was initiated in Uppsala by Vallbo and Hagbarth in 1968. Since long 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. We are one of these groups (Norway – Sweden – Germany). Since nociceptive axons are extremely thin, cannot be studied with intracellular electrodes in vivo and also cannot be studied, in a manner relevant for human pain, in vitro, the normal physiology of these axons is largely unknown. But we have revealed parts of their normal physiology that we believe are very relevant for chronic pain.
Pain and central sensitisation in man in experimental conditions is mainly mediated by specific mechanoinsensitive 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:*** Now we use our large reference data from recordings in healthy individuals and record from patients with chronic pain or itch. 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 et c.). Several pharmaceutical companies are now developing drugs targeting voltage gated sodium channels for treatment of neuropahtic 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 hyperexitability 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) Tormod Helås (2), Ellen Jørum (2), Inge Petter Kleggetveit (2), Barbara Namer(1), Ottilia Obreja (1), Kristin Ørstavik (2), Martin Schmelz (1), Christian Weidner (1).
1: Germany, Erlangen and Mannheim
2: Norway, Rikshospitalet

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16. P Mattsson, T Tomson, K Edebol Eeg-Olofsson, L Brännström and G Ringbäck Weitoft.: Association between sociodemographic status and antiepileptic drug prescriptions in children with epilepsy Epilepsia, e-publ 2012

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**Agencies that support the work/ Funding**

The Swedish Brain Foundation
ALF
Margarethahemmet
Wallenberg Foundation
Utvecklingsfonden Uppsala University Hospital
Svenska Läkarsällskapet
Swedish Chapter of ILAE (Svenska Epilepsisällskapet)
Stiftelsen Epilepsifonden

# Psychiatry

## *Psychiatry*

**Group leader**: **Lisa Ekselius, Professor**

**Members of the group during 2012**

Adriana Ramirez, MD, PhD
Agneta Markström, MD, PhD, associate professor
Anders Fredriksson, PhD, associate professor
Bergdahl, RN, PhD student
Björn Nilsson, MD, PhD
Caisa Öster, RN, PhD, university lecturer
Christina Nehlin Gordh, PhD
Dan Edvinsson, MD, PhD student
Emma Ponten, PhD
Eva Baghdassarian, MD, PhD student
Eva Lindström, MD, PhD, associate professor
Fotios Papadopoulos, MD, PhD, associate professor
Fredrik Folke, psychologist, PhD student
Georgios Karamanis, MD
Georgios Makris, MD, PhD student
Ioannis Kouros, MD, PhD student
Jan-Erik Broman, RN, PhD, associate professor
Janet Cunningham, MD, PhD
Johan Dyster-Aas, MD, PhD
Josefin Bäckström, RN, PhD student
Josefin Sveen, PhD
Kristina Haglund, RN, PhD, university lecturer
Lars von Knorring, Professor emeritus, MD, PhD
Leif Grönblad, PhD
Leif Lindström, Professor emeritus, MD, PhD
Lennart Jansson, PhD
Linda Jüris, psychologist, PhD student
Lisa Ekselius, MD, PhD, professor
Maria Holstad, MD, PhD
Maria Nilsson Markhed, MD
Mia Ramklint, MD, PhD, university lecturer

Mimmie Willebrand, PhD, associate professor
Niklas Hörberg, MD, PhD student
Rickard Färdig, PhD
Robert Bodén, MD, PhD
Tommy Lewander, MD, PhD, associate professor

Within the Department of Neuroscience research, related to psychiatry focusses on investigating factors relevant to psychiatric morbidity. The research group boasts a wide variety of competencies, 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 based on up-to-date knowledge of the enigmas of the nervous system. Individual projects are described below.

***Project 1: Vulnerability and resilience; medical, psychological and social adaptation after severe injury***

**Participants:** Lisa Ekselius, Mimmie Willebrand, Johan Dyster-Aas, Caisa Öster, Josefin Sveen, and Josefin Bäckström. From Deptof Surgical Sciences: Professor Bengt Gerdin, Morten Kildal, MD, PhD, Associate professor, Aili Low, MD, PhD, Björn Wikehult, RN, PhD, and Andreas Lindahl, MD, PhD student.

**Collaborators:** Associate professor Mats Stridsberg, Dept of Medical Sciences, Uppsala University (UU), Professor Elias Eriksson, Institute of Neuroscience and Physiology, Göteborg University, and Professor Folke Sjöberg, 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 adaptational 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 (HPA)-axis, are studied in relation to individual factors and to outcome. In the future, our objective is to study signs of neurobiological alterations using neuroimaging techniques. Outcome is broadly defined in medical, psychological and social terms. One specific outcome, to which we devote much interest, is return to work, and the societal actors that intervene later in the recovery process. Other specific outcomes of interest are cognitive function, e.g. attention and memory, and psychiatric morbidity in the form of 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.

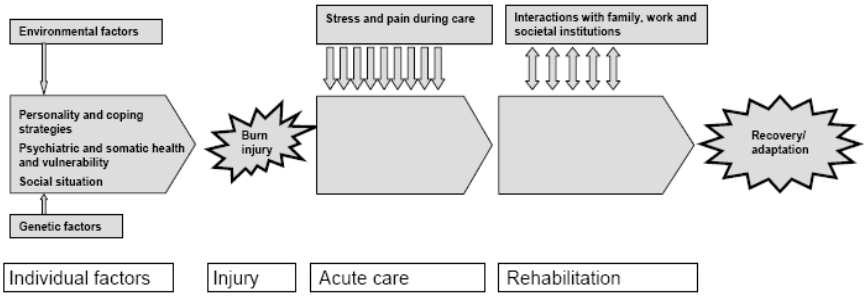


Figure 1. A model of trauma outcome.

***Project 2: Effects on neonatal exposure to drugs/chemicals during brain development***

**Participants:** Emma Pontén, Anders Fredriksson, Professor Per Eriksson and Henrik Viberg, researcher, Dept of Environmental Toxicology, UU, Professor Torsten Gordh, Dept Surgical Sciences.

Neonatal exposure to drugs/chemicals during brain development might be involved in the induction of psychiatric disorders. In the research we use a "neonatal animal model", which enables us to study the effects induced by low doses of drugs/chemicals during a defined critical stage of neonatal brain development in mice. We can study interacting effects between different agents when co-administered directly to neonatal animals, as well as the interaction between neonatal and adult exposure, in a controlled manner. Therefore, this animal model allows us to specify certain issues, which can be difficult to solve in both traditional neurodevelopmental studies and epidemiological studies. In this model we have shown that several drugs and environmental agents, though having differing mechanisms of action, can nevertheless cause the same functional disorder. This shows that functional disorders, measured with behavioural tests, in combination with neurochemical analyses, will provide a suitable endpoint for hazard identification of drugs/chemicals as well as finding safety periods/treatment of drugs in newborn and infants. Compounds currently under investigation are anaesthetics (propofol, ketamine), theopylline, caffeine, ethanol, diazepam, paracetamol, donepezil, nicotine and other agents in the environment.

***Project 3: Hazardous and harmful alcohol use among psychiatric patients. Development of secondary prevention efforts in routine psychiatric care***

**Participants:** Christina Nehlin Gordh, Anders Fredriksson, Leif Grönblad, Lennart Jansson

The general aim of this research project is to develop brief self-help interventions for psychiatric patients who are in an early stage of developing alcohol problems. Such secondary prevention efforts have been internationally tested, and found efficient, in primary care and somatic emergency care settings. Only a small number of studies have been reported from the psychiatric care setting, none of them from Sweden.

This research project has a pragmatic approach and intends to engage psychiatric staff in carrying out brief alcohol interventions. The studies are mainly quantitative. In a study of records, the impact of hazardous alcohol use on the utilization of health care will be examined. Staff attitudes to alcohol use will be investigated in connection with an education

in brief intervention. The prevalence of alcohol and substance use among psychiatric patients will be studied, together with the effects of brief alcohol intervention. In a qualitative interview study, patient experience of brief intervention will be explored from a gender perspective.

***Project 4: Implementation and outcome of the Illness Management and Recovery program for psychosis***

**Participants:** Rickard Färdig, Anders Fredriksson, Psychiatry, Tommy Lewander, Professor Lennart Melin, Dept of Psychology, UU

Schizophrenia is among the world top ten leading causes of disability. Today there are treatments to alleviate symptoms and improve functioning. A combination of medical and psychosocial interventions gives the best help to people suffering from the illness, and studies show that they can benefit from techniques included in the concept of *illness management.* Psychoeducation, cognitive behavioural therapy, social-skills training, relapse prevention, and behavioural tailoring for improved adherence to pharmacological regimens, are effective ways for people influencing the course of the illness. Unfortunately, only a fraction of people with schizophrenia have access to evidence-based psychosocial practices. To counteract this lack of evidence based practices, a comprehensive programme *Illness management and recovery (IMR),* was developed as a result of a national project in the USA. IMR consists of the above mentioned components, supported empirically, and with a focus on subjective recovery.

The aim of the present project is to implement and evaluate IMR through a randomized controlled trial at the UU Hospital. Forty participants with a diagnosis of schizophrenia or schizoaffective disorder have been randomized to either 'treatment as usual' or IMR in addition to 'treatment as usual'. The IMR programme last for about 9 months. Outcome is evaluated through measurement of symptoms and general functioning, prior to, after, and at 18 months and 27 months. The IMR groups are lead by mental health workers who have been trained in the method and who will receive weekly supervision throughout the study. After completing the program, participants are expected to show improvement in illness management, improvement in subjective recovery as well as a better understanding of schizophrenia.

***Project 5: Clinical psychiatric epidemiology***

**Participants:** Bodén Robert, Papadopoulos Fotios, Karamanis Georgios, Makris Georgios, Lisa Ekselius

**Collaborators:** Associate professor Johan Sundström, Professor Bertil Lindahl Dept of Medical Sciences, Jakob Hedberg, Magnus Sundbom, Surgical Sciences, UU, Tomas Jernberg, associate professor at Karolinska Institutet (KI). Dr Helle Kieler's psychopharmacology group at the Centre for Pharmacoepidemiology, KI, Dr Urban Ösby and Professor Claes-Göran Östenson Dept of Molecular Medicine and Surgery, KI, Professor Wolfgang Fleischhacker, Dept of Biological Psychiatry, Medical University Innsbruck, Innsbruck, Austria, Professor René Kahn, Dept of Psychiatry, Rudolf Magnus Institute of Neuroscience, University Medical Centre Utrecht, Utrecht, Netherlands, Professor Anders Ekbom, Deptof Medicine, KI.

Our project focuses on psychiatric epidemiology in severe mental illness, especially schizophrenia, bipolar disorder, anorexia nervosa and suicide. We investigate predictors of

both psychiatric and somatic longitudinal outcome. Our research projects encompass both clinical follow-up studies as well as national register-based studies.

Two cohorts of consecutive first-episode psychosis patients in Uppsala County have been followed up in order to study how baseline electrocardiographic measures of autonomic imbalance and neurocognition are associated with 5-year symptomatic remission and psychosocial functioning.

Severe mental illness and somatic comorbidity is another major track. We are using Swedish registers to study mortality and somatic outcomes in anorexia nervosa. Furthermore, we investigate differences in the care of metabolic syndrome related morbidity in patients with and without schizophrenia or bipolar disorder. Suicide seasonality and the role of psychotropic medications and climatic variables in its pathophysiology are investigated using register data including forensic data. Children with craniofacial disorders are followed-up using registers with focus on neuropsychiatric outcomes and severe mental illness. We also have several pharmacoepidemiology projects using the Swedish Prescribed Drugs Register, along with other registers. In these cohorts we study the impact of season and of antidepressant treatment initiation on suicidal behaviour, adherence and outcome in schizophrenia and the safety of psychotropic drug use, especially during pregnancy.

***Project 6: Emotional instability and impulsivity***

**Participants:** Mia Ramklint, Lisa Ekselius, Adriana Ramirez, Janet Cunningham, Fotis Papadopoulos, Maria Holstad, Martina Wolf, Dan Edvinsson, Ioannis Kouros, Linda Jüris, Niklas Hörberg

**Collaborators:** Professor Niklas Dahl, Dept of Immunology, Genetics and Pathology, Professor Gerhard Andersson, Dept of Behavioural Sciences and Learning, Linköping University, Hans Christian Larsen, Dept of Surgical Sciences, UU

Patients, who come for psychiatric assessment, often present with a clinical picture of emotional instability and impulsivity. Since they often have difficulty regulating their negative emotions, this can result in self-destructive behaviours such as self-harm, starvation, binge-eating, substance abuse or suicidal behaviours. Since problems with emotional regulation are common in patients with different clinical diagnoses it is likely they share some vulnerability. This vulnerability can be neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive or neuropsychological. This vulnerability might interact with specific environmental factors, creating different phenotypes or diagnoses.

Some psychiatric diagnoses with emotional instability share even more similarities with each other, such as ADHD, borderline personality disorder and bipolar disorder or anorexia nervosa, autism spectrum disorders and obsessive-compulsive disorder. The delimitations between these disorders, their common and shared etiology, and their pathophysiology are the focus of this project based on several minor projects.

The aims of this project are:

- to obtain further insights into diagnostic delimitations, common and shared etiologies and pathophysiologies in diagnoses characterized by emotional dysregulation and/or impulsivity
- to build up a psychiatric bio-bank with biological material from well characterized psychiatric patients
- to develop and validate diagnostic instruments that identify and discriminate between diagnoses characterized by emotional instability

- to develop new treatments targeting emotional dysregulation
- to develop and validate instruments measuring different aspects of emotional instability that are sensible to change during treatment
- to develop and validate methods for assessment of suicide risk and self-harm behaviours

The project is heavily integrated into the everyday clinical work of the Dept of General Psychiatry, UU Hospital, recruiting all participants from the clinic.

***Project 7: Uppsala Psychiatric Patient samples (UPP): Prospective Collection of Samples for the Study of Biological Mechanisms in Clinical Psychiatry***

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

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

UPP has been launched in conjunction with the Carolina project. In summary, the Carolina project entails that all new patients at General Psychiatry undergo the same complete systematic evaluation using a set of established tools for symptom evaluation and diagnostics. The test clinic, the "Psykiatrimottagningen för Unga Vuxna", UU Hospital, treats young adults between the ages of 18-25 with primarily affective and anxiety disorders. This clinic is a test base for the both UPP and the Carolina project and is ideal for the collection of well phenotypically characterized biological material for research. These models will be implemented broadly within the Dept of Psychiatry once the trial period has progressed.

***Project 8: A clinical trial comparing auricular acupuncture versus CBT in women suffering from insomnia***

**Participants:** Lena Bergdahl, Jan-Erik Broman, Lars von Knorring, Kristina Haglund, Agneta Markström.

**Collaborators:** Anne Berman, Jens Sörenssen, Lieuwe Appel

Auricular acupuncture, worked out by Paul Nogier 60 years ago, is worldwide a very common treatment for post acute alcohol abstinence. The evidence for the effectiveness of the treatment is not of high quality, according to some randomized trials. Over the last decades interest in using auricular acupuncture for substance dependence care has increased. The

specific auricular acupuncture protocol used follows the National Acupuncture Detoxification Association (NADA) definition.

In a paper in press 2012 the author describes patients' experiences of receiving auricular acupuncture during protracted withdrawal. Interviews were conducted with 15 patients treated at an outpatient clinic for substance dependence. Content analysis was used to analyse the interviews. The analysis resulted in seven categories of positive experiences and seven categories of negative experiences. The positive experiences were relaxation and well-being, peacefulness and harmony, new behaviours, positive physical impact, importance of context, anxiety reduction and reduced drug and alcohol consumption. The negative experiences were: nothing negative, disturbing context, short-term effect, depending on someone else, time-consuming, physical distractions and remaining cravings. The conclusion of this study is that all respondents appreciated auricular acupuncture treatment. This study supports further research on using auricular acupuncture in addiction treatment to reduce suffering during protracted withdrawal and in other contexts.

The object of our future studies are to evaluate whether auricular puncture is as effective as CBT in treating women suffering from insomnia who completed medication with non-benzoderivate. A lot of people are treated with non-benzodiazepines. They are effective for initiating sleep, but their prolonged use produces adverse effects similar to those observed with benzodiazepines.There is also some clinical evidence that auricular acupuncture may help in treatment of persisted insomnia. By using evaluated surveys to measure insomnia depression/anxiety, daytime sleepiness and quality of life evaluate improvement in insomnia symptoms during acupuncture and CBT. By using actigrafi and a sleep-diary we will objectively evaluate improvement in sleep quality.

Over the last few years, neuroimaging techniques have contributed greatly to the identification of the structural and functional neuroanatomy of anxiety and mood disorders. An additional aim of our research is to review neuroimaging studies investigating neural correlates during treatment of insomnia with auricular acupuncture and CBT.

***Project 9: Cognitive behavioural therapy for delayed sleep phase syndrome in young adults***

**Participants**: Katarina Danielsson, Jan-Erik Broman, Lars von Knorring and Agneta Markström.

**Collaborators**: Mats Stridsberg, Marcus Fröjmark-Jansson

The aim of our research group is to improve the diagnosing and the treatment of patients with Delayed Sleep Phase Syndrome (DSPS). We explore if Dim Light Melatonin Onset (DLMO) may better predict DSPS diagnosis compared to sleep diary. We aim to identify whether light therapy treatment improves if DLMO is used as a tool to set the time when treatment should be started in the morning. An additional objectiv is to investigate if cognitive behavioural therapy (CBT) decreases the risk of relapse after light therapy and what behavioural and cognitive factors may differ in persons with DSPS compared to a reference group.

By secretion of melatonin from the corpus pineale time information is forwarded to the entire human body. Melatonin is also the most reliable phase-marker of individuals' circadian rhythm. The DLMO has clinical implications and may be used for phase-typing patents with circadian rhythm disorders that are of importance in order to administer the treatment properly. CBT is commonly used and has evidence in treating insomnia, easy/moderate depression and anxiety. In persons with DSPS there are similar symptomatologies to thoses associated with insomnia, due to the fact that both groups have problems falling asleep. Our hypothesis is that CBT will be a good combination treatment for

patients with DSPS, but the light therapy is needed to first reset the diurnal rhythm. CBT may then help the DSPS patients to maintain their new diurnal rhythm and, by increased knowledge of sleep, prevent relapses.

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**Agencies that support the work/ Funding**

ALF
Ekhaga Foundation
The Fredrik and Ingrid Thurings Foundation
The Bror Gadelius Foundation
The National Stroke Foundation – Sweden
The Nicke and Märta Nasvell Foundation
The Swedish Research Council
The Söderström-Königska Foundation
The Swedish Society of Medicine
The Swedish Society for Sleep Research and Sleep Medicine
The Swedish Lundbecks Foundation

## *National Centre for Disaster Psychiatry*

**Group leaders: Per-Olof Michel, associate professor (1201-1211) and Mimmie Willebrand, associate professor (from 121201)**

**Members of the group during 2012**

Filip Arnberg, psychologist, PhD
Kerstin Bergh Johannesson, psychologist, Ph.D
Liselotte Englund, journalist, PhD, Post-doc
Ewa Johansson, research assistant
Tom Lundin, professor
Per-Olof Michel, MD, PhD, associate professor
Carin Nordenstam, social worker, PhD student
Lena Tillander, research assistant
Mimmie Willebrand, psychologist, PhD, associate professor

The National Centre for Disaster Psychiatry (KcKP) is a centre established and supported by the National Board of Health and Welfare, based at the Department of Neuroscience at Uppsala University, working in close collaboration with the Psychiatry department at Uppsala University Hospital. The main aim of the Centre is to extend our knowledge of the psychological and psychiatric effects of disasters and traumatic stress – from both a short and long term perspective. A second, related aim is to improve the preparedness of health care and society to meet the needs of those affected by severe accidents and disasters. Important outcomes are the prevalence of psychiatric disorders, primarily posttraumatic stress disorder (PTSD), affected general mental health and sick-leave. Factors studied are e.g. exposure to disaster in terms of geographical proximity, presence of life threat, physical injury, and loss of family members, and potentially contributing factors such as social support, personality traits and socio-demographic characteristics. The studies include a range of methods and study designs, e.g. registry-based studies, questionnaires, and in-depth interviews. Specific projects are listed briefly below.

***Project 1: Systematic follow-up and identification of persons at risk after a natural disaster***

Project leader: Kerstin Bergh Johannesson. Researchers: Filip Arnberg, Tom Lundin, Per-Olof Michel.

Collaborators: Professor Christina Hultman, Department of Medical Epidemiology and Biostatistics, Karolinska institutet, and MD PhD Abbe Schulman, CeFAM, Karolinska Institutet Huddinge.

This project concerns a longitudinal follow-up of Swedish survivors and home-staying relatives after the tsunami in South-East Asia in 2004. The large group of affected individuals creates a unique opportunity to study longitudinal effects of different exposure to a natural disaster. The database has rendered a series of publications.

***Project 2: Long-term effects of disaster trauma on mental health***

Project leader: Filip Arnberg. Researchers: Tom Lundin, Per-Olof Michel.

This project concerns longitudinal follow-ups of three disasters involving transportation: survivors of the m/s Estonia disaster up to 14 years afterwards, a twenty-year follow-up of school-children surviving the bus accident at Måbødalen in August 1988 and a 17-year follow-up of passengers surviving the air plane crash at Gottröra in December 1991. The project formed the basis for the PhD thesis of Filip Arnberg (2012).

***Project 3: Crisis support in the general emergency room.***

Project leader: Per-Olof Michel. Researchers: Filip Arnberg, Kerstin Bergh Johannesson.

This project concerns an inventory of resources and the state of knowledge concerning evidence-based crisis support in general emergency rooms around Sweden. The results are currently being processed.

***Project 4. Studies related to the Swedish twin registry***

Project leader: Filip Arnberg. Researchers: Kerstin Bergh Johannesson, Tom Lundin, Per-Olof Michel.

Collaborators: Professor Paul Lichtenstein, Department of Medical Epidemiology and Biostatistics, Karolinska institutet.

The main aim is to study psychiatric morbidity, treatment and cause of death among twins and siblings in the above-mentioned Tsunami cohort. The project is in a preparatory phase.

***Project 5: Treatment of sexually abused girls***

Project leader: Tom Lundin. Researcher: Carin Nordenstam.

This project concerns trauma-focused crisis-group treatment for underaged victims of rape in Stockholm County during 2008. Forty girls were randomized to the treatment group and compared with a control group treated as usual. Research questions are: What special needs do the victims and their parents have? Do medical services offer the right support at the right time? Does early treatment prevent mental health problems? Is group treatment valuable?

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2. Arnberg FK, Rydelius PA, Lundin T. A longitudinal follow-up of posttraumatic stress: from 9 months to 20 years after a major road traffic accident. Journal of Child and Adolescent Psychiatric and Mental Health. 2011;5(1):8.

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4. Bergh Johannesson K, Lundin T, Fröjd T, Hultman CM, Michel PO. Tsunami-exposed Tourist Survivors: Signs of Recovery in a 3-year Perspective. Journal of Nervous & Mental Disease. 2011; 199(3):162-169.

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**Reviews and books 2010-2012**

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2. Michel PO, Bergh Johannesson K, Lundin T, Nilsson D, Otto U. Psykotraumatologi. Lund: Studentlitteratur, 2010.

3. Bergh Johannesson K, Michel PO, Lundin T. Crisis support following disasters/serious events. In S. Lennquist (Ed.). Medical response to major incidents and disasters: A practical guide for all medical staff. Berlin, Heidelberg: Springer-Verlag. 2012 p. 363-377.

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**Agencies that support the work/ Funding**

ALF
The National Board of Health and Welfare

# Child & Adolescent Psychiatry

**Introduction**

Research within the unit is closely connected with clinical child and adolescent psychiatry at Uppsala University Hospital, where about half of the researchers are employed. Four senior researchers have reached associate professor level, and a further nine have obtained a Ph D degree. Five doctoral students are active in the unit. Our research is performed within six groups/themes: Affective disorders; Foetal and childhood developmental aberrations; Childhood Trauma; Clinical intervention; Psychophysiology and mental health; Child psychiatric epidemiology.

## *Affective Disorders*

**Group leader: Anne-Liis von Knorring, Professor emerita**

**Members of the group during 2012**

Hans Arinell, Statistician
Hannes Bohman MD, PhD
Ulf Jonsson, PhD
Gunilla Olsson MD, PhD
Aivar Päären MD, doctoral student
Anne-Liis von Knorring, Professor emerita
Lars von Knorring, Professor emeritus

**Collaboration**

Tord Næssén, Professor, Department of Women's & Children's Health, Uppsala University; Agneta Siegbahn, Professor, Department of Medical Sciences, Uppsala University

**Publications 2010-2012**

1. Bohman H, Jonsson U, Päären A, von Knorring A-L, Olsson IG, von Knorring L. Long term follow up of adolescent depression. A population based study. Upsala Journal of Medical Sciences, 2010, (115):21-9.

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depressive disorders. A pilot study using noninvasive high frequency ultrasound. World J Biol Psychiatry 2010, (11):71-5.

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**Other publications from the research network of Anne-Liis von Knorring 2009-2011**

1. Hartzell M, Seikkula J, von Knorring A-L. Parent's Perception of Their First Encounter with Child and Adolescent Psychiatry. Contemp Fam Ther 2010, (32):273-89.

## *Fetal and Childhood Developmental Abberations*

**Group leader: Viveka Sundelin Wahlsten, Associate professor**

**Members of the group during 2012**

Birgitta Johansson Niemelä, Psychologist, PhD
Viveka Sundelin Wahlsten, Psychologist, PhD

**Collaboration**: Gunilla Cardell Doctoral student, psychiatric social worker, registered at Dept of Clinical Neuroscience KI; Gunilla Hallberg, MD PhD, Dept of Women's and Children's Health, Uppsala University; Anders Helander, professor, Dept of Clinical Neuroscience, KI; Tor-Göran Henriksson, MD, Associate professor, Dept of Surgical Sciences, Uppsala University; Lars Oreland, professor, Dept of Neuroscience, Uppsala University; Maj-Liz Persson, MD, Associate professor Dept of Neuroscience, KI; Ihsan Sarman, Associate professor, Dept of Women and Children´s Health, KI; Valdemar Skoog. MD, Associate professor, Dept of Surgical Sciences, Uppsala University;

***Project II:1. Alcohol Consumption among Pregnant Women in a Swedish sample and its Effects on the Newborn Outcomes***
*Viveka Sundelin Wahlsten, Gunilla Hallberg, Lars Oreland, Anders Helander*

This project is a broad interdisciplinary study, involving several departments at the University of Uppsala and the University of Stockholm, with the purpose of investigating the role of prenatal alcohol, genetic inheritance and psychosocial environment for neuropsychological development in children. Regular FAS syndrome with anatomical features is relatively rare and little is known about the effect of maternal alcohol use for neuro-psychological development, wich is not necessarily being recognized by showing pathological dimensions (FASD). The study started from the work of the National Guidelines. A pilot study on analysis of alcohol markers EtG in hair samples has begun. These tests are now available to Anders Helander at the Karolinska Institute in Stockholm. A review and analysis of the Copyright VSW;'s "Infant and preschool Child Behaviour and Development Questionnaire" has now begun.

**Publication**

Comasco E, Hallberg G, Helander A, Oreland L, Sundelin-Wahlsten V. Alcohol consumption among pregnant women in a Swedish sample and its effects on the newborn outcomes. Alcohol Clin Exp Res. 2012;36:1779-86.

***Project II:2. Neurobehavioral developmental profile at preschool age in children exposed for Buprenorphine***
*Viveka Sundelin Wahlsten, Ihsan Sarman*

Buprenorphine maintenance treatment (BMT) was introduced in Sweden 1999, first in the Stockholm region, and the number of pregnant heroin dependent women who have been treated with methadone has successively decreased, while treatment with buprenorphine has become more frequent. All children of pre-school age, born to opiate dependent women from Stockholm County treated with buprenorphine maintenance during pregnancy,in 2001, 2002

and 2003 at the Karolinska University Hospital, Huddinge were invited for investigation by neuropsychological tests at 4.5-5.5 years of age. The aim of the present study is to examine the neuropsychological development of infants exposed to buprenorphine during foetal life in the era of BMT in Sweden. One manuscript has been submitted during 2012: Sundelin Wahlsten V, Sarman I, Neurobehavioral development of preschool age children born to addicted mothers given opiate maintenance treatment during pregnancy.

***Project II:3. Addiction and Psychiatric Diagnosis among Pregnant Women and the effect on the new-born***
Gunilla Cardell, Maj-Liz Persson, Viveka Sundelin Wahlsten

This project is about pregnant women with drug and / or alcohol addiction to mental illness and the effect on newborns. Data collection is ongoing at the Rosenlunds Maternal Clinic in Stockholm.

**Agencies that support the work, Funding**

Systembolagets råd för alkoholforskning (SR)
Project grant, Stockholms Läns Landsting 2011

## *Childhood Trauma*

**Contact person: Abdoulbaghi Ahmad, MD, PhD, Associate Professor**

**Members of the group during 2012**

Abdoulbaghi Ahmad, MD, PhD, Assoc. Professor
Nezar Ismet Taib, MD, doctoral student
Frank Lindblad, professor

Collaboration with the University of Duhok in the Kurdistan Region of Iraq been in place since 1991, producing child mental health professionals at three levels since 2001. The sixth Master thesis was successfully defended on 5th April 2012 concerning *Autism among children in Duhok*. One PhD student is struggling in the first year of his research plan about *Street children in Duhok*, and two other PhD research plans are ready for application. They concern *Conversion among children in Kurdistan*, and *Fainting among children of Duhok*, respectively.
The collected data from the *Child Center Trauma and Psychosocial Exposure (Maskrosen)* concerning traumatized and psychosocially exposed children continue to produce interesting results. Applications for funding regarding a research plan to *compare EMDR with CBT for treatment of PTSD in children* are ready to be prepared. Another research plan concerning *Risk and protecting factors in development of PTSD among children with cancer.* Request has been received from several international researchers to include our RCT on EMDR for children with PTSD and the child specific EMDR protocol in meta-analysis studies. Other researchers have requested permission to use our trauma instruments (Genogram, HUTQ-C and PTSS-C) in their studies. An international network for researchers on Childhood Trauma has been established, and the contact person has been appointed as a member of the IACAPAP Ambassadors network.

Collaboration has been started with Steven Lucas, the Head of Child Care System at the Uppsala Children's Hospital to start a study for early identification and management of children at risk during their ordinary visits to a Child Care Centre. An application for funding has been submitted to the Public Health Institute.
Frank Lindblad has been involved in a study on child physical abuse together with Gabriel Otterman, Medical Director, Child Protection Team, Uppsala Children's Hospital and Katrin Lainpelto, lawyer, PhD and researcher at the Faculty of Law, Stockholm University. The study aims at examining whether case characteristics such as the severity of the alleged abuse influence criminal investigative procedures and judicial outcomes. Submission is planned for early 2013. Funding from Brottsofferfonden (Crime Victim Fund, applicant Katrin Lainpelto) allows for a continuation of a study published in 2011 (Lindblad & Lainpelto, publication 12 under "Psychophysiology and mental health") and a more deep-going analysis of child sexual abuse in children with neuropsychiatric disorders.

**Publication**

Ahmad A. *Time is not healing all the wounds, psychosocial and biological risk factors in childhood*. In Ekman R & Arnetz B (red.), Stress, molecules, individuals, organisations and society (in Swedish language), 2011 (in press).

## *Clinical Intervention*

Projects related to the Child and Adolescent Psychiatry at Uppsala University Hospital

***Project IV:1 Follow-up of patients treated for eating disorder***

**Members of the group during 2012**

Agneta Rosling
Helena Salonen Ros

The Eating Disorder unit in the Dept of Child and Adolescent Psychiatry, Uppsala University Hospital, provides the only specialised treatment facility for Eating Disorders in the county. A treatment program, based on cognitive behavioural therapy, was introduced in January 2002. The treatment is in an out-patient and day-care setting with a multidisciplinary team including adolescent psychiatrists, paediatricians, family therapists and specialised nursing staff. Treatment includes motivational sessions, mealtime support followed by bed rest, and scheduled sessions with the nursing staff for problem solving as well as parental support and training. Follow-ups are continuously performed including analyses of biological markers. In an on-going project – directed by Samanta Brooks and Helgi Schiött - adolescents with eating disorders are recruited for functional neuroimaging.

**Collaboration:** Assoc. professor Ingemar Swenne, department of women & children's heath, Uppsala University; Professor Helgi Schiött, Section of Functional Pharmacology at our department; Samantha Brooks, PhD, postdoc, Section of Functional Pharmacology at our department.

### Publications

Swenne I, Rosling A. Do thyroid hormones mediate the effects of starvation on mood in adolescent girls with eating disorders? Psychoneuroendocrinology. 2010, 35:1517-24.

Swenne I, Rosling A, Tengblad S, Vessby B. Essential fatty acid status in teenage girls with eating disorders and weight loss. Acta Pediatr. 2011,100:762-7.

Rosling A, von Knorring A-L, Norring C, Sparén P. Mortality of Eating Disorders in Swedish specialist care. A proposal for staging of severity in Anorexia Nervosa. Int J Eating Disorders. 2011, 44:304-10.

Swenne I, Rosling A, Tengblad S, Vessby B. Omega-3 polyunsaturated essential fatty acids are associated with depression in adolescents with eating disorders and weight loss. Acta Paediatr. 2011, 100:1610-5.

Swenne I, Rosling A. No unexpected adverse events and biochemical side effects of olanzapine as adjunct treatment in adolescent girls with eating disorders. J Child Adolesc Psychopharm, 2011, 21:221-7.

Swenne I, Rosling A. Omega-3 essential fatty acid status is improved during nutritional rehabilitation of adolescent girls with eating disorders and weight loss. Acta Paediatr. 2012 Aug;101(8):858-61.

***Project IV:2. Psychosomatic and somato-psychic processes***

### Members of the group

Birgitta Johansson Niemelä, licensed psychologist, PhD
Barbro Thurfjell, MD, PhD

In this research we study the interplay between psychological and somatic factors. On one side, psychological factors may contribute strongly to the development of somatic symptoms, psychosomatics. On the other side, somatic conditions and symptoms may evoke psychological reactions. Both factors, which may be intertwined, may call for professional intervention.

***Mental Health in Children Undergoing Reconstructive Surgery: Studies on Self-Esteem and Social Interaction****. (Birgitta Johansson Niemelä, Valdemar Skoog, Tor-Göran Henriksson, Björn Tjernström, Viveka Sundelin Wahlsten)*
Studies on orthopaedic and other surgical treatments demonstrate that psychological problems are associated with lengthy procedures, lack of information and support to parents, lack of counselling to patients and parents, maladaptive coping behaviour, and child surgery at an inappropriate developmental level. However, cognitive ability is considered as a protective factor in studies of children at risk. Lower levels of reported parental stress were also related to better social skills in a child. Children´s reactions to reconstructive surgery in general have not been studied to any great extent.

A follow up study of patients with leg length inequality who have undergone leg lengthening has been completed: 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 years follow-up.

**Publications**
Niemelä Johansson B, Skoog V, Henriksson T-G, Sundelin-Wahlsten V. A Clinical Report: Mental Health, Self-esteem and Social Interaction in Adolescents with CL/P in the Context of Reconstructive Surgery. J of Depression & Anxiety. 2011. 1:102

**Funding during 2012**
Project funds Stockholm County Council 2012.

***Disorder of sex development patients (DSD) (****Birgitta Johansson Niemelä)*
A multicentre study (Stockholm, Uppsala, Göteborg and Lund) initiated by professor Agneta Nordenskjöld at KI. Children with DSD will be followed in a prospective study with an interdisciplinary perspective: surgical; endocrinological; genetic and psychological/psychiatric.

***Project IV:3 Neuropsychiatric disorders***

**Members of the group**

Najah Khalifa

**Collaboration:** Professor Niklas Dahl, department of genetics & pathology, Uppsala University; Associated professor Karin Edebol, department of neuroscience, clinical neurophysiology, Uppsala University; Professor Ann-Margret Rydell, department of psychology, Uppsala University.

***Tourette syndrome***
Tourette syndrome (TS) is common (about 1%) among primary school children. Most affected children also suffer from other neuropsychiatric disorders and poor self-esteem, and school failures are common. Diagnosis is important for early intervention. Several studies are in progress:
1. We want to map the potential genetic significance for the development of neuropsychiatric disorders in children, with a focus on Tourette syndrome. Genetic and environmental factors play a role in the aetiology of TS, but the exact causes are unknown. This study is designed to learn more about why TS, and related tic disorders, may occur more commonly in some families than others.

2. Treatment with repetitive transcranial magnetic stimulation (rTMS) for adolescents (15-19 years of age) with severe TS with the aim of reducing the intensity of the tics.

3. About 80% of children with TS have learning difficulties that require some type of support at school. We want to determine the frequency and describe the learning disabilities (LD) of children with TS with and without attention deficit hyperactivity disorder (ADHD). We aim at studying psychosocial, psychoeducational, and neuropsychological data from children 7-15 years of age. Two groups: TS only and TS plus ADHD.

4. We have received ethical approval for a planned study on treatment with repetitive transcranial magnetic stimulation (rTMS) for adolescents and adults with depression with the aim of reducing the intensity of the depressive symptoms.

***Sleep and neuropsychiatric disorder***
Sleep disorders are common in both children and adults with neuropsychiatric disorders. The underlying causes of these sleep disturbances are not fully understood. Pharmacological treatment that can normalize sleep without inducing short- or long-term adverse effects is important for many of these patients. Melatonin has well-known beneficial effects and has been used previously in Sweden. However, the Swedish Medical Products Agency today only grants licenses for a slow-release preparation of melatonin, which seems to be less efficient in children. One study of the Swedish current prescription pattern is in progress, also investigating treatment duration, effects and side effects in children and adolescents.

**Publications**

Khalifa N, Dalan M, Rydell AM. Tourette syndrome in the general child population: cognitive functioning and self- perception. Nord J Psychiatry 2010, (64):11-8.

***Project IV:4. Psychotherapy research and emotion regulation***

**Members of the group**

Martina Wolf, PhD, group leader
Andreas Claesson
Martina Datavs Johansson
Martina Hedman
Åsa Nyström

***Project1:***
Dialectical Behaviour Therapy (DBT) was originally developed by M. Linehan for patients with Borderline Personality Disorders (BPD). Standard DBT consists of individual therapy, group skills training, telephone coaching and team consultation meetings. Mindfulness practices are integrated in the treatment. In several RCTs concerning treatment of BPD, DBT was associated with better outcomes in the majority of clinical measures compared to the control condition, such as a reduction of impulsive suicide attempts, self-harm, drug consumption, psychiatric hospitalization, psychiatric emergency visits and treatment drop-out rate. In 2011, the DBT-team at the Uppsala University Hospital started a pilot study evaluating a DBT-group including skills training, psycho-education and chain analyses of dysfunctional behaviour (duration: 16 sessions) for patients with Bipolar Disorders (BD). In a small randomized trial, the DBT-group showed improved levels of mindfulness and reduced levels of depression compared to the treatment-as-usual-group (TAU). A second pilot study with an improved treatment manual will start in 2013. A larger RCT is planned to start during 2013/2014.

***Project 2:***
The DBT standard protocol was further developed and additional components added to target over control by Prof. Tom Lynch. Prof. Lynch has already showed that DBT targeting over control (DBT-OC) is effective in the treatment of chronic and treatment resistant depression. In DBT-OC, the depression is viewed as a consequence of problems related to over-control,

meaning that the person avoids critical and negative emotions by trying to achieve a complete control over his or her life. In contrast, Prof. Lynch suggests that OC can trigger both depression and anorexia.
The DBT-team at the Uppsala University Hospital has co-operated with Prof. Lynch for several years and is currently setting up a team offering DBT-OC to patients with anorexia nervosa. The treatment will also be evaluated in a pilot trial, in preparation for a larger RCT in 2014/2015.

***Project 3:***
Soundless singing is a new strategy to help patients: 1) relax: 2) increase positive emotions: and, 3) normalize breathing during arousal and negative emotional reactions. The strategy has already been evaluated in Germany with promising initial results in a first small trial. During soundless singing, the patient is asked to think of and sing a certain song, but without producing any sound. The song should be connected with positive emotions.
BPS-patients participating in standard DBT will be offered a new relaxation strategy called soundless singing as an add-on-intervention. The DBT+add on-group will then be compared with the standard-DBT-group (without add on intervention) regarding self-efficacy and the ability to relax. This study will start in 2013.

***Project IV:5. Barnahus as a communicative activity***

**Members of the group**

Monica Hartzell
Siamak Noroozy

Background. Barnahus is an interdisciplinary activity in which were the juridical system, the social services and the health services collaborate for the best benefit of children, who are or are suspected of being victims of crime. The child is interrogated/interviewed by an interviewer from the police. The child's story is fundamental to the legal process as well as for identifying the child's need for help and protection. The possibilities the child has to express her-/himself place limits on the data available for making further decisions.

Aim. The project aims at studying how the child and the interviewer orient themselves to handle the interaction in three speech situations: the beginning, the introduction of questions about difficult experiences, and the end.

Method. The analysis method is based on CA (conversation analysis), which means the interaction during the interviews is studied in detail, concentrating on the interviewer's and the child's utterances and actions connected to building a relation, mutual understanding and creating meaning. Factors like initiative and response to an initiative from one of the participants are noticed along with utterances and body language expressing rapprochement or rejection. The context is analysed with respect to discourses connected to the child and the interviewer respectively.

## *Psychophysiology and Mental Health*

**Contact person: Frank Lindblad, Professor**

**Members of the group during 2012**

Åsa Hogmark, Master of Public Health, research assistant
Johan Isaksson, licensed psychologist, doctoral student
Malena Ivarsson, doctoral student (registered at Stockholm University)
Frank Lindblad, MD, PhD
Carl Lindgren, MD, PhD
Jackie Swartz, MD, doctoral student

**Collaboration**

Professor Marie Allen, Department of Immunology, Genetics and Pathology, Genomics; Researcher, M.D. Johan Alm, KI; Professor Jan Gustafsson, Department of Women's and Children's Health, Uppsala University; Professor Anders Hjern, CHESS, Stockholm University; Professor Ulf Högberg, Department of Women's and Children's Health, Uppsala University; Ass. Professor Lene Lindberg, KI; Professor Kent Nilsson, Centre for Clinical Research, County of Västmanland, Professor Fred Nyberg, Faculty of Pharmacy, Uppsala university; Professor Göran Pershagen, KI; Professor Finn Rasmussen, KI; Professor Ralf Reintjes, Hamburg University of Applied Sciences; Professor Annika Scheynius, KI; Professor emer. Töres Theorell, Stress Research Institute, Stockholm university; Professor Bo Vinnerljung, Department of Social Work, Stockholm university; Professor Torbjörn Åkerstedt, Stress Research Institute, Stockholm university: Ass. Professor Viveca Östberg, CHESS, Stockholm University.

This research forms part of a programme established in April 2008 with a grant from the Swedish Council for Working Life and Social Research. The aim of the programme is to investigate the ***interplay between genetic and environmental vulnerability in the development of psychological symptoms/psychiatric disorders***. Various methods are applied: psycho-physiological methods (saliva cortisol, heart rate variability, and activity/motions), epidemiological methods (using the Swedish national registers with data on health, child welfare and socioeconomic indicators); genetic analyses (SNP – Single Nucleotide Polymorphism); qualitative methods (for interview data and legal documents). Two epidemiological and two psycho-physiological studies (cortisol in relation to ADHD and to life style) have been published during 2012. One publication from the group concerns how young adolescents perceive dental malocclusion: presented together with other research concerning “Clinical intervention”.

**Epidemiology**. One register study comprising 13 368 individuals born and raised as twins demonstrates that the educational and vocational careers for twins in Sweden who survive infancy are as good or - for educational outcomes - even slightly better, than for those born as singletons. Male twins and twins with co-twins of the same sex gain an educational advantage from being raised as a twin. The comparatively small differences between twins and singletons support the common practice of drawing conclusions from twin analyses in respect of singletons.
Another register study investigated educational outcomes from compulsory school for

447 929 children born during 1973-1977. School performance was found to be an important mediator through which parental socioeconomic status translates into a risk for non-fatal suicidal behaviour, demonstrating the health promoting potential of educational interventions.

**ADHD**. The first report from our study on HPA-axis functioning in children with ADHD-symptoms (the focus of the doctoral studies of Johan Isaksson) was published during 2012, demonstrating substantially lower saliva cortisol levels than comparisons, at waking-up and 30 minutes later and also in the evening. Subtype of ADHD and co-occurring symptoms did not affect the cortisol levels. The low levels may be related to the hypothesized under-arousal possibly underlying several of the core symptoms of ADHD. A manuscript on early (foetal or during first six years of life) exposure to adversities is pending and one manuscript concerning the associations between ADHD-medication and cortisol levels has been submitted. Genetic and metabolic studies are in progress. Frank Lindblad has been invited by the British Science Network - in co-operation with Aarhus University and Professor Michael Rutter from King´s College in London - to present the epidemiological studies on ADHD together with professor Anders Hjern (CHESS, Stockholm University and KI) at an international workshop in Aarhus (publications 1,6,8,13 and 14).

**Life style**. An anthroposophic lifestyle protects against developing allergy during childhood. This finding has been the starting point for a research program directed at finding the components that mediate this preventive capacity. Our contribution is to investigate stress-related issues. As a part of the doctoral studies of Jackie Swartz, one article has been published during 2012: Evening cortisol levels in children from anthroposophic families were lower than in comparisons at 12 months of age and at 24 months of age also in the afternoon. At age 12 months the differences in the evening cortisol were statistically explained by a meat-free diet and at age 24 months by the anthroposophic life style as such. Components of the anthroposophic environment may thus have a health promoting influence, at least partly mediated via the HPA-axis. Analysis of Sense of Coherence in relation to life style are in progress.

**Violent gaming**. In this research we have applied another psycho-physiological approach measuring Heart Rate (HR) and Heart Rate Variability (HRV). The regulating systems of the heart differ in time between activation and inhibition (i.e. cycle time). These cycle times can be extracted into different frequency bands, which have been found to correspond to different parts of the Autonomous Nervous System (ANS). One of these parts is anatomically and neurophysiologically linked to social communication via regulation of the striated muscles of the face and head, which underlie, for example, eye gaze, facial expression, listening and prosody. It also has the capacity to dampen the HPA-axis. We have studied reactions to violent and non-violent TV-gaming in naïve versus experienced gamers (boys, 13–15 years of age) (Ivarsson et al, submitted). The boys were invited to play two different games (violent and non violent game) on two different occasions in their homes. The manuscript – the final part of the doctoral thesis of Malena Ivarsson – is pending.

**Fetal and recent exposure/s to maternal stress (Nicaragua).** This project is directed by Professor Ulf Högberg, Department of Women's and Children's Health, Uppsala University. The overall purpose is to answer the question of the importance of perinatal exposure for children´s cognitive and emotional development in relation to adaptive and supportive environment during childhood. Our group is primarily involved in the branch addressing HPA-axis regulation of the children in relation to foetal and recent exposure/s to psychosocial

environmental challenges, particularly maternal exposure to intimate partner violence. Data has been collected and analyses will be performed during 2013.

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**Agencies that support the work/ Funding**

Swedish Council for Working Life and Social Research
Swedish Brain Foundation

## *Child Psychiatric Epidemiology*

**Contact person: Vladislav Ruchkin, Associated Research Scientist**

**Members of the group**
Vladislav Ruchkin

**Collaboration:** Elena Grigorenko, Yale University; Roman Koposov, Child Psychiatric Unit, Tromsö University; Denis Sukhodolsky, Yale University**;** Lars Oreland, University of Uppsala;
Britt af Klinteberg, Stockholm University;

This research program - integrated into the research of Child & Adolescent Psychiatry at Uppsala University during 2012 - aims at assessing epidemiological aspects of an adverse environment and its impact on social competence and adjustment in children. The collaborative studies that conducted in the framework of the program are described below based on the types of populations involved in the studies (juvenile delinquents, pre-school children, adolescents from the general population, high-risk children (e.g. children of the street, children from isolate populations).

Several large studies address the prevalence of psychopathology and recidivism in juvenile offenders. To date, the database on the prevalence of psychiatric disorders in Russian juvenile delinquents is one of the largest in the world, with over 400 youth assessed by means of semi-structured psychiatric interview (K-SADS), as well as by use self-reports and teacher reports. Another research project related to antisocial behavior in youth includes a collaborative study of effectiveness of social problem solving training in detained juvenile delinquents State of Connecticut, USA (in collaboration with Dr. Elena Grigorenko, Yale University).

Two large epidemiological studies with younger children were conducted. The first study has focused on the developmental precursors of behavior problems in Russian preschool children (1.5-4 years old, N=800), based on extensive self-reports from mothers. The second study assessed the role of institutional environment for attachment and social-emotional development in children from Russian orphanages (1-3 years old, N=150) that included a detailed developmental assessment of children, including the data on attachment, socio-emotional and cognitive development and behavior problems. Information was collected from multiple informants. The long-term outcomes of early placement in an institutional environment has been further investigated in a collaborative study of 'Risk and protective factors for the development of learning disorders in children adopted from Russia: a multi-group comparison' (with Dr. Elena Grigorenko, Yale University).

A large epidemiological survey of students from the general population (13-17 years old), the Social and Health Assessment (SAHA) was conducted in several countries (Belgium, Czech republic, Gambia, Germany, Iran, Japan, Korea, Lithuania, Mexico, Netherlands, Russia, Surinam and the US). The study focuses on the prevalence of problem behaviors, both internalizing and externalizing, as well as family and school environment, and involved 1,000-3,000 students at each site (the data are being analyzed).

Other collaborative research projects included an assessment of effectiveness of cognitive-behavioral therapy for posttraumatic stress in street children in Mexico city (in collaboration

with Dr Janet Szydlo), and epidemiological study of the phenotypic and etiological overlap between disorders of spoken and written language in an isolate population in Northern Russia (in collaboration with Dr. Elena Grigorenko, Yale University).

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## *Experimental Neuroscience*

## Developmental Genetics

### *Formation and Function of Neuronal Circuits*

**Group leader: Klas Kullander, Professor**

**Members of the group during 2012**

Chetan Nagaraja, PhD student
Christiane Peuckert, Post doc
Fatima Memic, PhD student
Hanna Pettersson, Post doc
Hanna Wootz, Post doc
Johan Zelano, Post doc
Kalicharan Patra, PhD student
Katarina Leao, Post doc
Katarzyna Rogoz, PhD student
Martin Larhammar, PhD student
Martina Blunder, Post doc
Sharn Perry, PhD student
Siv Strömberg, Technician
Tomas Sandberg, Post doc

We are interested in the function of neuronal circuits in the central nervous system. Our goal is to increase knowledge of how neuronal networks develop into functional units.

Neuronal circuits are essential components of the nervous system and determine various body functions. In a screen of genes expressed in the ventral spinal cord we identified ERRβ and Chondrolectin as putative markers for slow and fast motor neurons (JCN, 2010). The Renshaw cells are inhibitory interneurons located in the ventral horn of mammals that mediate recurrent inhibition of alpha motoneurons. We have identified a genetic marker for this cell population, which opens the possibility of performing genetic modifications of the whole population and of studying the role of these cells in spinal neuronal networks. The group has succeeded in producing and characterizing a transgenic mouse line that expresses Cre in Renshaw cells. By using the Cre-loxP system we can now specifically label and/or disrupt the Renshaw cells in mice to examine their role in spinal neuronal circuits. To visualize activity of the Renshaw cells, and the neighbouring motor neurons, we have devoted substantial energy and resources into the development of a novel imaging system for spinal cord neurocircuitry, which is now working based on custom-built 3D two-photon microscopy.

The set-up is combined with electrophysiological ventral root recordings to allow for simultaneous recording of motor output and interneuronal activity. The spinal cord is well suited for this approach since the penetration of two photon microscopy covers the entire tissue depth of interest. After application of Ca2+ sensitive dyes, we are able to detect two fluorescent signals reporting Ca2+ entry in Renshaw cells together with ventral root motor activities.

Glutamate is the main excitatory neurotransmitter in the central nervous system (CNS), and plays vital roles in normal brain function, including pain perception, neuronal plasticity, learning, and memory formation. Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease that primarily affects motor neurons. We have genetically reduced Vglut2 in mice that develop ALS, and analyzed the result with respect to disease onset, life span and survival of different types of motor neurons. In a recent publication we describe how motor neurons are to some extent rescued whereas life span is not (Neurobiology of Disease, 2010). Moreover, we have crossed Vglut2-lox mice with Cre-mice deleting VGLUT2 protein from different components of the sensory pathways involved in pain and itch signalling. We have successfully generated several different Cre/Vglut2 lines; one that targets the dorsal root ganglia and one that affects catecholaminergic neurons. We have performed various pain studies on these mouse lines, and concluded that the latter display a significant decrease in acute thermal pain sensitivity as well as inflammatory pain perception. These knockout mice also display an increased spontaneous itch frequency, a phenotype that we were able to reverse by administration of the TRPV1 agonist capsaicin (Neuron, 2010). We have also investigated mice that lack Vglut2, specifically in NAv1.8 neurons, and show that such mice display a significant decrease in acute mehanical pain sensitivity but no increase in their spontaneous scratch frequency. The inflammatory pain was normal; however, when treated with substance P antagonists, the inflammatory pain decreased significantly demonstrating a clear role for substance P mediated signalling in inflammatory pain (PNAS, 2011).

We have recently discovered that a novel member of the solute carrier co-transporter family is exclusively expressed in the presynaptic vesicles of cholinergic and monoaminergic neurons. We have named this transporter vesicular aminergic-associated transporter, VAAT, to reflect its location in presynaptic vesicles and its exclusive expression in aminergic neurons of the brain. Most people have heard of, and understand, the aminergic systems of the brain through common drugs such as Prozac, nicotine, cocaine and amphetamine and through Parkinson's and Alzheimer's disease, two of the disorders of the brain related to dopamine and acetylcholine. As a surprising twist to this story, the other members belonging to the same family as VAAT are bile acid transporters found in the gut. Thus, functions shared by the bile system and the brain, has the capacity to modulate our behaviour. The discovery of the VAAT transporter also raises the possible presence of a so far undiscovered neurotransmitter. To explore its function and its transporter substrate, we have established a colony of VAAT knock-out mice. Using this and other tools we have generated behavioural, immunohistochemical and electron microscopy data that has been of considerable value in answering our questions regarding its function in the nervous system.

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**Agencies that support the work/ Funding**

Swedish Medical Research Council
Royal Swedish Academy of Sciences
Quality and Renewal UU
Göran Gustafsson foundation
Swedish Brain Foundation
Hållsten Foundation

## *Neurocircuitry of the Basal Ganglia*

### Group leader: Åsa Mackenzie, Associate Professor

### Members of the group during 2012

Anna Andrén, Graduate student
Carolina Birgner, Post doc
Casey Smith, Post doc
Emelie Perland, Graduate student
Emma Arvidsson, PhD student
Ernesto Restrepo, Post doc
Johan Sandell, Graduate student
Julia Pedersen, Graduate student
Karin Nordenankar, PhD student
Nadine Schweizer, PhD student
Stefano Pupe Johann, PhD student
Thomas Viereckel, Graduate student

### External Collaborators

***Sweden and Denmark:*** Klas Kullander, Richardson Leao, Håkan Hall, Malin Andersson, all UU; Lars Olson (KI), Åsa Fex Svenningsen (Odense), Martin Lundblad (LU).

***US, Canada and Japan:*** Louis-Eric Trudeau (STINT-funded) (Université de Montréal, UdeM, Laurent Descarries (UdeM,) Daniel Levesque (UdeM), Salah El Mestikawy (McGill), Marisela Morales (NIH), Thomas Knopfel (Riken Institute), Greg Gerhardt (Kentucky University).

Our research group is interested in understanding how specific neuronal circuits in the brain regulate behaviour of relevance to psychiatric conditions, such as schizophrenia and substance dependence, as well as aspects of tremor disorder, e.g. Parkinson´s disease. Common to these behaviours is regulation by interacting dopamine- and glutamate-signalling neurons in the basal ganglia, as well as component of transmitter co-release. Our research goal is to advance knowledge of neuronal circuits that use glutamatergic and dopaminergic neurotransmission, as this may be of importance from a therapeutical point of view. Dopamine-signaling neurons act as major modulators of brain function, mainly via projections from the midbrain to subcortical, cortical and limbic structures. Within these structures, dopamine is involved in the control of voluntary movement and also cognitive and affective behaviour. Dopamine is also a key component of the brain reward system. The functional role of dopamine is often linked with the actions of glutamate, the main excitatory neurotransmitter of the brain which is present in most neuronal circuitries. The critical modulatory roles of dopamine in the brain often involve regulation of, or by, glutamatergic signaling. We are specifically interested in extending the current understanding of both dopaminergic and glutamatergic neurons in the ventral midbrain, as well as the newly described type of neurons that possess a glutamate/dopamine cophenotype. Another specific target area is the subthalamic nucleus, which is essential for basal ganglia function. By using mouse genetics and optogenetics in combination with studies of anatomy, gene expression, pharmacology, in vivo transmitter release, and behaviour, we target the function of specific neuronal circuits in the basal ganglia.

## Publications 2010-2012

Fortin G, Bourque JM, Mendez A, Leo D, Nordenankar K, Birgner C, Arvidsson E, Rymar V, Anne-Claveau M, Descarries L, Sadikot A, **Wallén-Mackenzie Å** and Louis-Eric Trudeau. Glutamate corelease promotes growth and survival of midbrain dopamine neurons. J Neurosci 2012, Nov 28;32(48):17477-91.

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Lagerström MC, Rogoz K, Abrahamsen B, Perssson E, Nordenankar K, Ölund C, Smith C, Mendez JA, Reinius B, Chen C-F, Wood JN, **Wallén-Mackenzie Å**, Kullander K. VGLUT2- dependent sensory neurons in the Trpv1 population regulate pain and itch. Neuron, 2010, Nov 4:68(3):529-42.

Birgner C, Nordenankar K, Lundblad M, Mendez JA, Smith C, leGreves M, Olson L, Fredriksson A, Trudeau LE, Kullander K, **Wallén-Mackenzie Å**. VGLUT2 in midbrain dopamine neurons is required for psychostimulant-induced behavioural activation, Proc Natl Acad Sci USA 2010 Jan 5; 107(1):389-94.

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### Agencies that the work/ Funding

The Swedish Research Council Medicine
Parkinsonfonden
Major Gösta Linds minnesfond
Åhlén Foundations
The Swedish Brain Foundation
The Swedish Brain Foundation/ Hållstens fond; shared grant with prof Klas Kullander
Support from Uppsala University, Medical Faculty

## *Neurodynamics*

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

**Members of the group during 2012**

Sanja Mikulovic, PhD student
Stefano Pupe Johann, visiting PhD student

***Project1: How brain oscillations are generated***

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

In this project we use genetic tools to target a specific neuronal population of the hippocampus. We found that a specific type of inhibitory cell is capable of controlling the the generation of rhythmic activity in the brain, which in turn control numerous cognitive processes. Distinct inhibitory neuron populations specifically modulate principal neurons of the hippocampus, leading to information processing tasks as diverse as navigation and memory formation. For example, it has been shown that perisomatic inhibition by fast spiking parvalbumin (PV)+ interneurons is the main mechanism behind the generation of gamma oscillations. O-LM neurons are morphologically characterised by a particular morphology: soma and horizontally spreading dendrites located in the stratum oriens (SO) and high density axonal projections targeting the distal apical dendrite of pyramidal cells (PC) at the stratum lacunosum-moleculare (SLM). Modelling studies have suggested that O-LM cells can integrate PV+/PC cell assemblies and produce coupling between theta and gamma oscillations. There has also been indirect evidence that by modulating the distal dendrite of PC in CA1, O-LM cells can control long-term potentiation of synapses to principal cells. These mechanisms may help to explain the dual role of the hippocampus in memory encoding and retrival.

***Project 2. Synchronisation of basal ganglia circuits in Parkinson disease?***

**Participants:** Stefano Pupe Johan, Richardson N. Leão

The main goal of this collaborative project (Leao group and Åsa Mackenzie's group, Uppsala University) is to understand and control abnormal brain rhythms seen in individuals with Parkinson's disease (PD). To do this we need to determine the functional interplay and connectivity within the cortex-basal ganglia-brainstem-cerebellum structures. We intend to:

- Find the sources of synchronised, rhythmic neuronal activity in the parkinsonian basal ganglia, and structures functionally connected to the basal ganglia, at a neuronal, nuclei and network level;
- Develop stimulation strategies to desynchronise, and thereby normalise, network activity in the basal ganglia in a PD rodent model.

PD is the most common neurodegenerative disorder and with a described "primary" cause, the degeneration of SNc DA neurons, much research is focused on restoring DA function, both by exploration of classical pharmacology, where the DA precursor levodopa still is the most commonly prescribed medication, and by more novel therapeutic paradigms, such as gene

therapy and stem cell approaches. A more straightforward therapy is the surgically-based DBS, in which the increased synchronization in oscillatory activity in the STN and several other nuclei, is targeted. DBS has proven an effictive approach in severely diseased people, however, the mechanisms behind its efficacy remain unresolved. It is therefore, plausible to assume the maximal potential of this promising therapy has not yet been reached. During recent years, there has been a striking development of neuroscience research techniques, which enable high-precision analysis of neural activity function in the living brain on a level that may be highly significant for brain disease prevention and intervention as we can now, for the first time, control and read in vivo brain activity in real time. The activity and connectivity between basal ganglia structures, including the STN, and neuronal populations of relevance for its function, can now be resolved at the temporal and spatial level necessary to allow for real-time recordings that will serve useful at a functional level. Recordings can be made in slice preparations but also in the living animal while it is performing a behavioural task, a feature of essence as the correlation between brain activity and behaviour can be studied. Based on such knowledge, we will subsequently be able to use the novel technology to directly desynchronize the identified nuclei and analyse the effect in a parkinsonian model. The gain from such experiments is high as it can be directly applicable to the clinical use of DBS in PD. Our labs have developed the relevant know-how and state-of-the-art technology required to functionally address the pathophysiology of synchronized oscillations in PD, and the results of our focused proposal is highly likely to contribute novel knowledge of cortico-basal ganglia-brainstem-cerebellum network function that may be of immediate benefit for near-future improvement of DBS on such a level that therapeutic development can be efficiently progressed.

**Publications 2010-2012**

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Borgius L, Restrepo CE, Leão RN, Ole Kiehn. (2010) A transgenic mouse line for molecular genetic analysis of excitatory glutamatergic neurons in brain and spinal cord. Mol. Cel. Neurosci. 45(3):245-57.

**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 2012**

Bejan Aresh, PhD student
Ludvig Stjärne, Master student
Felicia Båvenholm, Bachelor student
Edda Blumel, project student
Prathyusha Pendekanti, project student

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 neurons, 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*** *i*s 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 *vivo* two-photon microscopy, *in situ* hybridization, immunohistochemistry and optogenetics to reach our goals.

***Project 2*** is focused on the pathophysiology of chronic pain and the identification of new chronic pain biomarkers, target proteins and therapeutics. This project is partially performed in collaboration with the chairman of the multidisciplinary pain centre at Uppsala University hospital, Dr Torsten Gordh. Gordh has established a biobank consisting of plasma and cerebrospinal fluid samples from chronic pain patients and controls. Our role focuses on investigating if the biomarkers, found be the Gordh group, could be used as a diagnostic tool for the development of chronic pain. We are also studying the role of the identified biomarkers in the regulation of pain, using transgenics and behaviour models. Our goal is to find biomarkers that are visible before a state of chronic pain; is reached. We we are also use our neuropathic, pain-insensitive animal-model to search for biomarkers for chronic pain and are currently evaluating the top 100 most differentially regulated genes in this line compared to control mice.

**Publications 2010-2012**

1. Rogoz K, Lagerström MC, Dufour S, Kullander K. VGLUT2-dependent glutamatergic transmission in primary afferents is required for intact nociception in both acute and persistent pain modalities. *Pain.* 2012 May 25.

2. Lagerström MC, Rogoz K, Abrahamsen B, Lind AL, Olund C, Smith C, Mendez JA, Wallén-Mackenzie Å, Wood JN, Kullander K. A sensory subpopulation depends on vesicular glutamate transporter 2 for mechanical pain, and together with substance P, inflammatory pain. *Proc Natl Acad Sci U S A.* 2011 Apr 5;108(14):5789-94.

3. Zhao J, Yuan G, Cendan CM, Nassar MA, Lagerström MC, Kullander K, Gavazzi I, Wood JN. Nociceptor-expressed ephrin-B2 regulates inflammatory and neuropathic pain. *Mol Pain*. 2010 Nov 8;6:77.

4. Lagerström MC, Rogoz K, Abrahamsen B, Persson E, Reinius B, Nordenankar K, Olund C, Smith C, Mendez JA, Chen ZF, Wood JN, Wallén-Mackenzie A, Kullander K. VGLUT2-dependent sensory neurons in the TRPV1 population regulate pain and itch. *Neuron*. 2010 Nov 4;68(3):529-42.

**Agencies that support the work/ Funding**

The Swedish Research Council
The Åke Wiberg Foundation
The Jaensson Foundation

## *Molecular Cell Biology*

**Group leader: Professor Manfred W. Kilimann, MD, PhD**

**Members of the group during 2012**

Manfred Kilimann, professor
Siv Strömberg, technician

At chemical synapses, neurotransmitter vesicles undergo calcium-dependent exocytosis and local recycling in a multi-step life cycle. Exocytosis is fast and precise, yet highly restrained and subtly regulated, to enable a meaningful interplay of the vast number of $10^{15}$ synapses in the human brain. This is achieved by a complicated and precisely adjusted protein machinery. Moreover, before synapses can take up their work, the elaborate cytoarchitecture of the nervous system must be built up during embryogenesis. Neurons extend processes, these must find their targets, and form synapses at appropriate points. These ontogenetic events of neuritogenesis and synaptogenesis are recapitulated during regeneration after trauma, such as injury or stroke. Finally, the functional properties of synapses are not constant, but can be remodelled as a consequence of previous synaptic activity. This "synaptic plasticity" is fundamental to learning and memory.

Our group has identified several new synaptic proteins, and we now work to elucidate their biological functions, and the molecular mechanisms through which these functions are performed. Some of our proteins are involved in the fast events of neurotransmitter vesicle exocytosis or recycling, whereas others have roles in the slower events of the morphogenesis or plasticity of the nervous system. Some were also found to be involved in neurological diseases. Our current work focuses on the three proteins aczonin/piccolo, paralemmin and neurobeachin, and their homologues and interaction partners.

We investigate the functions of these proteins through various approaches, much of this in collaboration with other laboratories:

- Biophysics (molecular structures and their functional dynamics)
- Biochemistry (identification of interaction partners and regulatory mechanisms)
- Cell Biology (functional analysis in cellular model systems)
- Cellular Neurophysiology (roles of individual domain interactions in synaptic signaling)
- Immunohistology (cellular and subcellular location of proteins)
- Genetic / organismic / medical (gene-modified mice).

**Publications 2010-2012**


1. M. Corell, G. Wicher, C. Limbach, M.W. Kilimann, D.R. Colman & A. Fex Svenningsen
   Spatiotemporal distribution and function of N-cadherin in postnatal Schwann cells: a matter of adhesion? *J. Neurosci. Res*. 88 (2010) 2338-2349.

2. I. del Pino, I. Paarmann, M. Karas, M.W. Kilimann & H. Betz
   The trafficking proteins Vacuolar Protein Sorting subunit 35 and Neurobeachin interact with the glycine receptor beta subunit.
   *Biochem. Biophys. Res. Commun.* 412 (2011) 435-440.

3. K. Niesmann, D. Breuer, J. Brockhaus, G. Born, I. Wolff, C. Reissner, M.W. Kilimann, A. Rohlmann & M. Missler
   Dendritic spine formation and synaptic function require neurobeachin.
   *Nat. Commun*. 2 (2011) 557 (doi: 10.1038/ncomms1565)

4. C. Limbach, M.M. Laue, X. Wang, B. Hu, N. Thiede, G. Hultqvist & M.W. Kilimann
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Paralemmin-1 is over-expressed in estrogen-receptor positive breast cancers.
*Cancer Cell Int.* 12 (2012) 17

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Neurobeachin, a regulator of synaptic protein targeting, is associated with body fat mass and feeding behavior in mice and body-mass index in humans.
*PLoS Genet.* **8** (2012) e1002568 (doi:10.1371/journal.pgen.1002568).

7. G. Hultqvist, D. Ocampo Daza, D. Larhammar & M.W. Kilimann
Evolution of the vertebrate paralemmin gene family:
Ancient origin of gene duplicates suggests distinct functions.
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8. R. Nair, J. Lauks, S.Y. Jung, N.E. Cooke, H. De Wit, N. Brose, M.W. Kilimann, M. Verhage & J.S. Rhee
Neurobeachin regulates neurotransmitter receptor trafficking to synapses.
*J. Cell Biol.* (2012) in press

***Project 1: Biochemical and cell-biological analysis of the paralemmin protein family involved in plasma membrane dynamics***

The paralemmin protein family comprises four proteins – paralemmin-1, paralemmin-2, paralemmin-3 and palmdelphin. They were initially identified as molecular constituents of synaptic plasma membranes. Current results indicate an association with lipid rafts and suggest functions in cellular membrane dynamics, membrane/cytoskeleton interactions, and in the control of cell shape. Paralemmin-1 is a hydrophilic protein of 40 kDa which is anchored to membranes through prenylation and di-palmitoylation of a C-terminal CaaX lipidation motif. It is expressed in many different tissues and cell types, but most abundantly in brain, where it is located at the plasma membranes of postsynaptic specializations, axonal and dendritic processes, and perikarya. The paralemmin family seems to represent a novel functional principle in cellular membrane dynamics, and it is the purpose of our research to elucidate this.

We have identified numerous phosphorylation sites by mass-spectrometry after purification of native paralemmin-1 and palmdelphin. These phosphorylation sites were mutated, and by expression of mutant paralemmin-1 in neuronal cell culture it was determined that they are involved in the maturation of dendritic spines. Functional expression in cell culture demonstrates similar effects of all paralemmin isoforms in membrane dynamics, including interactions with small G-proteins of the Rho family. The molecular mechanisms underlying the functions of the paralemmin protein family members are investigated by identifying and characterizing protein-protein interactions. The structures of the paralemmin isoforms and their individual domains are studied by biophysical techniques such as NMR.

***Project 2: Molecular architecture of the synaptic active zone***

The final steps of neurotransmitter exocytosis from storage vesicles take place at the "active zone", a specialized region of the presynaptic plasma membrane. It is a complex proteinaceous structure that determines the extreme spatial and temporal accuracy of neurotransmitter release. Recent progress in the identification and characterisation of active zone components has identified several large multi-domain proteins which organize the various steps of neurotransmitter release. Our research has demonstrated that several of these proteins interact closely with each other, converging on a multidomain complex that is probably a hotspot of functional interplay.

Aczonin and several other proteins of the active zone are large multi-domain proteins. We have determined the in-situ topology of the different domains of aczonin and other presynaptic organizer proteins in their actual location at the presynapse. For this purpose, antibodies were raised against different recombinant sequence sections, and their location in the synaptic terminal were mapped by immunogold electron microscopy, revealing a highly defined and differential nanometer-scale localization pattern of these molecules at the active zone.

***Project 3: Neurobeachin and Lrba, regulators of the subcellular targeting of membrane proteins***

Neurobeachin is a neuron-specific protein that is suspected to play a role in the trafficking of multiple membrane proteins (e.g. neurotransmitter receptors, ion channels, growth factor receptors or adhesion receptors). Its absence in knock-out mice causes total or partial defects in pre- and postsynaptic functions, depending on the type of synapses, and modifies the surface expression of neurotransmitter receptors. Lrba is an isoform of neurobeachin expressed in many cell types, and its deficiency in knock-out mice manifests in the perturbation of renal, sensory and immune functions. Our research aims to characterize the underlying molecular mechanisms. Neurobeachin and Lrba belong to a protein family characterized by the BEACH domain. These proteins seem to be involved in a novel pathway of membrane protein traffic and are connected to various diseases, and our studies are expected to provide insights into the fundamental principles of this pathway and of the functioning or malfunctioning of BEACH proteins.

***Project 4: Gene-modified mice, system biology, and molecular medicine***

The aim of this line of investigation is to reveal the biological functions of the synapse-associated proteins under study in our laboratory. The functional knowledge about these proteins is very limited, but it is believed that they are involved in different aspects of the transport of membranes and membrane proteins. We generate and analyse mice where these genes have been mutated. The biological consequences are explored by subjecting the mutant mice to a comprehensive phenotyping screen at the German Mouse Clinic (München). Phenotypes discovered in this screen are studied in more detail to understand their cellular and molecular basis, often in collaboration with specialists in the respective field. The effects of the mutant genes are investigated by dissecting out tissues for histological, anatomical and biochemical analyses. Cells from different tissues are cultured and used for cell biological and electrophysiological studies. These studies are expected to improve our understanding of the normal development and plasticity of the nervous system, and of the pathophysiological mechanisms involved in the recovery from nervous system injury or stroke, in inflammation, wound healing or tumor invasion. Human disorders or mouse models of such, in which our

proteins of interest are implicated, include autism, multiple myeloma, obesity, hearing impairment, immune deficiency, and cancer growth, invasiveness and metastasis.

**Agencies that support the work/ Funding**

The Swedish Research Council (Medicine & Health)
Deutsche Forschungsgemeinschaft

# *Ophthalmology & Retina Biology*

## Ophthalmology

### *Ophthalmic Biophysics*

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

**Members of the group during 2012**

Bucht, Curry, BScTechn, physics, PhD-student, deceased during 2012.
Galichanin, Konstantin, MD, PhD-student
Kronschläger, Martin, MD, PhD-student
Talibizadeh, Nooshin, MD, PhD-student
Yu, Zhaohua, MD, PhD student
Wang, Jing, MD, PhD, spec. ophthalmology, part time post-doc
Zoega, Gunnar, MD, spec. ophthalmology, PhD-student
Sandberg-Melin, Camilla, Ögonkliniken, spec ophthalmology, PhD-student
Schultz-Key, Steffen, MD, spec. ophthalmology, research student
Nikos Merkoudis, MD, spec. ophthalmology, research student

**External collaboration 2012**

Jan Bergmanson, OD, Professor, College of Optometry, University of Houston, Tx, USA
Jonas Bergquist, BSc, Professor, Dept. of Analytical Chemistry, Uppsala University
Joakim Ekström, BSc, PhD, Dept of Statistics, UCLA, Los Angeles, CA, USA
Marjorie Lou, BSc, Professor, Veterinary & Biomed Sciences, University of Nebraska-Lincoln, NE, USA
Shambhu Varma, BSc, Professor, Univeristy of Maryland, School of Medicine, MD, USA
Ove Steinvall, BSc, Docent, FoI, Linköping
Carl-Gustav Laurell, MD, PhD, specialist ophthalmology, St. Erik's Eye Hospital, KI, Stockholm.
Stefan Löfgren, MD, Docent, specialist ophthalmology, St. Erik's Eye Hospital, KI, Stockholm.
Göran Manneberg, BSc, Docent, Biomedicinsk och Röntgenfysik, KTH, Stockholm
Fabrice Manns, BcTechn, PhD, Professor., Bascom Palmer Eye Institute, University of Miami, Fl, USA
Lennart Nilsson, BScTechn, physics, Professor, Inst. f. Inst. f Biovetenskaper och Näringslära, KI
Ralph Morgenstern, BSc, PhD, Professor, Institutet för Miljömedicin, KI

Jean-Marie Parel, BSc, PhD, Professor, Bascom Palmer Eye Institute, University of Miami, Fl, USA
Eva Skarman, Bsc, PhD, simulator designer, Melerit Medical AB, Sweden
Karl Schulmeister, BSc, PhD, Dr, Health Physics Division, Austrian Research Centers, Austria
Alfred Wegener, Bsc, Privatdozent, Dept. of Experimental Ophthalmology, University of Bonn, Germany

***Overall aim main project***
Reduce cataract disease and contribute to safer cataract surgery.

***Significance***
Cataract is the most common cause of bilateral blindness in the world and a rapidly increasing burden on the world health economy due to increasing and aging world population.

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

***Participants:*** Curry Bucht, Konstantin Galichanin, Martin Kronschläger, Nooshin Talibizadeh, Jing Wang, Zhaohua Yu, Jan Bergmanson, Joakim Ekström, Marjorie Lou, Fabrice Manns, Ralph Morgenstern, Jean-Marie Parel, Karl Schulmeister, Alfred Wegener

***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 (MTD2.3:16) estimates, experimental single and repeated exposure of lenses in vitro and in vivo in experimental animals to spectrally and radiometrically define optical radiation, macroscopic imaging of damage, quantitative measurement of intensity of forward light scattering, light and electron microscopy.

***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, Martin Kronschläger, Nooshin Talibizadeh, Jing Wang, Zhaohua Yu, Juan Zhang, Jonas Bergquist, Marjorie Lou, Stefan, Löfgren, Ralph Morgenstern, Alfred Wegener

***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, that may be used for prevention or delay of cataract formation.

***Methods***
Morphologic events in 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 PCR. Oxidation defense systems in the lens are studied biochemically. The antioxidant α-tocopherol is analyzed quantitatively with HPLC coupled with massspectrometry. The antioxidant caffeine is investigated as a potential anticataract agent.

***Significance***
Considering the increasing problem of cataract disease in a world perspective, it would be of substantial value to identify possibilities for cheap pharmaceutical intervention against cataract.

***Project 3: Contributing to safer cataract surgery***

***Participants:*** Markus Erngrund, Carl-Gustav Laurell Eva Skarman, Curry Bucht, Göran Manneberg, Lennart Nilsson, Gunnar Zoega

***Aims***
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***
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) In collaboration with software engineers specialized in medical, simulators develop a phacoemulsification cataract surgery simulator, develop a strategy for evaluation of training sessions with the instrument, and compare learning with the simulator to standard clinical learning.

***Significance***
Pre-operatively not detected rel. insufficiency of the corneal endothelium is one of the key remaining problems of modern cataract surgery and 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. Further, there is a long coordination learning curve that currently has to be learnt when working with patients. We have developed a virtual reality simulator that avoids extended learning on patients. A curriculum for the use of the simulator remains to be developed.

**Additional projects; group leader involved as collaborator/co-tutor**

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

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

***Participants:*** Ove Steinvall, Zhaohua Yu, Per Söderberg

***Methods***
Drivers are exposed to green laser light while driving on a test track. The eyes are examined before and after exposure. The driving behaviour 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 drivning.

***Clinical evaluation of Heidelberg Retinal Tomography (HRT) for evaluation of glaucoma progress***

***Aim***
To develop a measurement procedure that allows evaluation of glaucoma progresson with HRT.

***Participants:*** Camilla Sandberg-Melin, Curt Eriksson, Albert Alm, Per Söderberg

***Methods***
The variability in measurements with HRT has been analyzed in clinical data sets; and, based on that information, a measurement strategy was designed. The strategy will now be evaluated on a large cohort of patients for which HRT and visual field has been recorded.

***Significance***
If HRT allows valid measurements of progression of glaucoma, the clinical follow up of glaucoma patients would be cheaper and faster than current clinical routine with visual field.

***Clinical evaluation of 23 gauge vitrectomy***

***Aim***
To evaluate the clinical outcome after use of 23 gauge vitrectomy technology.

***Participants:*** Steffen Schultz-Key, Zoran Tomic, Per Söderberg

***Methods***
The clinical outcome of a large clinical material of patients that have undergone 23 gauge vitrectomy is being analyzed retrospectively.

***Significance***
Clinical evaluation of this new technology is needed.

***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 Merkoudi, Eva Landgren, Elisabet Granstam, Per Söderberg

***Methods***
Subconjuctival 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***
Subconjuctival 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.

**Administrative Commissions**

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

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

Organizer of the 2012 Danish ophthalmological meeting.

**Publications 2010-2012**

***Books***
Manns F, Söderberg PG, Ho A (eds) Ophthalmic Technologies XX SPIE Proc 7550, 2010
Manns F, Söderberg PG, Ho A (eds) Ophthalmic Technologies XXI SPIE Proc 7885, 2011
Manns F, Söderberg PG, Ho A (eds) Ophthalmic Technologies XXII SPIE Proc 7163, 2012

***Review articles***
ICNIRP: Söderberg PG, Schulmeister K, Stuck B, Césarini JP, de Gruijl F, Hietanen M, Sliney D ICNIRP Statement. Protection of Workers against Ultraviolet Radiation. Health Physics, 2010;99:66-87.

Söderberg PG Optical radiation and the eyes, with special emphasis on children. Prog. Biophys. Mol. Biol., 2011, 2011;107:389-392, E-pub. doi:10.1016/j.pbiomolbio.2011.09.009

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Wang J, Löfgren S, Dong X, Galichanin K,, Söderberg PG Evolution of light scattering and redox balance in the rat lens after in vivo exposure to close to threshold dose ultraviolet radiation. Acta Ophthalmol, 2010: doi: 10.1111/j.1755-3768.2009.01826.x :1-.

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Lee RMH, Cuthbertson FM, Liu CS, Söderberg PG A possible strategy for implanting blue-blocking intraocular lenses. Acta Ophthalmologica, 2011; DOI: 10.1111/j.1755-3768.2011.02166.x.

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Kronschläger M, Galichanin K, Joakim Ekström, Lou M, Söderberg PG Protective Effect of The Thioltransferase (Grx1) Gene On In Vivo UVR-300 nm Induced Cataract. IOVS, 2012;53:248-252, DOI: 10.1167/iovs.11-8504

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Meyer LM, Löfgren S, Holz F, Wegener A, Söderberg PG Bilateral cataract induced by unilateral UVR-B exposure- evidence for an inflammatory response. Acta Ophthalmologica 2012; DOI: 10.1111/j.1755-3768.2012.02384.x

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Galichanin K, Talebizadeh N, Söderberg PG Characterization of Molecular Mechanisms of In vivo UVR Induced Cataract. JoVE 2012;69, 10.3791/4016

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2. Söderberg PG, Erngrund M, Skarman E, Nordh L, Laurell CG VR-simulation cataract surgery in non-experienced trainees, evolution of surgical skill. SPIE Proc. 2011; 7885:OL1-OL8

**Agencies that support the work/ Funding**

Karolinska Institutets KID-grants x2
Karolinska Institutet Research Foundation
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
Stockholms läns landsting research grants (FoUU)
Uppsala Läns Landsting's Research grants (ALF)

## *Paediatric Ophthalmology*

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

**Members of the group during 2012**

Eva Larssson, MD, PhD, Assoc Prof, Ophthalmologist
Dordi Austeng, MD, PhD, Ophthalmologist
Hanna Åkerblom, MD, PhD Student, Ophthalmologist
Jonina Hreinsdottir, Orthoptist
Eva Nuija, research nurse.

**Collaborators**

Uwe Ewald, MD, PhD, Prof Neonatology
Bo Strömberg, MD, PhD, Assoc Prof Paediatric Neurology
Katarina Strand-Brodd, MD, PhD (2011-GH partly supervisor), Neonatologist
Marie-Louise Bondesson, PhD, 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
Prof Karel Marsal, Dep of Gynecology and obstetrics, Lund University
Assoc Prof Karin Källen, statistician and epidemiologist, Tornbladsinstitutet, Lund University

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, geneticists (Prof G Anneren, Marie-Louise

Bondesson and their team, Uppsala) and neurophysiologists. Since 2009 - 2010 we have established 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. 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 Paediatric. The 2.5-year ophthalmological outcome together with a test of visual perception was presented by J Hreinsdottir et al at the European Paediatric Ophthalmologica Association (EPOS) held in Uppsala in June 2012 and a paper is prepared to be submitted in 2013.
The LOVIS study will hopefully lead to early detection, possibly prevention and we hope early intervention of future visual perceptual difficulties.

***Project 2: National study on extremely preterm infants born before the 27$^{th}$ 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 two and a half years. GH is responsible for the organization and logistics of the ophthalmologic part of this national project, which includes two parts: eye screening in the neonatal period and a follow-up at two and a half years later. Dordi Austeng was a PhD student working on the project - dissertation 12 June 2010.

Two papers were published in 2009; one on Incidence of ROP and one on Treatment of ROP in this population. One paper on the Natural course of ROP was published in 2010: and one on Screening for ROP in 2011. G Holmström has been a coauthor of one paper on Survival of this extreme population of prematurely-born infants (JAMA 2009) and one on Incidence and risk factors for neonatal morbidity (Acta Paediatrica 2010). A general follow-up at 2,5 years has been submitted in November 2012, GH coauthor. Data on the ophthalmological follow-up at two and a half years on all 500 children has been analysed and a paper has been written, and will be submitted for publication shortly.

A second national follow-up at six and a half years of age started 2010 and will be finished in the autumn 2013.

***Project 3: Longterm follow-up at 10 years of prematurely-born children.***

This is an epidemiological, population-based study of prematurely born and full-term children born in the County of Stockholm. Various functions of these children have been studied and compared to children born at term. The results have been published continuously since 2004. During 2011, analysis of data on accommodation of preterm and fullterm children was completed and the resultant paper published in "Strabismus" 2012.

***Project 4 : The SWEDROP register***

A national register for retinal disease (ROP) in prematurely born infants with GH as register holder, has been established. 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 (PNQ), 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 increasing and during 2008-9 96% of infants were registered. Analyses on data from 2008 to 2009 have been analysed and recently published in Arch Ophthalmology (Nov 2012). Further evaluation of the register is ongoing and results were presented at a World ROP meeting in Shanghai in October 2012.

***Project 5: Retinal morphology and function in children born at term and preterm and with various diagnoses***

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 retinoschizis (Eriksson et al, Acta Ophtalmol 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). Similar studies relating to other diseases in children are ongoing.

During 2009 equipment for ERG (electroretinography) was purchased and installed. Clinical set-up was established with the help of Professor Sten Andreasson, Lund. Investigations of the retinal function in children 6 – 16 years with the help of ERG are ongoing and preliminary results have been presented at various international meetings. Studies on Multifocal ERG (MfERG) in prematurely-born children are performed in collaboration with Prof Sten Andreasson, the university of Lund. MfERG equipment has now been installed in Uppsala and an ethic application for studies on children born at term has recently been submitted.

**Publications 2010-2012**

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14. Storm T, Tranebjærg L, Frykholm C, Birn H, Verroust PJ, Nevéus T, Sundelin B, Hertz JM, Holmström G, Ericson K, Christensen EI, Nielsen R. 'Renal phenotypic investigations of megalin-deficient patients': novel insights into tubular proteinuria and albumin filtration. Nephrol Dial Transplant. 2012 Oct 9. [Epub ahead of print]

15. Holmström GE, Hellström A, Jakobsson PG, Lundgren P, Tornqvist K, Wallin A. Swedish National Register for Retinopathy of Prematurity (SWEDROP) and the Evaluation of Screening in Sweden. Arch Ophthalmol. 2012 Nov 1;130(11):1418-24.

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**Agents that support the work/ Funding**

Carmen och Bertil Regners Foundation
Läkarsällskapet

## *Glaucoma*

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

**Members of the group during 2012**

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 1979-85, new cases of glaucoma at the Eye Department in Tierp were registered. In all, 177 patients with definite open-angle glaucoma were identified. To increase the cohort, 35 cases diagnosed with open-angle glaucoma at follow-up of a population survey were included. A further number of 115 cases, found in a case-control study, were also enrolled.

Thus, the cohort comprises 327 cases. Blindness is defined as the occurrence of advanced visual field defects. While masked to clinical information, a nurse practised in perimetry judged 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 participants in studies undertaken at the Eye Department in Tierp. In all, the cohort comprises 201 individuals followed for at least 3 years. 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 judged the visual fields. Cox proportional hazards models are used to assess the relationship between potential risk factors and glaucoma blindness.

***Project 3: Pseudoexfoliation and Alzheimer´s disease***

**Participants:** Curt Ekström, Lena Kilander.

**Background:** Pseudoexfoliation is an age-related disorder, characterized by production and accumulation of a fibrillar extracellular material in the anterior segment of the eye. Outside the eye, exfoliation material has been found in skin, heart, visceral organs, vessels, and meninges. Pseudoexfoliation is a risk factor for open-angle glaucoma. Common sequence variants in a gene involved in elastin formation confer susceptibility to glaucoma. Similarities between accumulation of exfoliation material and other amyloid disorders have raised the question of whether subjects with pseudoexfoliation run an increased risk of Alzheimer´s disease.

**Purpose:** Associations between exposure to pseudoexfoliation and open-angle glaucoma and the development of dementia are studied in a cohort of people 65-74 years of age.

**Methods:** The cohort is based on the glaucoma survey undertaken in Tierp in 1984-86. To increase the cohort, participants in other studies in Tierp were enrolled. By this means, the cohort comprises more than 1,100 individuals. Information about incident cases of dementia is obtained by searching medical records. As a rule, diagnoses are based on clinical judgement by general practitioners. A specialist in geriatrics accomplishes classification of cases. Study results are evaluated by calculating standardized rate ratios.

***Project 4: The role of imaging in the follow up of eyes with glaucoma***

**Participants**: Albert Alm, Camilla Sandberg-Melin, Börje Nordh, Eva Nuija.

**Background:** Glaucoma progression is due to loss of optic nerve axons, which results in structural changes in the optic disc and nerve fibre layer and visual field defects. The rate of progression is important for determining the effects of treatment. Automatic perimetry is the main tool for follow-up, but it requires several fields and a long follow-up. New instruments for imaging the optic nerve head and the retinal nerve fibre layer are now used in clinical work. However, there is little data on their use in follow-up of the disease.

**Purpose:** The potential of imaging in the follow-up of glaucoma is evaluated.

**Methods:** Thirty normal individuals were examined with repeated measurements over 4 weeks in order to determine different types of variance components. A total of 80-100 patients will be followed every 4 months for 2-5 years with imaging and visual field examination. Multiple linear regression is used to analyse study results.

**Preliminary results:** Studies in normal eyes demonstrate that using the mean of three measurements instead of one single measurement with imaging instruments improves the power to detect a clinically meaningful rate of loss of nerve tissue by about 50%. Scanning laser tomography may signal disease progression earlier than visual field examination.

***Project 5: Proteomic studies on aqueous humor in eyes with pseudoexfoliation***

**Participants:** Amelie Botling-Taube, Albert Alm, Jonas Bergquist, Emilia Hardenborg, Magnus Wetterhall, Jörg Hanrieder, Marit Andersson**.**

**Background:** Pseudoexfoliation is an inherited, age-related condition. The presence of pseudoexfoliation in the anterior eye segment increases the risk for capsular glaucoma, a form of open-angle glaucoma. The pathogenesis of pseudoexfoliation is not fully understood. Studies on the chemical composition of exfoliation material have been restricted due to small sample volumes and problems in dissolving the substance.

**Purpose:** Methods for proteomic studies are developed. The protein content in aqueous humor from normal eyes and eyes with pseudoexfoliation is compared, and the chemical composition of exfoliation material is analysed.

**Methods:** Proteomics are applied to identify proteins in pooled samples of aqueous humor from eyes with and without pseudoexfoliation. Aqueous humor is obtained at cataract surgery. Proteomic imaging techniques are used in studies on exfoliation material adhered to the lens capsule.

**Preliminary results:** It is possible to analyse very small samples of aqueous humor. The protein content differs between eyes with and without pseudoexfoliation. Osteopontin, angiotensinogen and -crystallines B2 have altered concentrations in eyes with pseudoexfoliation.

**Publications 2010-2012**

1. Hardenborg E, Botling-Taube A, Hanrieder J, Andersson M, Alm A, Bergquist J: Protein content in aqueous humor from patients with pseudoexfoliation (PEX) investigated by capillary-LC MALDI-TOF/TOF MS. Proteomics: Clin.

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**Agencies that support the work/ Funding**

ALF
Uppsala County Council

**Awards**

Albert Alm, Acta Ophthalmologica Honorary Award 2012

## Retinal Stem and Progenitor Cell Development

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

**Members of the group during 2012**

FinnHallböök, PhD,Professor
Henrik Boije, PhD (post-doc)
Miguel Jarrin PhD (post-doc)
Niclas Lindqvist PhD (post-doc)
Henrik Ring, Med Mag PhD (defended his thesis in Dec 2012)
Shahrzad Shirazi-Fard, MSc, PhD Student
Maria Blixth, Msc, PhD student
Rashid Harun Msc, PhD student
Alireeza Bagherpoor Master student
Per Hendner Master student

One aim of our research is to be able to direct the in vitro development of stem- or progenitor cells to more mature cells that can be used for cell therapy in the eye. The activation of endogenous stem cells after injuries, or by exogenous stimulation to the retina, is also studied. This includes aspects of the activation of Müller cells post injury and their capacities to

generate new cells that can differentiate into neurons. We also study the role of Müller cells in the protection of retinal neurons in the injured retina. We have specialized in the use of the chicken embryo as a model system for early neuronal development. This experimental approach, using the chick embryo, has led to several collaborations with developmental biologists and animal geneticists aimed at discovery of genes that contribute to specific selection traits.
Another aim is to understanding how the cancer retinoblastoma is formed. This is the cancer that is derived from the development of neuronal cells – namely retinoblastoma.

***Project 1: Generation of retinal neurons***

**Participants:** Blixt, Ring, Shirazi-Fard, Boije, Hallböök

The overall aim of this project is to understand how "early" retinal neurons (ganglion cells, cones and horizontal cells) are generated; and to use this knowledge to instruct progenitor cell development to enable the production of retinal cells for cell therapy, and to explore the possibilities of counteracting the death of retinal ganglion cells. 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 as playing a pivotal role in the generation of horizontal and amacrine cells; two types of interneurons in the retina. We have characterized their expression in the chick retina, and have analysed both over-expressing and shRNA knock-down of their expression to elucidate their role in the generation of these cell types. During our work on analysis of the terminal mitosis of horizontal cells, we discovered that the horizontal cells arrest in their last cell cycle during the G2-phase, followed by ectopic mitoses.

One important task is to establish a method for cell-specific lineage tracing during embryonic development in the chicken retina. In ovo electroporation of expression vectors is used to study gene function; and a minimal TATA box promoter a in combination with hyperconserved non protein -coding DNA elements, is 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.

***Project 2: Factors that regulate proliferation of retinal stem cells***

**Participants:** Ring, Hallböök

As in most vertebrates, the chicken has two different types of photoreceptor cells (PRCs) namely cones and rods. These cells are formed during embryonic day 3 to 5 and 6 to 8 respectively. Cones are responsible for colour vision and are involved in vision during normal and bright light. Rods are on the other hand, involved in vision under dim light conditions. We investigate different candidate genes and conditions that may have important roles in the formation of the PRCs, and our goal is to set up a protocol for cell therapy using stem cells from ie. the ciliar marginal zone (CMZ) and expression vectors containing genes essential for formation of PRCs. The direction of the project is supported by two major and recent scientific break-throughs: First, conclusive evidence exists that transplanted retinal progenitor cells can reintegrate into adult retina if they are in the correct developmental state; and, secondly, therapeutic regimens to deliver cells to the posterior parts of the eye are now feasible in treatment programs. We will analyze the development of retinal neurons. Focus

will be on intrinsic determinants, mainly transcription factors that are important for the early-generated neurons. In a longer perspective this is important for in vitro differentiated CMZ stem-cells to functionally integrate into the retina and to restore vision.

***Project 3: Regulation of the final cell division in retinal progenitor cells and their relation to development of childhood Retinoblastoma***

**Participants:** Shirazi-Fard**,** Jarrin, Hallböök

The most common intraocular cancer is retinoblastoma. It represents approximately 4% of all paediatric malignancies. Recent results from animal studies imply that the cancer retinoblastoma originates from specific retinal celltype – the retinal horizontal cell (Hc) or from their immediate progenitors. It has been shown that the Hcs have properties that separate them from other retinal cells, and even from nervous system cells in general. With Hsc unorthodox cell cycle control, with cell cycle arrest in G2, resistance to death, and an "eagerness" to migrate, they possess properties that can, if de-regulated, be associated with malignant cancer. The aim of this project is to investigate the retinoblastoma cell-of-origin in regard to its special characters, using animal models and human retinoblastoma material collected at St Eriks children's eye clinic. The identification of the retinoblastoma cell-of-origin and molecular mechanism behind retinoblastoma will provide novel targets for retinoblastoma therapy.

***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, Hallböök

Retinal ganglion cells play a crucial role in the relay of visual signals from the eye to the brain. This cell type is affected and eventually lost in the eye disease glaucoma, resulting in progressive and irreversible loss of vision. This project is directed to understand what determines the fate of the Müller cells after injuries that trigger their proliferation and how this response may be modulated to contribute to restoration of neural functions in the eye. A major question is wether a regenerative response that produces new neurons is entirely of benefit for the retinal ganglion cells in the injured retina.

***Project 5: Functional genetics using domestic chicken***

**Participants:** Ka, Boije, Ring, Harun-Or-Rashid, Shirazi-Fard**,** Hallböök and Leif Andersson and co-workers

These different projects are part of collaborative efforts to utilize the domestic chicken 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. 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.
2. Analysis of endogenous retrovirus expression and retrovirus integrations in the high- and low selection lines, and their relation to the establishment of the divergent 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.

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**Agencies that support the work/ Funding**

Swedish Research Council (M)
Barncancerfonden
Stiftelsen för Strategisk Forskning SSF
Ögonfonden/Kronprinsessan Margaretas arbetsnämnd för synskadade KMA
Synfrämjandets forskningsfond SFF

# *Physiology and Pharmacology*

## Physiology

### *Gastrointestinal Physiology*

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

**Members of the group during 2012**

Olof Nylander, Professor in Physiology
Markus Sjöblom, Assistant Professor
John Sedin, PhD student
Anna Sommansson, PhD student
Wan Salman Wan Saudi, PhD student
Annika Jägare, Technician (40%)
Vera Wallmo, Project student
Evelina Rosenqvist, Project student
Hedvig Olander, Project student

**External collaborations**

Dr Ursula Seidler, Hannover Medical School, Germany.
Dr Gerolf Gros, 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, perform a number of important physiological functions. Beside its important task of absorbing nutrients, vitamins,

electrolytes and water, it also neutralizes the acidic juice discharged from the stomach, adjusts luminal osmolality and prevents 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.

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**Agencies that support the work/ Funding**

Uppsala University, Medical Faculty
Magnus Bergvalls Stiftelse
Lars Hiertas Minne
Emil och Ragna Börjessons Minnesfond

## *Neurophysiology of Motion Vision*

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

**Members of the group during 2012**

Yu-Jen (Frank) Lee, MSc, PhD student
Roel de Haan, researcher
Linus Nilsson, programmer
Sarah Kaspar, Erasmus master student
Malin Thyselius, biomedicin bachelor thesis student
Andrea Adden, master student

**Research background**

As an animal moves through the world, its own movement generates widefield optic flow across the visual field that it can use for several behavioural tasks, such as maintaining a straight trajectory or avoiding obstacles. Biological visual systems can also disambiguate the motion of objects that move *independently* of the surroundings from such self-generated optic flow. In the vertebrate visual cortex, and the insect optic ganglia, we find neurons specialized for detecting these two types of motion: Some respond optimally to widefield optic flow, whereas others are specifically tuned to the motion of small targets.

The underlying mechanisms that allow sensory systems to extract salient features from noisy surrounds are still poorly understood, despite being important for several senses. The visual detection of target motion is an interesting example of such feature extraction: Target visualization is computationally challenging, but evolution has solved it beautifully, even in the tiniest of insects, despite carrying low-resolution eyes and small brains, as evidenced by their aerobatic sophisticated flight behaviour during conspecific interactions or prey capture. As insects are physiologically accessible for *in vivo* recordings of single neurons, such as the exquisitely tuned small target motion detectors (STMDs), they provide an excellent model system for investigating the mechanisms underlying sensory selectivity. We are particularly interested in how the small insect nervous system efficiently extracts targets from cluttered backgrounds, with amazingly short behavioural delays. We approach these questions using intracellular electrophysiology of single neurons in the optic lobes of intact insects while they view experimenter-controlled visual stimuli, enabling us to correlate the exact visual input with the neural response on a frame-by-frame basis.

*Higher order motion sensitivity*

In another series of experiments we have been investigating the neural mechanisms

underlying higher-order motion sensitivity. It is generally agreed upon that motion is computed locally by elementary motion detectors (EMDs), in both flies and vertebrates. Fly lobula plate tangential cells (LPTCs) and motion sensitive neurons in the vertebrate visual cortex spatially pool output from many local EMDs to generate sensitivity to widefield optic flow. The detection of elementary motion relies on a coherent correlation of luminance across space and time. However, motion signals in nature do not always form clean space-time correlations, but may also be comprised of higher-order signals related to changes in contrast or texture, e.g. when viewing a gap in the foliage from different distances, or an object that moves in and out of shadows. The term higher-order motion refers to movement of visual objects that have no net motion energy or that contain paradoxical motion cues. During 2012 we published a paper showing that LPTCs, which are traditionally believed to act as pure EMD filters, also respond to higher order motion cues (PNAS, 2012). This came as quite a surprise, and has received a lot of attention from colleagues.

*Stimulus development*

We have invested a great deal of time in developing visual software for generating visual stimuli with high precision and at high frame rates (www.flyfly.se), as well as data acquisition software (sampsamp). Flyfly was inititated by a master´s student during 2010 (Jonas Henriksson) who developed new software using the Matlab Psychophysics toolbox. The software is freely available (www.flyfly.se), easy to use, and the end user can generate almost any imaginable type of stimulus from the available GUIs. This means that new biology students are immediately setting up and running quite complex experiments, and the software has, therefore, had a massive impact on research in our lab. Sampsamp uses the data acquisition toolbox in Matlab. It also allows for both real-time data analysis and for, the user to choose to analyze the data offline. We share this software freely with colleagues across Europe and in the US.

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**Agencies that support the work/ Funding**

The Swedish Research Council
US Air Force Office Research Laboratory

## *Molecular Physiology and Neuroscience*

**Group leader: Bryndis Birnir, Professor**

**Members of the group during 2012**

Bryndis Birnir, Professor
Omar Babateen, PhD student
Amol Bhandage, PhD student
Yang Jin, PhD student
Zhe Jin, Researcher
Sergiy Korol, Postdoctoral fellow
Suresh Kumar Mendu, PhD student
Karen Nygren, Technical engineer
Jacob Wall Medical student
Louise Flood Medical student
Yifan Zhou Master student
Hanna Taylor administrator

***Project 1: Neuronal inhibition***

The main 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 GABA-A channels (Birnir et al., 1994) that have been shown to significantly alter basic firing frequency and neuronal survival. These channels, 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 at physiological concentrations induces tonic GABA-activated currents in hippocampal neurons (Jin et al., 2011). This has great implications as the hippocampus is the centre for memory and learning plus has an important role in metabolic homeostasis. Our results can be very important for diseases like diabetes, dementia and Alzheimer´s disease but also epilepsy and MS. We are continuing these studies with the aim of understanding metabolic hormones modulation of GABAergic inhibition in the hippocampus using animal models, but also venturing into collaborations with groups studying effects of nutrition on brain structures and activity in health and disease. We further plan to study immunomodulation of neuronal astivity (Liu et al., 2006). We examine tissue from diseased healthy humans and alcoholics (collaboration with prof. Georgy Bakalkin, Uppsala University and prof. Esa Korpi, Univ. of Helsinki) characterizing GABA-A (Jin et al., 2012) and glutamate receptors subunits expression in different brain regions.

***Project 2: GABA signalling in the pancreas***

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 channels. In rats and mice only the alpha cells have GABA-A channels. We record from cells in intact islets using

the patch-clamp technique. There are not many labs in the world this procedure as most work on isolated cells. But based on our experience of working on brain slices we have now been able to the patch-clamp technique in both human and rat islets. Our results show that the ambient GABA concentration in the islets affects the electrical activity of both the alpha and beta cells thus probably affecting hormone secretion and the balance of insulin and glucagon release that 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 channels as central parts of the normal physiology of healthy islets as well as the pathophysiology in type 2 diabetes. We are continuing these studies in order to establish the role played by GABA signalling in determining insulin and glucagon secretion, as well as looking at how it can be modulated by medicines. We focus on human tissue from the Uppsala Human Tissue Lab within the strategic research initiative EXODIAB.

***Project 3: GABAergic immunomodulation and cross-talk with excitable cells***

Tonic GABA-A channels have affinity for GABA in the pM - nM range or more than million times higher affinity than synaptic channels. After making this discovery (Lindquist and Birnir, 2006) we decided to examine if lymphocytes expressed GABA-A channels as there are low concentrations of GABA present in the blood. And yes, lymphocytes have GABA-A channels and activation of these channels decreased the T cell proliferation. We have proposed that the GABA-activated break on immune cell proliferation is an important mechanism in keeping toxic lymphocytes in check and if it is not on, 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 channels are expressed. We are moreover, in collaboration with dr Antonio Barragan (KI), studying how parasites use GABA signalling to "hijack" dendritic cells and use them as means of entering the brain (Fuks et al., 2012). We focus on human and rodent immune cells.

***Project 4: GABA-A channels in tumours***

In collaboration with professor Anja Smits (Uppsala University and Uppsala University Hospital) and Prof Eleonora Aronica (Neuropathologist, Netherlands) we have characterized expression of GABA-A subunits in human gliomas of various malignancy. Our results show that GABA-A channel 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. We are proceeding with these studies.

***Project 5: Selective changes of GABA-A channel subunit mRNAs in the brain of human alcoholics.***

Beverages containing alcohol are commonly consumed in today's societies and often abused. The brain is one of the main targets of alcohol. Long-term excessive consumption of alcohol can change the brain and lead to a variety of behavioural changes such as addiction and cognitive dysfunction. Magnetic resonance imaging studies have showed reduced hippocampal and prefrontal cortex volume of individuals suffering from alcohol dependence, wich may contribute to the cognitive deficit associated with chronic alcohol exposure. These

averse effects may be associated with the direct and indirect actions of alcohol on various neurotransmitter and neuropeptide systems within the central nervous system (CNS). Among those neurotransmitter receptors, a special focus has been on the association of alcohol action and alcoholism with γ-aminobutyric acid type A (GABA-A) ion channels during the last 30 years. Many GABA-A channel subunit genes have been suggested to be associated with human alcoholism, but detailed mechanisms remain poorly known and are inconsistent between studies.

We have examined mRNA expression of the GABA-A channel subunit genes in three brain regions in individuals with or without alcohol dependence using quantitative real-time RT-PCR assay (Jin et al, 2012). The levels of selective GABA-A channel subunit mRNAs were altered in specific brain regions in alcoholic subjects. Significant increase in the α1, α4, α5, β1 and γ1 subunit mRNAs in the hippocampal dentate gyrus region, and decrease in the β2 and δ subunit mRNAs in the orbitofrontal cortex were identified whereas no changes in the dorsolateral prefrontal cortex were detected. It is of particular interest that several of the subunits that change with chronic alcohol consumption (e.g. α4, α5 and δ) are present in many extrasynaptic GABA-A channels mediating tonic inhibition. As tonic inhibition has a significant role in determining baseline excitability of neurons this is perhaps not surprising, but highlights the importance of GABA-A channels located outside of synapses for drug effects.

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**Book Chapters**

*14.* Jin Z, Mendu SK, Bhandage A and Birnir B (2012) GABA is an effective immunomodulatory molecule in the brain and in the periphery. In "Nerve-Driven Immunity: Neurotransmitters and Neuropeptides in the Immune System" Edited by Dr Mia Levite *Published by Springer*

**Agencies that support the work/ Funding**

Swedish Research Council project grant
EXODIAB (PI), Strategic research grant, diabetes
Swedish Research Council samverkans anslag (PI)
The Swedish Diabetes Foundation
Fredrik and Ingrid Thurings Foundation
Svenska Sällskapet för Medicinsk Forskning
Ernfors Foundation
Uppsala University

Bryndis Birnir is the Secretary General of the Scandinavian Physiological Society and Treasurer of the Federation of the European Physiological Societies.

## *Behavioural Neuroendocrinology*

### Group leader: Svante Winberg, Professor

### Members of the group during 2012

Svante Winberg, Professor
Per-Ove Thörnqvist, Research Associate
Hanna Olsén, PhD-student
Josefin Dahlbom, PhD-student
Dean Basic, PhD-student (supervised together with Dr E. Höglund, DTU)
Maria Moltesen, PhD-student (supervised together with Dr E. Höglund, DTU)
Chinmaya Sindagi, project student
Johan Dagh, Project 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 West Scotland, UK
University of Exeter, UK
University of Oslo, Norway

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*

**Participants:** Josefin Dahlbom, Hanna Olsén, Johan Dagh, Per-Ove Thörnqvist, 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 of behavioural 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 behavioural and physiological traits.

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

**Participants:** Hanna Olsén, Josefin Dahlbom, Chinmaya Sadangi, 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 behaviour 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 behaviour and neuroendocrine stress responses of reactive and proactive rainbow trout are affected by social interaction. Moreover, we will study the effects of stimulation on the 5-HT system on behavioural profiles and stress responses in a non-selected hatchery population as well as in rainbow trout strains selectively bread for high (HR) and low (LR) post-stress plasma cortisol, respectively. There is considerable interest in generating a 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 are linked to aggressiveness. Moreover, environmental enrichment is often discussed, and is believed to have positive effects on fish welfare and performance. Still our knowledge of the effects of environmental enrichment on fish performance is very limited.

***Project 3: Improved production efficiency and animal welfare in aquaculture through elevated dietary tryptophan (TRP) levels***

**Participants:** Dean Basic, Svante Winberg (collaboration with BioMar AS, Norway, and Norwegian School of Veterinary Science, University of Bergen and Danish Technical University)

The aim of this project is to develop a cost-effective method for using TRP supplemented feed to enhance production efficiency and welfare of fish in aquaculture. TRP, a naturally occurring amino acid and precursor of serotonin, has been shown to reduce stress responsiveness in all vertebrates. This effect has a wide variety of implications as elevated levels of TRP have proven to increase appetite after stressful situations as well as reducing aggression. Moreover, TRP also contributes to increased circulating levels of melatonin. In addition to reducing aggression, melatonin affects sexual maturation and seasonal cycles in growth and fat deposition.

***Project 4: Sustainable smolt production - an integrated approach (SMOLTPRO)***

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

The main aim of SMOLTPRO is to develop ecologically and ethically sound methods for supplementary rearing of salmonids. To achieve these goals SMOLTPRO integrates the competences and resources in this field of research using a multidisciplinary approach, where experiments will be conducted in a series of full-scale hatchery model systems. The results will be evaluated together with novel meta-analyses of existing data, and new hatchery guidelines will be developed in close dialogue with stakeholders.

*Partners:* University of Gothenburg (Prof. Jörgen Johnsson, coordinator), Uppsala University, Swedish University of Agricultural Sciences and Umeå University, Norwegian Institute for Nature Research and Norwegian University of Science and Technology, Technical University of Denmark and the National Institute for Aquatic Resources, Ocean Science Centre, Memorial University of Newfoundland.

SMOLTPRO started in January 2010, and is a four-year strategic project funded by the Swedish Research Council Formas.

***Nordic Network for Integrative Fish Behavioural Neuroscience (http://www.bifine.org/section.cfm?path=122)***

The aim of this network is to encourage exchange of ideas and enable collaboration across disciplines in the Nordic front-line research in behavioural neuroscience. The network is funded by NORDFORSK for a four-year period (2010-2014). Fish are rapidly becoming an important experimental vertebrate model organism in neuroscience, with a growing interest in using fish for studies of the neuronal and neuroendocrine mechanisms of cognition, learning, and various behavioural patterns. To date, international research, based mostly on comparative analyses, has shown remarkable similarities between teleost fish and higher vertebrates, such as rodent models. There are a number of strong Nordic groups working with fish in the area of integrative behavioural neuroscience. However, these groups come from different disciplines, such as biomedicine, ecotoxicology, evolutionary biology, ecology and aquaculture. By tradition, these fields have had limited contact and exchange of ideas, which has restricted cross-disciplinary research training. The partners of the network are: Uni Environment, Uni Research AS, Bergen, University of Bergen, Norwegian University of Life Sciences, Norwegian School of Veterinary Science, Danish Technical University, Dept. Zoology Göteborg University, Sahlgrenska Academy at Göteborg University, University of Helsinki, Swedish Agricultural University, Evolutionary Biology Centre Uppsala University and Dept. of Neuroscience Uppsala University.

***A new integrative framework for the study of fish welfare based on the concepts of allostasis, appraisal and coping styles (COPEWELL)( http://www.imr.no/copewell)***

The aim of COPEWELL is to establish, evaluate, and further develop, a new scientific framework for the understanding and application of the concept of animal welfare in farmed fish derived from the evolutionary based concepts of allostasis, allostasic load and overload. The project will propose and implement, as a whole and in the particular, Tasks, an innovative hypothesis-driven multidisciplinary approach, where a range of hypotheses will be tested. The COPEWELL project will, through four scientific work packages, focus on underpinning mechanisms in four essential welfare-relevant concepts: COPING STYLES, APPRAISAL, ALLOSTASIS and ONTOGENY. The consortium consists of 17 groups from all over Europe.

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**Agencies that support the work/ Funding**

The Swedish Research Council for Environment
Agricultural Sciences and Spatial Planning (FORMAS)
FACIAS
Uppsala University Medical Faculty
The European Union's 7th Framework Programme
NordForsk

# Pharmacology

## *Pharmacology*

**Group leader: Dan Larhammar, PhD, Professor**

**Members of the group during 2012**

Björn Edlund, medical student, SOFOSKO student
Bo Xu, PhD student
Christina Bergqvist, research engineer
Daniel Ocampo Daza, PhD student
David Lagman, PhD student
Heidi Naboth, undergraduate project student
Ingrid Lundell, PhD, reader (lecturer)
Jasna Pruner, PhD student
Jenny Widmark, research assistant (forskningsassistent)
Judith Bezgovsek, undergraduate project student
Kataryna Lapshyna, research assistant (forskningsassistent)

Lars G. Lundin, docent, reader (lecturer) emeritus
Maja Ericsson, undergraduate project student
Nina Mohell, docent, adjunct professor
Xesus Abalo, PhD, researcher
Xiao Zhang, PhD, researcher
Ravi Singh Parihar, undergraduate project student
Roja Saffari, undergraduate project student
Sofia Kaneberg, medical student, SOFOSKO student

**Our research has two primary aims:**
1) To resolve and understand the evolution of important gene families in vertebrates, particularly gene families expressed in the nervous system and in the endocrine system. Importantly, we wish to find out at which point new functions have arisen and how functions have changed during evolution. We are primarily investigating gene families for G-protein-coupled receptors and genes involved in vision.
2) To characterize the NPY (neuropeptide Y) system of peptides and G-protein-coupled receptors, and their closest relatives, with regard to ligand-receptor interactions and receptor regulation import for appetite regulation.

Many hundreds, perhaps thousands, of vertebrate gene families are now known to have expanded in two dramatic events that took place approximately 500 million years ago, namely two genome doublings or tetraploidizations (called 2R for two rounds of genome duplication). In addition, a third tetraploidization (3R) took place in the ancestor of teleost fishes. These events explain a great deal of the complexity of presently living vertebrates, and also explain functional overlap for members of many gene families. We are using a combination of phylogenetic sequence analyses and chromosome comparisons across species to distinguish gene duplication events in gene families of special functional interest. This approach is very useful for identifying corresponding genes (orthologues) in different species for comparisons of functions. The results have important implications for our ability to understand how functions arise, change, and, frequently, even disappear during evolution. Among the gene families that we have studied, or are presently studying, are the opioid peptides (enkephalins etc.) and their receptors, growth hormone and prolactin and their receptors, oxytocin-vasopressin receptors, somatostatin receptors, voltage-gated sodium and calcium channels, and the gene families involved in signal transduction in the rods and cones of the eye.

NPY is one of the most abundant neuropeptides, in the brains of all mammals, including humans. Together with its two related peptides, PYY and PP, it regulates appetite, metabolism and numerous other physiological functions. We are engaged in characterizing the NPY-family peptides and their 4-7 receptors in species representing different vertebrate classes. Our comparative approach aims to delineate the opposing roles of NPY and PYY/PP in appetite, using methods that range from molecular genetics and molecular pharmacology via cell biology to *in vivo* physiology. We also investigate the correlation of genetic variation in one of the receptor genes with body weight and obesity.

***Project 1: Evolution of vertebrate neuronal and endocrine gene families***

**Participants:** Daniel Ocampo Daza, Görel Sundström, Jenny Widmark, Bo Xu, Christina Bergqvist, Ingrid Lundell, Lars G. Lundin

Our studies of several neuronal and endocrine gene families show that many of these have quadrupled in the two ancient vertebrate tetraploidizations. These extensive duplications have,

for instance, expanded and elaborated the opoid system involved in pain and reward mechanisms. The evolution of the NPY system in vertebrates is even more complicated and we have investigated this for many years. Our work has demonstrated that most of the complexity of the NPY system arose very early in vertebrate evolution, prior to the origin of jawed vertebrates, with a first local triplication and subsequent chromosome duplications resulting in no less than seven NPY receptors in the vertebrate ancestor. Unexpectedly, mammals have lost 2-3 of these, whereas other species, such as the coelacanth *Latimeria chalumnae,* have retained all seven. Teleost fishes have acquired duplicates of both NPY and PYY. We are also engaged in characterizing receptor families that are closely related to the NPY family, but bind other neuronal and endocrine peptides.

Other projects include growth hormone and prolactin and their receptors as well as some of the most important regulators of growth hormone release, namely the large family of somatostatin receptors. The oxytocin-vasopressin receptor genes also multiplied in the tetraploidizations and, again, mammals have lost at least one of the ancestral receptors. Both the voltage-gated sodium channels and the calcium channels were duplicated in the tetraploidizations. These gene families are important for neuronal signalling, such as pain transmission.

***Project 2: Functional and genetic studies of the NPY system***

**Participants:** Bo Xu, Jasna Pruner, Kataryna Lapshyna, Nina Mohell, Ingrid Lundell

In mammals, NPY stimulates appetite primarily via receptor subtypes Y1 and Y5, whereas the related gut endocrine peptide PYY reduces appetite via receptor Y2 and pancreatic polypeptide (PP) inhibits appetite via Y4. Future drugs might therefore be agonists acting on Y2 and Y4. We investigate the ligand-binding properties of the human Y2 receptor using a large panel of receptor mutants generated by site-directed mutagenesis and expressed in cultured mammalian cells. We have identified important interaction sites between peptides and receptors, and are now exploring the selectivity of the peptides to the receptor subtypes. The results will help improve structural models for facilitating development of receptor subtype-selective drugs for reducing appetite. We are also starting to investigate how relatives of the NPY receptors, such as PRLH receptors and QRFP receptors, have evolved selectivity after duplication from a common ancestral receptor.

Recent studies have shown that the PP receptor Y4 is associated with childhood obesity and adult body weight. Our functional studies in vitro revealed that one receptor variant (allele) displayed reduced functional coupling to signal transduction pathways. We are now resolving the complicated inheritance of this gene, which displays both copy number variation (CNV) and single nucleotide polymorphisms (SNPs). The hypothesis is that a lower number of gene copies leads to reduced satiety, resulting in increased food intake and eventually obesity.

***Project 3: Evolution of colour vision in vertebrates***

**Participants:** Xesus Abalo, David Lagman, Daniel Ocampo Daza

Numerous gene families are involved in vertebrate vision. We have found that the genome duplications in early vertebrate evolution generated gene duplicates that became specialized on expression in cones or rods, i.e., for color vision and dim-light vision, respectively. A surprising conclusion from these comparisons is that colour vision arose before faint-light vision. We are investigating a large number of gene families involved in the

phototransduction signalling cascade, starting with the light receptors themselves, the opsins, via transducins and beyond. For this purpose, we study the zebrafish because it has retained more of the ancestral vertebrate colour vision genes than mammals. Furthermore, the zebrafish shares with other teleost fishes the third tetraploidization that has resulted in additional gene duplicates. We have already found that many gene duplicates display distinct expression patterns for mRNA in the zebrafish retina, Thus, the gene duplications resulting from the tetraploidizations have paved the way for the elaboration of vertebrate vision by supplying additional gene copies that have evolve new functions (neofunctionalization) as well as more specialized functions (subfunctionalization).

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2. Larhammar, D. Comment on study of acupuncture for herpes zoster pain. Focus on Alternative and Complementary Therapies 17(1), 56-57 (2012).

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2. Larhammar, D. Evolution på molekylnivå. Biologen (Biologilärarnas förening) nr 3, sid 10-13, 2012. (Återutgivning)

3. Larhammar, D. och Lundin, L. G. Tacka dna-explosionerna för att du finns. Forskning och Framsteg nr 9, 34-38, 2012. http://fof.se/tidning/2012/9/artikel/tacka-dna-explosionerna-for-att-du-finns

**Agencies that support the work/ Funding**

The Swedish Research Council

**Honours**

Dan Larhammar is president of the European Society for Comparative Endocrinology (ESCE) 2010-2014.

## *Functional Pharmacology*

**Group leaders: Helgi B. Schiöth, Professor and Robert Fredriksson, Assoc. Professor**

**Members of the team during 2012**

Helgi B. Schiöth, Professor
Robert Fredriksson, Associate Professor
Madeleine Le Grevés, Lecturer
Michael Williams, Researcher
Christian Benedict, Post doc
Samantha Brooks, Post doc
Sonchita Bagchi, Post doc
Pleunie Högenkamp, Post doc
Ashley Hutchinson, Post doc
Josefin Jacobsson, PhD student
Maria Hägglund, PhD student
Markus Sällman-Almén, PhD student
Mathias Rask-Andersen, PhD student
Sahar Roshanbin, PhD student
Åke Västermark, PhD student
Anica Klockars, PhD student
Arunkumar Krishnan, PhD student
Philip Goergen, PhD student
Olga Titova, PhD student
Miguel Xavier, PhD student
Sofie Hellsten, PhD student
Anders Eriksson, PhD student
Emelie Perland, PhD student
Ludwig Hedberg, PhD student
Jonathan Cedernaes, PhD student,part-time
Andreas Johansson, PhD student, part-time
Maria Ling, PhD student, part-time
Björn Sundberg, PhD student, part-time

***General:*** The team studies pharmacological, genetic and behavioural aspects of, primarily, of membrane-bound proteins, with particular focus on functions related to the central regulation of food intake. We functionally characterize newly identified genes that code for solute carriers, GPCRs and other membrane-bound proteins that are involved in food-intake regulation, reward, obesity and anorexia. This involves neuronal mapping with multiple markers, association to human body weight phenotypes using human genetics, and prediction of their functions using conditional Cre-Lox knockout mice and other animal models. We also study the neuronal network of food intake with emphasis on explaining how reward functions and how these are integrated with the network of food intake regulators. Specific focus is on transporters and receptors in these networks. We use bioinformatics studies to identify and characterize new genetic elements, and we study the evolutionary mechanism that shaped

large gene families among membrane-bound proteins. We study the functional neuroanatomy of anorexia, sleep and reward with help of fMRI. The research group was ranked in 2011 at the highest category of "top international class" by external international panel evaluation of Uppsala University (KoF2011), which stated that the "research output of this group is exceptional" with projects "highly relevant for society".

***Progress 2012:*** We have been very productive in 2012 with more than 40 paper published. We continued to publish papers in high-impact journals during the year, including papers in *Am J Clin Nutr*., (impact 6.606), (Chapman et al.,.), *Age* (impact 6.280), (Titova et al,.), *Cell Mol. Life Sci*. (impact 7.047), (Williams et al.,), *Neurobiology of Aging* (impact 6.634), (Benedict et al.), *Int. J. Obesity (3x)*, (impact 5.125), (Sällman-Almen et al., Brooks et al. and Jacobsson et al.), *Plos Genetics* (impact 9.532) (Olszewski et al.), *Frontiers in Neuroendocrinology*, (impact: 12.750), (Alsio et al.), *Diabetes Care*, (impact 7.141), (Benedict et al.), *J Clin Endocr Metab.x2*, (impact 6.495), (Benedict et al.), *Neuroimage*, (impact 5.937), (Brooks et al.), *Annu Rev Pharmacol Toxicol*. (impact 21.639) (Civelli et al.,) *Obesity Reviews* (impact 7.038), (Jacobsson et al.,), *Arch. Intern. Med.* (impact 10.639) (Schiöth et al.), *Mol Neurobiol* (impact 6.068), (Schiöth et al.), *Mol Aspects Med* (2x) (impact 9.970) (Schiöth et al., Rask-Anderson et al., ).

The unit of functional pharmacology is currently the most productive unit at the department of Neuroscience, when the total impact of published papers over the last four years is considered. The unit contributes with papers of total impact of above 75 (ISI total impact of papers) in average per year during recent years, and currently contributes about 21 percent of the entire publication impact of the department according to the most recent four-year measures. Recent papers have continued to receive high number of citations during 2012: the total number of citations received by Schiöth HB (ISI) was above 800 during 2012: while Fredriksson R can also boast a high number of citations, with about 400 citations in average for the last 3 years. Recent papers generated entirely at this department contribute a very important part of this high rate of citations, including papers such as Fredriksson et al., *Mol. Pharmacol*. 2003, that has received in total more than 500 citations. This paper is one of the most cited papers to have been entirely produced at Uppsala University published 2003 or later. Recent papers in high impact journal such as Lagerström and Schiöth, *Nat Rev Drug Discov*. 2008, (impact 28.712), Olzewski et al., *Neurosci Biobehav Rev*. 2008 (impact 9.015), Olzewski et al *Brain Res Rev*. 2008 (impact 8.842), Bjarnadottir et al., *Cell Mol Life Sci*. 2007, (impact 7.047), Sällman-Almén, et al., 2009, *BMC Biol.* (impact 5.203) as well as Fredriksson et al., *Endocrinology*, 2008, Fredriksson et al., *Mol Pharmacol* 2005 have contributed to the high number of citations seen in 2012.

***Grants:*** The unit for functional pharmacology has been very successful during year 2012 in receiving external grants. The unit has currently three VR-projects grants. The main grant to professor Schiöth is from VR-M, at 1.4 mSEK/year for 3 years "Central regulation of food intake and reward". This plan describes research to identify the molecular mechanisms of how the obesity gene FTO acts, and how novel transporters and a novel membrane trafficking protein are important for obesity. The plan also describes studies to elucidate the mechanisms behind determination of the molecular mechanisms involved in the initiation and termination of meals. Schiöth has also a VR-NT grant of 0.7 mSEK/year for 3 years for "Evolutionary mechanism that shaped large gene families among membrane bound proteins". The aim is to unravel the evolution of large gene families such as the GPCRs, SLCs, 4TMs and others using an advanced bioinformatics platform. Associate professor Robert Fredriksson has also a VR-NT project grant for 0.8 mSEK/year for 3 years, on "Functional characterization of novel

amino acid transporters". This plan aims to understand how novel amino acid transporters function regarding substrate specificity, intracellular partner proteins, cell-type specificity and physiology. We are using histological methods (immunohistochemistry and in situ hybridization), uptake assays in oocytes and biochemical and molecular biology methods to ultimately identify the substrate specificity and physiological role for each neuronal amino acid transporter. Fredriksson has also a VR-M senior researcher grant for salaries of 1.2 mSEK/year, 3 + 3 years. We also had a post-doctoral grant from VR for Christian Benedict, 0.7 mSEK/year, 2 years for the project "Sleep deprivation increases food intake and decreases energy expenditure: From behavioral to molecular insights". This plan describes both clinical and preclinical work. Schiöth has also grant at Hjärnfonden 0.5 mSEK/year for studies on novel transporter using conditional knockout mice and another for 0.5 mSEK/year for anorexia research. Fredriksson has grant from NOVO Nordisk of 0.4 mDDK/year for endocrinology and molecular biology of novel transporters involved in food intake and several other smaller grants.

***Development of the laboratory and techniques:*** The group has a strong molecular biology laboratory, creating conditional knock-outs, neuroimaging using fMRI, immunohistochemisty, human genetics, animal behaviour, pharmacology on cellular expression systems and bioinformatics. While the group has had strong focus on molecular biology of food intake with emphasis on key functional nodes such as GPCRs and transporters for many years, we are now focusing increasingly on human genetics and pathology. For example, we are using the new SOLiD sequencing system (at Rudbeck laboratories in collaboration with prof. Ulf Gyllensten) for large scale re-sequencing of the entire genomic segments of obesity genes from both obese and lean individuals in the cohort of 500 severely obese and well phenotypes Swedish children (prof. Claude Marcus, KI). The massive parallel sequencing on the SOLiD platform has been highly successful, providing us with the nearly complete SNP and insertion/deletion pattern of several genes gene. We also use a cohort of 2500 Greek children with large number of phenotypes, the ULSAM cohort (collaboration Ulf Riserus/Lars Lind) as well other cohorts. We are also studying the same genes in animal models and biochemical assays to identify the substrate for the novel transporters and their general molecular function.

We have set up a fly (drosophilia) lab, which studies the genetics of obesity and molecular mechanisms of aggression under the leadership of researcher Michael Williams. This has enabled us to study gene knock-outs in a large number of genes involved in behaviour. The team has also been strengthened with two additional post-doctoral fellows and post doctoral fellows Christian Benedict, Samantha Brooks and Pleunie Högenkamp are very productive. We are performing 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. We use a 3T scanner available 1-2 days a week, evenings and weekends. We have new evidence that humans show stronger activation in brain-reward centeres in response to the visual presentation of food images after a single night of sleep loss. We are also working in very close collaboration with the radiology unit led by Håkan Ahlström, professor in radiology and professor Lars Lind, Acute and Internal Medicine, who runs the PIVUS longitudinal cohort study. We are working on genome wide association SNP studies in these individuals to correlate the genetics to nutritional data and their relationship to brain and body image MR scans. We are also using the genetic platforms at the medical faculty for large scale human genetics, both SNPs, epigenetics and also gene expression. We are collaborating with Prof. Dr. Bernd Schultes, Head of the Interdisciplinary Obesity Center, St. Gallen, Switzerland. Through him, we have access to unique cohort data (very detailed

phenotypes and follow up) with over 1000 individuals that have undergone bariatric surgery resulting in large weight loss over short periods of time. We are performing genetics on the cohort and setting up new controlled studies addressing the epigenetic changes using genome wide methylation chips on human adipose biopsies, sperm and blood. The molecular biology lab has been strengthened with an oocyte injection facility, allowing functional characterization of novel transporters in terms of substrate and drug specificity. This will allow us to clarify the role of each individual transporter in neurons, and to identify transporters with unique, as well as redundant, functions in specific neuronal cell types. We have several new conditional knock-out mice lines in the pipeline on novel amino acid and neurotransmitter transporters and we have one novel mouse line that we are now analyzing. We are developing the project specifically to use new technologies in form of whole genome epigenetic assays and large scale identification of copy number variations (CNVs) and insertions through sequencing. CNVs and epigenetics are likely to contribute to the 'missing heritability' factor that SNP do not explain.

**Publications 2010-2012**


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**Agencies that support the work/ Funding**

Swedish Research Council
Swedish Brain Foundation
Åhlens Foundation

Novo Nordisk Foundation
Åke Wikberg Foundation,
Magnus Bergvall Foundation,
Tore Nilsons Foundation,
Gunvor och Josef Aners Foundation

## *Neuropsychopharmacology*

**Group leaders: Lars Oreland, Prof. em. and Erika Comasco, Ph.D.**

**Members of the group during 2012**

Comasco Erika, Post doc
Göktürk Camilla, Post doc
Hallman Jarmila, Prof. Psychiatry
Henrietta Henningsson, Bachelor student
Oreland Lars, Prof. em. Pharmacology
Robin Brostedt, Master student
Robin Midhage, Master student
Sara-Lisa Eriksson, Master student
Shahriar Faezi Razi, Master student
Shreyas Balachandra Rao, Master student
Todkar Aniruddha, PhD student
Wargelius Hanna-Linn, Post doc

**External collaborators:**

Center for Clinical Research, Västerås (prof. K. Nilsson)
Dept. Child and Adolescent Psychiatry, Linköping University (prof. C.-G. Svedin)
Dept. Psychology, Estonian Centre of Behavioural and Health Sciences, University of Tartu, Estonia (prof. J. Harro)
Dept. Women's and Child's Health, Uppsala University (prof. I. Sundström-Poromaa, doc. A. Skalkidou)
Maria Ungdom, Kings College of London (prof. S. Hodgins)
Dept. of Pharmaceutical Biosciences, Uppsala University (prof. Nylander I)

We have been aiming at investigating the importance of the central monoamine systems, and the serotonin system in particular, for personality, behaviour and risk of developing drug dependence and related risk behaviours, through the following projects:

- Studies on gene – environmental interactions for behaviour and psychiatric vulnerability
- Non-human primates models for alcoholism
- A rodent model for studying development of the serotonergic neuro-circuitry, and the role of serotonin-reuptake-inhibitors and alcohol during foetal development
- Studies on mechanisms underlying the association between trbc-MAO and personality/behaviour in dogs
- Behavioural and epigenetic studies on effects of early-life trauma and -drug exposure in rats

**Publications 2010-2012**

1. Biological aspects of postpartum depression. Skalkidou A, Hellgren C, Comasco E, Sylvén S, Sundström Poromaa I. *Womens Health* (Lond Engl). 2012
2. Influence of catechol-O-methyltransferase Val158Met polymorphism on startle response in the presence of high estradiol levels. Comasco E, Hellgren C, Sundström-Poromaa I. *Eur Neuropsychopharmacol.* 2012

3. Self-Reported Family Socioeconomic Status, the 5-HTTLPR Genotype, and Delinquent Behavior in a Community-Based Adolescent Population. Aslund C, Comasco E, Nordquist N, Leppert J, Oreland L, Nilsson KW. *Aggress Behav.* 2012
4. The effect of premenstrual dysphoric disorder and menstrual cycle phase on brain activity during response inhibition. Bannbers E, Gingnell M, Engman J, Morell A, Comasco E, Kask K, Garavan H, Wikström J, Sundström Poromaa I. *J Affect Disord*. 2012
5. Alcohol consumption among pregnant women in a Swedish sample and its effects on the newborn outcomes. Comasco E, Hallberg G, Helander A, Oreland L, Sundelin-Wahlsten V. *Alcohol Clin Exp Res.* 2012
6. The impact of adverse life events and the serotonin transporter gene promoter polymorphism on the development of eating disorder symptoms. Akkermann K, Kaasik K, Kiive E, Nordquist N, Oreland L, Harro J. *J Psychiatr Res*. 2012
7. Associations of MAOA-VNTR or 5HTT-LPR alleles with attention-deficit hyperactivity disorder symptoms are moderated by platelet monoamine oxidase B activity. Wargelius HL, Malmberg K, Larsson JO, Oreland L. *Psychiatr Genet*. 2012.
8. Postpartum depressive symptoms and the BDNF Val66Met functional polymorphism: effect of season of delivery. Comasco E, Sylvén SM, Papadopoulos FC, Oreland L, Sundström-Poromaa I, Skalkidou A. *Arch Womens Ment Health*. 2011
9. Postpartum depression symptoms: a case-control study on monoaminergic functional polymorphisms and environmental stressors. Comasco E, Sylvén SM, Papadopoulos FC, Sundström-Poromaa I, Oreland L, Skalkidou A. *Psychiatr Genet.* 2011
10. Maltreatment, MAOA, and delinquency: sex differences in gene-environment interaction in a large population-based cohort of adolescents. Aslund C, Nordquist N, Comasco E, Leppert J, Oreland L, Nilsson KW. *Behav Genet.* 2011
11. MAOA genotype, family relations and sexual abuse in relation to adolescent alcohol consumption. Nilsson KW, Comasco E, Åslund C, Nordquist N, Leppert J, Oreland L. *Addict Biol.* 2011
12. Ethanol-induced effects on the dopamine and serotonin systems in adult Wistar rats are dependent on early-life experiences. Oreland S, Raudkivi K, Oreland L, Harro J, Arborelius L, Nylander I. *Brain Res*. 2011
13. Do alcohol-dependent individuals with DRD2 A1 allele have an increased risk of relapse? A pilot study. Dahlgren A, Wargelius HL, Berglund KJ, Fahlke C, Blennow K, Zetterberg H, Oreland L, Berggren U, Balldin J. *Alcohol Alcohol.* 2011
14. Effects of serotonin transporter promoter and BDNF Val66Met genotype on personality traits in a population representative sample of adolescents. Hiio K, Merenäkk L, Nordquist N, Parik J, Oreland L, Veidebaum T, Harro J. *Psychiatr Genet.* 2011
15. Effects of the serotonin transporter (5-HTTLPR) and α2A-adrenoceptor (C-1291G) genotypes on substance use in children and adolescents: a longitudinal study. Merenäkk L, Mäestu J, Nordquist N, Parik J, Oreland L, Loit HM, Harro J. *Psychopharmacology* (Berl). 2011
16. Why do adolescents drink? Motivational patterns related to alcohol consumption and alcohol-related problems. Comasco E, Berglund K, Oreland L, Nilsson KW. *Subst Use Misuse.* 2010
17. Neuroticism-related personality traits are related to symptom severity in patients with premenstrual dysphoric disorder and to the serotonin transporter gene-linked polymorphism 5-HTTPLPR. Gingnell M, Comasco E, Oreland L, Fredrikson M, Sundström-Poromaa I. *Arch Womens Ment Health.* 2010
18. The clock gene PER2 and sleep problems: association with alcohol consumption among Swedish adolescents. Comasco E, Nordquist N, Göktürk C, Aslund C, Hallman J, Oreland L, Nilsson KW. *Ups J Med Sci*. 2010

19. Does the transcription factor AP-2beta have an impact on the genetic and early environmental influence on ethanol consumption? Oreland S, Daoura L, Gustafsson-Ericson L, Damberg M, Hyytiä P, Oreland L, Nylander I. *J Neural Transm*. 2010
20. Genetic variation of the ghrelin signaling system in females with severe alcohol dependence. Landgren S, Jerlhag E, Hallman J, Oreland L, Lissner L, Strandhagen E, Thelle DS, Zetterberg H, Blennow K, Engel JA. *Alcohol Clin Exp Res.* 2010
21. Environment and the serotonergic system. Oreland L, Nordquist N, Hallman J, Harro J, Nilsson KW. Eur Psychiatry. 2010
22. Platelet monoamine oxidase activity predicts alcohol sensitivity and voluntary alcohol intake in rhesus monkeys. Wargelius HL, Fahlke C, Suomi SJ, Oreland L, Higley JD. *Ups J Med Sci.* 2010
23. Serotonin, genetic variability, behaviour, and psychiatric disorders--a review. Nordquist N, Oreland L. Ups J Med Sci. 2010
24. Foreword. Oreland L, Magnusson G. *Ups J Med Sci.* 2010
25. Aggressive behavior, related conduct problems, and variation in genes affecting dopamine turnover. Grigorenko EL, De Young CG, Eastman M, Getchell M, Haeffel GJ, Klinteberg Ba, Koposov RA, Oreland L, Pakstis AJ, Ponomarev OA, Ruchkin VV, Singh JP, Yrigollen CM. *Aggress Behav.* 2010
26. Variation in the catechol-O-methyltransferase Val 158 Met polymorphism associated with conduct disorder and ADHD symptoms, among adolescent male delinquents. DeYoung CG, Getchell M, Koposov RA, Yrigollen CM, Haeffel GJ, af Klinteberg B, Oreland L, Ruchkin VV, Pakstis AJ, Grigorenko EL. *Psychiatr Genet.* 2010
27. Serotonin transporter gene promoter polymorphism affects the severity of binge eating in general population. Akkermann K, Nordquist N, Oreland L, Harro J. *Prog Neuropsychopharmacol Biol Psychiatry*. 2010

**Agencies that supported the work / funding**

Swedish Research Council, Västmanland County
Märta and Nicke Nasvells foundation for Psychiatric research
Regionala forskningsrådet in Uppsala- and Örebro region
Fredrik and Ingrid Thurings Foundation
Forskningsrådet för arbetsliv och socialvetenskap
Systembolagets råd för alkoholforskning

**Prizes and Awards**

1. Honorary Doctor, Tartu University, Dec 2010, Estonia (Lars Oreland)

2. Uppsla Läkareförening chooses our publication “Serotonin, genetic variability, behaviour, and psychiatric disorders--a review.” as the best article during 2010 in Upsala J Med Sci.

# *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 programme is to provide new knowledge on important brain injury mechanisms in cell culture and animal models, to be translated for exploration in the NICU. Several group members are active in both neurosurgical programmes, 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) is currently in action.

**Members of the group during 2012**

Per Enblad, MD, PhD, Professor of Neurosurgery
Lars Hillered, MD, PhD, Professor of Neurochemistry
Fredrik Clausen, PhD, Research Engineer, Animal modelling
Andeas Dahlin, Researcher, Materials science and proteomics (part time)
Sara Ekmark Lewén, BSc, PhD Student
Anna Erlandsson, PhD, Assistant Professor, Stem cell biology
Johanna Flygt, PhD student
Anders Hånell, BSc, PhD, currently post doc at Medical College of Virginia, USA
Tim Howells, PhD, Researcher, Computer science
Charlotte Israelsson, PhD, Post-Doc (part time)
Ulf Johnson, MD, Radiology Resident, PhD Student

Anders Lewén, MD, PhD, Neurosurgeon, Associate professor (50% research time)
Camilla Lööv, BSc, PhD Student
Niklas Marklund, MD, PhD, Neurosurgeon, Associate professor, Researcher (50%), Swedish Research Council
Pelle Nilsson, MD, PhD, Neurosurgeon, Pediatric neurosurgery chief
Christoffer Nyberg, MD, Neurosurgery Resident, PhD Student
Lena Nyholm, NICU Nurse, PhD Student
Karlis Purins, MD, Neurosurgery Resident, PhD-student
Elisabeth Ronne, MD, PhD, Adjunct professor, Neurosurgeon (20% research time)
Elham Rostami, MD, Ph D, Neurosurgery resident (Forskar-ST block)
Mats Ryttlefors, MD, PhD, Neurosurgeon
Karin Skoglund, NICU Nurse, PhD
Inger Ståhl-Myllyaho, NICU Technician
Maria Zetterling, MD, PhD, Neurosurgeon

**Undergraduate students and project researchers**

Nina Farrokhnia (30 hp MD program)
Hjalmar Flygt (30 hp MD program)
Gudrun Andrea Fridgeirsdottir (30 hp Master thesis + 15 hp Project)
Aishwarya Geeyarpuram Nadadhur (45 hp Master thesis Applied Biotechnology)
Johanna Hedin (20 hp Project)
Hanna Jönsson (15 hp Biomed program)
Olivia Kiwanuka (30 hp MD program)
Öykü Kocak (30 hp Project, Master thesis)
Frida Lenne (7.5+30 hp Project)
Asha Modugo (15 hp, Elective course in Neuroscience)
Lovisa Sylvén (30 hp MD program)
Eddie Söderberg Modig (15 hp Biomed program)

***Project 1: Clinical brain injury program – Neurocritical care***

**Participants:** Per Enblad (Group leader), Lars Hillered, Tim Howells, Ulf Johnson, Anders Lewén, Niklas Marklund, Pelle Nilsson, Christoffer Nyberg, Lena Nyholm, Karlis Purins, Elisabeth Ronne, Elham Rostami, Mats Ryttlefors**,** Karin Skoglund, Inger Ståhl, Maria Zetterling.

***Background***
Traumatic brain injury (TBI) and subarachnoid haemorrhage (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 and Networks***

*Multimodality monitoring* – The technical equipment available in our NICU allows for continuous monitoring of intracranial pressure, systemic blood pressure, cerebral perfusion pressure, intracerebral neurochemistry changes (e.g. energy metabolic perturbations and biomarkers), neurophysiology (e.g. post traumatic seizure activity), brain temperature, 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. The recently acquired mobile CT scanner with a xenon CBF device will provide a powerful additional monitoring tool for the future.

*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), 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). All TBI patients treated in our NICU during the last 5 years are included in the database to date.

*Biobanking facilities*

Approved systems for biobanking of body fluid samples, brain biopsies and resected brain tissue have been 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). Information technology (IT) is used to collect patient data for a common web-based database for TBI research. This will provide 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, cellculture 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 newly renovated Uppsala NICU is of top international standard, providing one of the major research platforms within the UBIC. The UBIC 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 research assistant (100%) and one PhD student (100%).

Another multidisciplinary project was launched in 2007 in a collaborative effort between UBIC and the Uppsala Berzelii Technology Center for Neurodiagnostics (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 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 2012***

For main results in 2012 the reader is referred to the list of publications below. In addition, the Mobile CT Xenon CBF technique has been set up in the NIC unit during 2012 and is now in full use.

***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, Sara Ekmark Lewén, Anna Erlandsson, Johanna Flygt, Anders Hånell, Charlotte Israelsson, Anders Lewén, Camilla Lööv, Niklas Marklund, Inger Ståhl, Lovisa Tobiesson, Aishwarya Geeyarpuram Nadadhur, Eddie Söderberg Modig, Asha Modugo.

***Overall goal***

*Uppsala Brain Injury Center (UBIC)* – Experimental neurotrauma research is organised as a translational research network with focus on 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, cell culture systems, animals 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 intraparechymal 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 Fluid Percussion Injury Model) for rodents. All the models are widely used internationally, thus facilitating comparison of data between research groups.

Another novelty is our recently established cell culture facility, allowing for studies of stem cell biology and *in vitro* trauma of individual cells as well as the interactions between cell types following injury in mixed cell culture models. In 2011 we obtained and set up a time-lapse microscopy for these studies.

A few years ago, a long term strategy was adopted 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. This effort is being made in close collaboration with Prof Bengt Meyerson, BMC. 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 and cell culture 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-IL1β 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 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 2012***

For results in 2012 the reader is referred to the below list of publications. In the following a few high lights of the most recent results are mentioned:

- We have in 2012 continued to characterise a model of diffuse axonal injury (a major injury mechanism in TBI patients) in rat, as well as in mouse (for use in transgenic mice) in collaboration with Prof John Povlishock, MCV, USA. This central fluid percussion injury (cFPI) model has been characterized and has widely distributed bilateral traumatic axonal injury and inflammation as key features (Ekmark Lewén et al: revised manuscript under peer review). In preliminary experiments anti-IL1β antibody treatment improved

functional outcome in cFPI mice strongly supporting link between inflammation and axonal injury following TBI. The cFPI model will be excellent for studies on the molecular mechanisms and biomarkers of axonal injury and inflammation, and may lead to identification of novel targets for intervention.

- In a NICU biomarker study we found that the levels of the $F_2$-isoprostane 8-iso-$PGF_{2\alpha}$ was much higher in microdialysate samples compared to CSF or plasma in TBI patients (Clausen et al, 2012). The results support the notion that 8-iso-$PGF_{2\alpha}$ and 15-keto-$PGF_{2\alpha}$, widely used biomarkers of oxidative stress and inflammation, may be useful biomarkers in the NICU setting. We are currently planning to set up a highly sensitive analytical proximity ligation assay within the Berzelii Centre to test this hypothesis.
- In our *in vitro* model of TBI proteomic screening revealed injury specific release of actin-related proteins (ezrin and moesin) presumably from injured astrocytes. Since the proteins were also found to increase after *in vivo* TBI in mice the proteins may be potentially useful biomarkers of TBI (Lööv et al: ***PLoS ONE*** 2013, in press).

The group actively participated in the following international scientific meetings in 2012:

1. Hillered L (2012) Traumatic brain injury - Animal modeling and translation to the Neuro-ICU setting (invited speaker). ***New strategies and models to investigate pathophysiology and therapeutic approaches in traumatic brain injury and neurological diseases.*** University of Rijeka, Croatia, March 1-2, 2012.

2. Kocak O, Fridgeirsdottir GA, Hillered L, Clausen F (2012) Endogenous free radical production by NADPH oxidase 2 contributes to the secondary injury cascade after traumatic brain injury in mice. ***Ninth World Congress on Brain Injury***, The International Brain Injury Association (IBIA), Edinburgh, Scotland, March 21-25, 2012. ***Brain Injury*** 26(4-5): 503-504.

3. Loov C, Shevchenko G, Hillered L, Wetterhall M and Erlandsson A (2012) Identification of unique proteins after injury in a cell culture model of TBI. ***Ninth World Congress on Brain Injury***, Edinburgh, The International Brain Injury Association (IBIA), Scotland, March 21-25, 2012. ***Brain Injury*** 26(4-5): 487-488.

4. Ekmark Lewén S, Hedin J, Kiwanuka O, Andrea G, Clausen F, Lewén A, Hillered L, Marklund N (2012) Neuroinflammatory responses and glial cell reactions after traumatic diffuse axonal injury in mice. ***Ninth World Congress on Brain Injury***, The International Brain Injury Association (IBIA), Edinburgh, Scotland, March 21-25, 2012. ***Brain Injury*** 26(4-5): 598-598.

5. Kenne E, Erlandsson A, Lindbom L, Hillered L, Clausen F (2012) Neutrophil depletion reduces edema formation and tissue loss following traumatic brain injury in mice. ***Experimental Biology Meeting***, APR 21-25, San Diego, CA, USA. ***FASEB J*** 26(Apr).

6. Dahlin AP, Hjort K, Hillered L, Sjödin MOD, Bergquist J, Wetterhall M (2012) Quantification of Proteins Adsorbed to Surface Modified and Non-Modified Microdialysis Membranes using on-Surface Enzymatic Digestion (oSED) iTRAQ-MALDI-TOF/TOF MS. ***60th ASMS Conference on Mass Spectrometry and Allied Topics***, May 20 - 24, Vancouver, Canada.

7. Marklund N, Farrokhnia N, Hanell A, Enblad P, Zetterberg H, Blennoow K, Hillered L (2012) Monitoring of Amyloid-β dynamics after human traumatic brain injury. ***30th Annual National Neurotrauma Society Symposium***, July 22-26, Phoenix, AZ, USA. ***J Neurotrauma*** 29(10): A185-A185.

8. Wetterhall M, Sjödin MOD, Bergquist J, Hillered L, Hjort K, Dahlin AP (2012) Mapping the protein distribution within a microdialysis sampling system by on-surface enzymatic digestion in combination with mass spectrometry. ***Monitoring Molecules in Neuroscience, 14th International Conference***, September 16-20, 2012, London, UK.

9. Nyberg C, Karlsson T, Hillered L, Ronne-Engstrom E (2012) Acute cerebral energy metabolic crisis after experimental SAH in pigs. ***8th World Stroke Congress***, October 10-13, 2012, Brasilia, Brazil.

***Significance***

The basic science part of the research within the animal and cell culture modelling platforms will provide important novel knowledge on the secondary injury mechanisms following TBI and identify novel targets for intervention for neuroprotection and neurorepair. These advances may be translated to the NICU setting with the ultimate goal of improving the outcomes for human victims of TBI.

**Publications 2010-2012**


1. Ekmark-Lewén S, Lewén A, Israelsson C, Li G-L, Farooque M, Olsson Y, Ebendal T, Hillered L: Vimentin and GFAP responses in astrocytes after contusion trauma to the rat and mouse brain. ***Restorative neurology and neuroscience*** 28(3): 311-21, 2010 [IF 2.0].

2. Israelsson C, Bengtsson H, Lobell A, Nilsson L, Kylberg A, Isaksson M, Wootz H, Lannfelt L, Kullander K, Hillered L and Ebendal T: Appearance of Cxcl10 expressing cell clusters common for neurodegenerative disorders and traumatic brain injury. ***Eur J Neurosci*** 31:852-863, 2010 [IF 3.7].

3. Zetterling, M, Hallberg L, Hillered L, Karlsson T, Enblad P, Ronne Engström E: Brain energy metabolism in patients with spontaneous subarachnoid hemorrhage and global cerebral edema. ***Neurosurgery*** 66(6):1102-10, 2010 [IF 3.0].

4. Dahlin AP, Wetterhall M, Caldwell KD, Larsson A, Bergquist J, Hillered L and Hjort K: Methodological aspects on microdialysis protein sampling and quantification in biological fluids – An in vitro study on human ventricular CSF. ***Anal Chem*** 82:4376-4385, 2010 [IF 5.7].

5. Hånell A, Clausen F, Björk M, Jansson K, Philipsson O, Lannfeldt L, Hillered L, Weinreb P, Lee D, McIntosh TK, Strittmatter SM, Marklund N: Genetic Deletion and Pharmacological Inhibition of Nogo-66-Receptor Impairs Cognitive Outcome Following Traumatic Brain Injury in Mice. ***J Neurotrauma*** 27(7):1297-309, 2010 [IF 4.3].

6. Ekmark-Lewén S, Lewén A, Meyerson BJ, Hillered L: The Multivariate Concentric Square Field Test Reveals Behavioral Profiles Regarding Risk Taking, Risk Assessment and Exploration in Mice Subjected to Traumatic Brain Injury. ***J Neurotrauma*** 27(9):1643-55, 2010 [IF 4.3].

7. Purins K., Enblad P., Sandhagen, B. and Lewen, A: Brain tissue oxygen monitoring: a study of in vitro accuracy and stability of Neurovent-PTO and Licox sensors. ***Acta Neurochir*** (Wien):152:681-8, 2010. [IF 1.5].

8. Salci K, Enblad P, Goiny M, Contant CF, Piper I, Nilsson P: Metabolic effects of a late hypotensive insult combined with reduced intracranial compliance following traumatic brain injury in the rat. ***Ups J Med Sci*** 115(4):221-31, 2010.

9. Ryttlefors M, Enblad P, Ronne-Engström E, Persson L, Ilodigwe D, Macdonald RL: Patient age and vasospasm after subarachnoid hemorrhage. ***Neurosurgery*** 67:911-17, 2010.

10. Piper I, Chambers I, Citerio G, Enblad P, Gregson B, Howells T, Kiening K, Mattern J, Nilsson P, Ragauskas A, Sahuquillo J, Donald R, Sinnott R, Stell A; BrainIT Group: The brain monitoring with Information Technology (BrainIT) collaborative network: EC feasibility study results and future direction. ***Acta Neurochir*** (Wien). 152:1859-71, 2010.

11. Ryttlefors M, Howells T, Ronne-Engström E, Nilsson P, Enblad P: Neurointensive care is justified in elderly patients with severe subarachnoid hemorrhage--an outcome and secondary insults study. ***Acta Neurochir*** (Wien). 152:241-9, 2010.

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**Agencies that support the work/ Funding**

The Swedish Research Council (project grant)
The Swedish Research Council (Research Position 50%)
The Swedish Research Council/Vinnova-Uppsala Berzelii Centre
EU
Uppsala University Hospital (ALF funds)
Uppsala University Faculty of Medicine
Swedish Brain Foundation
Berzelii Technology Centre for Neurodiagnostics
Åhlén Foundation
Selander Foundation
Swedish Society of Medicine
Jeanson Foundation
Lars Hiertas Memorial
Magnus Bergvall Foundation
Tore Nilsson Foundation

## Developmental Neuroscience

### *Molecular and Genetic Analysis of Experimental Traumatic Brain Injury*

**Group leader: Ted Ebendal, Professor**

**Members of the group during 2012**

Ted Ebendal, Ph.D., Professor
Nestor G. Carri, M.D., Ph.D., Visiting Scientist
Charlotte Israelsson, Dr. Med. Sci., Researcher
Annika Kylberg, Research Engineer
Anders Hedin, Research Assistant

When a traumatic brain injury (TBI) afflicts a person, e.g. caused by a traffic accident or fall, many severely debilitationg processes are initiated. At present, there is no effective pharmacological treatment available for reducing damaging effects to the brain. This is largely due to a lack of detailed understanding of the molecular mechanisms involved in brain response to trauma. Our research strategy is to identify key actors of importance for functions in TBI, as a basis for development of novel neuroprotective therapies. Findings are likely to be applicable also to other major neurological problems, such as stroke and degenerative diseases, based on our observations of reactions in the brain that are similar in several models of brain injuries and pathological conditions.

Thus, our research focuses on the molecular and cellular consequences of TBI. Increased knowledge of fundamental cell interactions and activation of various genes is crucial when designing novel treatment strategies postinjury. We have performed experimental TBI in mice and detected several critical events involved in inflammation. In particular, expression levels

are strongly affected among various chemokines and their receptors linked to specific cells in the immune system.

After an injury, a number of peripheral immune cells are stimulated to enter the brain, beginning in the first hour and continuing for a period that may be as long as several months. When this cell invasion following brain damage occurs, it results in a strong inflammatory response, which may worsen the tissue damage. Inflammation is a two-edged sword with beneficial as well as detrimental effects, and gives a complex picture of damage to the brain. The involved chemokines and their receptor in our material show a central uniting role in TBI, both with inhibitory and promoting effects, of interacting molecules and pathways. Thus, an induced trauma shows differences in temporal expression levels which differs both in time and regarding the strength of the response. Moreover, we have observed similar effects in comparative studies using other neurodegenerative conditions such as in mouse models of Alzheimer's disease, ALS and multiple sclerosis.

We have characterized several groups of cells and transcripts altered after trauma with cell sorting, microarray analysis and quantitative RT-PCR from neocortex in mice subjected to focal injury. These regulations cover mainly inflammation and immunity, tissue remodeling, and cell signaling.

The research group is located at the Biomedical Center and collaborates closely with the Neurosurgery Unit of our Department, located at the University Hospital, in a Neurotrauma research consortium. Additionally, the research group is also part of the Uppsala University Brain Injury Center (UBIC).

***Project 1: Transcriptional responses after inflicting injury to the mouse brain***

**Participants**: Charlotte Israelsson, Annika Kylberg, Anders Hedin, Ted Ebendal

A large survey of transcriptional alterations was carried out in the neocortex and hippocampus at different time-points postinjury. Many of the upregulated genes encode proteins that serve functions in inflammatory responses and tissue remodeling. Among cellular growth factors the chemokine family showed the most robust responses to injury. In particular, we identified activation of *Ccl3* (macrophage inflammatory protein–1 alpha) and its receptors *Ccr1* and *Ccr5*, as well as a strong up-regulation of *Ccl2* (monocyte chemoattracting protein-1) and *Ccl12* (monocyte chemoattracting protein-5) and their shared receptor *Ccr2*. A strong upregulation of *Cxcl10* (interferon induced protein-10) in clustered cells, partly dependent of the two pathways mentioned above, was also detected and likely represent inflammatory monocyte-derived cells invading the injured brain.

***Project 2: Genetic inactivation of chemokine signalling pathways – clues for therapeutic strategies in TBI***

**Participants**: Ted Ebendal, Annika Kylberg, Nestor Carri, Charlotte Israelsson

To explore how the central chemokines and their receptors interact, we have been breeding several lines of knockout mice used to define the role of each of the chemokine pathways. We also exposed these mice to controlled cortical impact (CCI) injury. *Ccr2*-/- mice were studied to reveal the function of monocyte chemoattraction by *Ccl2* and *Ccl12*. Overall, the activation of antigen-presenting dendritic cells was markedly reduced after TBI in these knockouts compared to wildtype mice. In contrast, the mice lacking the *Ccl3* gene revealed increased levels of injury-induced transcripts in the ipsilateral neocortex. Also, *Cxcl10* knockout mice

were subjected to a CCI injury which demonstrated a dependance downstream of both *Ccl3* and *Ccr2*.

With *in situ* hybridization, the distribution of the chemokine *Cxcl10* gave reactive clusters of cells after an injury. These clusters, likely to represent the subset of mouse "inflammatory monocytes", appear not only near the focal injury, but also in deep areas of the brain, in axon-rich areas such as corpus callosum and at large distances from the site of primary injury. We have carried out comparative studies of mouse models of TBI and of mouse models of Alzheimer's disease, of multiples sclerosis (MS) and of amyotrophic lateral sclerosis (ALS). The results demonstrate that the clustered *Cxcl10*-expressing cells are a common feature among all these conditions. The findings suggest that invasion of inflammatory monocytes may represent a hitherto unrealised common feature for neurotrauma, and may represent a potential target in the treatment of TBI.

***Project 3: Outcome of treatment strategies in TBI***

**Participants**: Ted Ebendal, Annika Kylberg, Charlotte Israelsson

After TBI, the distribution of the chemokine *Cxcl10* give reactive clusters of cells revealed by *in situ* hybridization.These clusters appear in the penumbra zone, but also at some distances from the primary injury as well as, to a minor extent, also contralaterally. We have carried out comparative studies of mouse models of TBI and neurodegenerative diseases. Under these disease conditions the clustered *Cxcl10*-expressing cells, possibly representing plasmacytoid dendritic cells, are apparent. In line with this, treatment strategies applicable for several brain-damaging disorders and diagnosis thus become obvious. We have tested several compounds with anti-inflammatory actions in order to find candidate therapies for TBI and with the reduction of postinjury inflammation, as a primary focus. The cytostatic cyclophosphamide, in use in patients with cancer or systemic lupus erythematosus, has during 2012 given promising results. The compound is a well-known pharmaceutical substance impairing leukocytes, and has given robust reductions in injury-induced transcripts, reminiscent of those seen in the injured *Ccr2*-/- mice (project 2). In particular, the agent seems to block the recruitment and activation of antigen-presenting conventional dendritic cells.

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**Agencies that support the work/ Funding**

The Swedish Research Council
The Swedish Brain Foundation

**Honours**

Ted Ebendal was selected to present the Karl-Johan Öbrink Lecture at Uppsala University Biomedical Center, December 2012.

## Regenerative Neurobiology

**Group leader: Elena N. Kozlova, Assoc. Professor**

**Members of the group during 2012**

Andreas Oster, amanuensis, medical student
Anongnad Ngamjariyawat, PhD student
Carl Trolle, PhD student
Håkan Aldskogius, MD, PhD, Professor emeritus
Johan Olerud, PhD, Postdoc
Mariya Kozhevnikova, PhD, Postdoc
Niclas König, PhD student
Ninnie Abrahamsson, biomedical analyst
Svitlana Vasylovska, PhD, Postdoc

**External Collaborations**

*National:* Docent Alfonso Garcia Bennett, Dept of Engineering Sciences, Uppsala Univ; Profs Leif Jansson, Nils Welsh, and Per-Ola Carlsson, Dept of Med Cell Biology, Uppsala Univ; Profs Åke Seiger, and Erik Sundström, and Docent Elisabet Åkesson, Karolinska institutet, Stockholm, Prof Jens Schouenborg, Neuronano Res Ctr, Lund Univ, Lund.

*International:* Dr Christian Berens, Dept of Microbiology, Univ Erlangen-Nuremberg; Profs Elisabeth Bock, and Vladimir Berezin, Panum Institute, Copenhagen Univ, Denmark; Prof Eugen Lukanidin, Danish Cancer Res Inst, Copenhagen, Denmark; Prof Thomas Knöpfel, Riken Brain Res Inst, Japan; Prof Harry Heimberg, Diabetes Research Center, Brussels, Belgium; Inst of Developmental Biology, Russian Academy of Sciences, Moscow, Russia; Inst of Cytology, Russian Academy of Sciences, St Petersburg, Russia.

**Our research has two long-term objectives:**

- Promote functional recovery after dorsal root and spinal cord injury.
- Exploit the beneficial potential of stem cells for renewal and repair of insulin producing beta-cells.

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 objective is to restore those functions that are lost following spinal cord injury, by
– promoting regeneration of injured nerve fibres in the spinal cord,
– promoting functionally useful reorganization of neural connections (plasticity), and
– repairing lost connections by transplantation of stem cells, which are guided to become desired type of neurons.

In recent studies we have also shown that growth, survival and function of insulin producing cells in the pancreas are promoted if the cells are cultured or transplanted together with stem cells from the nervous system. These observations can offer novel opportunities to treat patients with type 1 diabetes who have lost large amounts of their insulin producing cells. Our objective is
– to identify the mechanisms underlying these stimulating effects, and
– to contribute to their exploration for the treatment of patients with diabetes type 1.

***Differentiation of stem cells by intrinsic and extrinsic factors***

Stem cells are attractive as a source for replacement of lost nerve cells in the injured or diseased nervous system by transplantation. A major problem with this approach is to improve survival of transplanted stem cells (which first have to be immature in order to survive) and to differentiate them later to the desired type of nerve cells. Our research aims at developing novel tools to regulate long-term survival and specific differentiation of transplanted stem cells. Using a gene-regulatory system we have been able to promote differentiation to specific types of neurons from transplanted human neural stem cells (Stem Cells Dev, 2011). In parallel with these studies, we employ novel delivery systems for in vivo release of molecules, which drive normal differentiation of specific neurons. The results of these studies can contribute to improved survival and differentiation of stem cells for cell replacement therapy in neurological disorders.

***Transplantation of stem cells to restore control of lost motor functions after spinal cord injury***

The lesion area after spinal cord injury becomes extremely hostile for growth of nerve fibres and blocks any possible extension of injured nerve fibres. Our approach is to circumvent the lesion area by creating, outside the spinal cord, a neuronal station, which will relay information from above to below the injury. In this way, it may be possible to restore descending control of motor functions below the injury. By inserting a piece of a peripheral nerve we induce nerve fibres from above a spinal cord injury to grow into this peripheral nerve graft. At the other end of this graft, outside the spinal cord, we place a transplant of stem cells with the aim of generating nerve cells, which on one hand, will be contacted by nerve fibers growing in the peripheral nerve graft and, on the other hand, will grow their own nerve fibres into the spinal cord below the lesion. In this way, we have created, around the injury, a bridge composed of host-descending nerve fibres making contacts with peripherally transplanted stem cell-derived nerve cells, which, in turn, relay the descending information into the spinal motor networks below the injury.

***Transplantation of stem cells to restore lost sensory functions after injury to the dorsal roots***

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. After injury to these roots, often referred to as plexus avulsion injury, sensory nerve fibres are unable to regenerate into the spinal cord. As a result avulsion injuries result in 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 implant stem cells at the junction between the dorsal root and spinal cord with two different aims: i) To provide the injured dorsal root nerve fibres with a cellular environment supportive for growth into the spinal cord, or ii) To generate neurons which can serve as functional relay at the dorsal root-spinal cord interface by receiving contacts from injured dorsal root nerve fibers and, thereafter, transmit this information into the spinal cord. In a long term perspective, our findings can help to develop novel treatment for patients who have suffered plexus avulsion injury.

***Neural stem cells promote survival and function of insulin producing beta-cells***

Transplantation of pancreatic islets is en established treatment for patients with diabetes type I. Islet survival after transplantation to these patients is, however, insufficient and new strategies to enhance transplant viability need to be developed. We previously showed that cultures or transplants of neural stem cells together with insulin producing beta-cells are able to stimulate proliferation and promote survival and function of beta-cells (Diabetologia, 2009; Pancreas, 2012). Using culture systems combining neural stem cells and beta-cells we have determined that these cells need to be in direct contact with each other in order for neural stem cells to exert their beneficial effects (Diabetologia, 2012). These findings present the possibilities of improvement to the outcome of islet or beta-cell transplantation, and of increasing the endogenous beta-cell mass in patients with diabetes type 1. We now aim to determine the nature of the mechanisms that are involved in mediating beta-cell proliferation.

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**Agencies that support the work/ Funding**

The Swedish Research Council (M)
The Swedish Institute
The Swedish Foundation for International Cooperation in Research and Higher Education (STINT)
Signhild Engkvist's Foundation

## Physiotherapy

### *Rehabilitation and Physical Activity in Patients with Chronic Diseases*

**Group leader: Margareta Emtner, Associate Professor**

**Members of the group during 2012**

Elisabeth Anens, PhD, Reg Physiotherapist
Charlotte Urell, Reg. Physiotherapist, PhD-student
Carina Hagman, Reg. Physiotherapist, PhD-student
Mikael Andersson, Reg. Physiotherapist, PhD-student
Henrik Johansson, Reg. Physiotherapist, PhD-student

**External Collaborators**

Christer Janson, Professor, Medical Sciences, Uppsala University
Hans Hedenström, Associate Professor, Medical Sciences, Uppsala University
Harpa Arnardottir, PhD, Medical Sciences, Uppsala University
Elisabeth Westerdahl, PhD, Örebro University
Karin Hellström, PhD, Neuroscience, Uppsala University
Mats Arne, PhD, Medical Sciences, Uppsala University
Lena Kallings, PhD, Exercise physiologist, Stockholm University
Karin Wadell, PhD, Umeå University, Sweden
Ulla Svantesson, Professor, Gothenburg University, Sweden
Richard Casaburi, Professor, UCLA, Los Angeles, California, USA
Anne Lindberg, PhD, Umeå University, Sweden
Kjell Larsson, Professor, Karolinska Institute, Stockholm, Sweden

Evidence links higher levels of physical activity to improved health. Increased physical activity improves quality of life, and individuals reaching recommended physical activity levels are more likely to have a better overall health-related quality of life and perceived health status than those who do not. Regular physical activity is widely accepted as behaviour that is likely to improve a number of health outcomes and reduce all-cause mortality.
In subjects with chronic diseases the level of physical activity is markedly reduced compared to healthy individuals. It has also been recommended that physical activity should be one of the highest priorities for preventing and treating disease.

Our group and collaborators include researchers from the fields of physiotherapy, clinical physiology, pulmonary medicine, cardiology, epidemiology, and surgical sciences.
Our main focus is on clinical research with the aims of identifying physical activity and physical capacity in subjects with chronic diseases; investigating reasons for physical inactivity and physical limitations, identifying simple tests to measure physical capacity; and, evaluating rehabilitation interventions.
Our current research includes studies in subjects with chronic obstructive pulmonary disease (COPD), asthma, sleep apnoea, heart diseases, dysfunctional breathing, and subjects with exercised induced breathing problems.

**Our ongoing research is pursued in four main projects**

***Project 1: Physical activity on prescription and behavioral medicine interventions to maintain health enhancing physical activity (HEPA)***

- Maintenance of physical activity in patients with chronic obstructive pulmonary disease who have participated in pulmonary rehabilitation

***Project 2: Measures of physical activity and capacity***

- Validation of three different accelerometers in patients with chronic obstructive pulmonary disease (COPD).
- Reliability and validity of the 30 metre walking test.
- Reliable and valid physical performance tests to evaluate interventions and to predict morbidity and mortality in patients with COPD

***Project 3: Breathing - identification of breathing pattern and breathing problems and interventions to improve impaired breathing and its consequences***

- Breathing exercises after open heart surgery – effects of breathing exercises on oxygenation and pulmonary function in the first few days following cardiac surgery, and two months thereafter.
- Dysfunctional breathing – identification and description of patients with dysfunctional breathing and interventions to improve breathing pattern, health, and health care costs.
- Exercise-induced breathing problems in 13-14 year old subjects – a population based study in Uppsala County to identify subjects with breathing problems, reasons for their breathing problems, and their level of physical activity.

***Project 4: Supplemental oxygen during physical activity***

-To study the effects on exercise capacity, physical activity, inflammatory markers and quality of life of supplemental ambulatory oxygen, to be used during physical activity, in patients with COPD who are normoxic at rest but hypoxemic during a 6-min walk test (6 MWT).

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**Agencies that support the work/ Funding**

The Faculty of Medicine, Uppsala University
Heart and Lung Foundation, Sweden
Heart and Lung Patient Association, Sweden
Uppsala County Council
ALF

## *Rehabilitation of Patients with Neurological or Geriatric Impairments*

**Group leader: Karin Hellström, Ph.D, Reg. Physiotherapist**

**Members of the group during 2012**

Birgitta Lindmark, Senior Professor in Physiotherapy
Lena Zetterberg, Ph.D, Reg. Physiotherapist
Elisabeth Anens, Ph.D, Reg. Physiotherapist
Birgit Vahlberg, Reg. Physiotherapist, PhD-student
Helena Grönstedt, Reg. Physiotherapist, PhD-student
Susanna Tuvemo-Jonsson, Reg. Physiotherapist, research assistant (PhD applicant)

**External Collaborators**

Professor Tommy Tommy Cederholm, Dept. of Public Health and Caring Sciences/ Clinical Nutrition and Metabolism, Uppsala University.
Docent Kerstin Frändin, Department of Neuroscience, KI, Stockholm.
Professor Astrid Bergland, Oslo University Collage, Norge.
Associate Professor Lis Puggaard, University of Southern Denmark, Odense, Danmark.
Ph D Jorunn Helbostad, Trondheim University, Norge.

Professor Anne Söderlund, Mälardalen University, School of Helath, Care and Social Welfare Physiotherapy.
Ph D Ann-Christine Johansson, Mälardalen University, School of Helath, Care and Social Welfare Physiotherapy.

The neurological and geriatric group conducte research into rehabilitative and preventive methods that aim to increase and preserve, levels of independence in daily living in persons with neurological and geriatric diseases or impairments. Our main focus is on clinical research i.e. elderly patients with stroke, nursing home residents, fall prevention in community-dwelling older people, patients with cervical dystonia, Parkinsons' disease, MS and Charcot-Marie Thooths' disease.
One of our main areas of research focuses on how to develop strategies for prevention of falls in both elderly persons and in persons with neurological disease. Research topics currently studied include: the impact of a high intensity functional exercise program with a behavioural medicine approach on level of physical activity; fear of falling; depression; health related quality of life; body mass index (BMI); and, costs of care in elderly patients with stroke. A new study focuses on the interrelations between fatigue, fear of falling, and social influences on physical activity, level of impairment with level of physical activity in persons with Parkinson' disease, Multiple sclerosis, Charcot-Marie-Tooth disease or Cervical Dystoni. A further study is planned with the objective of identifying experiences of pain, and the predictive variables for pain, in patients with amyotrphic lateral scleros (ALS) as well as investigation of the presence of fatigue, depression, falls and level of physical activity.

***Projects during 2012***

1) Physical and psychological problems and the effect of an intensified physical activity intervention for patients with stroke – a combination of physical training and behavioural medicine principles.
2) Effects of individually-tailored physical and daily activities for residents in nursing home settings – A Nordic multi-centre study.
3) A comparison of Dysport (100 U/ml) and Botox (100 U/ml) using dose conversion factor 3:1 and 1.7:1 in the treatment of cervical dystonia.
4) Physical activity in persons with neurological disease.
5) Effects of fall-prevention intervention in community dwelling elderly people over 75 years – a CRT
6) The ability of the Functional Balance Test for Geriatric patients to predict fall

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**Agencies that support the work/ Funding**

Faculty of medicine, Uppsala University
Regionnämnden
Uppsala community
Landstinget i Uppsala
Strokeförbundet
ALF

## *Behavioural Medicine and Physiotherapy*

**Group leader**: **Pernilla Åsenlöf, Associate Professor**

**Members of the group during 2012**

Annika Bring, PhD student/PhD
Ingrid Demmelmaier, PhD
Christina Emilson, PhD student
Sara Holm, PhD student
Helena Igelström, PhD student
Cecilia Rastad, Post doc
Sören Spörndly-Nees, PhD student

**External Collaborators**

Magnus Lindberg, PhD (Gävle County Council)
Per Lindberg, Professor (Psychology, Uppsala University)
Åsa Revenas, PhD student (Karolinska Institutet)
Maria Sandborgh, PhD (Mälardalen University)

The Behavioural Medicine and Physiotherapy group is an interdisciplinary research group with a strong focus on clinical behavioural medicine intervention research. Current members include physiotherapists, nurses and psychologists associated with the Faculties of Medicine and Social Sciences. The group does ground-breaking work in behavioural medicine interventions within the physiotherapy context, showing that physiotherapy interventions benefit from including health behaviour change strategies that are theoretically based and tailored to the individual patient.

Research activities focus on issues related to adoption and maintenance of health-related behaviours (e.g. physical activity and sedentary behaviours, eating behaviours, and self-

management behaviours) within a bio-psycho-social framework. The understanding of how biological, psychological and social variables interact during development of chronic conditions as well as recovery is the basis for research. Theoretical principles from social cognitive theory and 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 benefit from which dose and content of behavioural medicine treatment at which time point?"Aspects unifying as well as differentiating conditions and patient profiles regarding prerequisites and effects of health behavior interventions are expected.

Ongoing research targets acute and chronic musculoskeletal conditions in adults and children respectively, rheumatoid arthritis, obstructive sleep apnea and overweight, and schizophrenia. Methods applied are guided by the research questions and as a consequence the group has its main expertise in clinical trials which is combined with competencies in qualitative methods and participatory designs for implementation. An important branch of our research is on how to cost-effectively implement the new and effective treatments developed in health and well care respectively.

Ongoing main projects are entitled:

1. A Behavioural Medicine Perspective on Acute Whiplash Associated Disorders

2. Development, evaluation and cost effectiveness of a treatment program with a behavioral medicine approach for adolescents with persistent pain

3. Stepped care and tailored pain management. A randomised controlled trial for the study of a stepped-care model of tailored behavioral medicine pain in treatments in primary care.

4. Health related behaviour change in obstructive sleep apnea syndrome and overweight

5. Integration of patients' innovations in a web-based intervention targeting physical activity. A case study among individuals with rheumatoid arthritis.

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**Agencies that support the work/ Funding**

The Swedish Rheumatism Association; The Pain Initiative
The Swedish Rheumatism Association; The Rheumatism Foundation
Uppsala University Medical Faculty Caring Sciences Funding

## Speech and Language Pathology

**Group leader: Margareta Jennische, Assistant Professor**

**Members of the group during 2012**

Per Alm, PhD, visiting teacher
Monica Blom Johansson, PhD, senior lecturer
Martina Hedenius, PhD student
Margareta Jennische, PhD, senior lecturer
Per Östberg, PhD, senior lecturer

The research of the group focuses on normal and pathological speech and language 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 evaluate therapeutic effects of transcranial current stimulation (tRNS/tDCS) in rehabilitation, to understand the causal mechanisms of stuttering from a neuroscience perspective, and to study speech and language deficits in neurodegenerative disorders.

***Project 1: Declarative and procedural learning in children with Specific Language Impairment (SLI) and children with Dyslexia***

**Participants**: Martina Hedenius, Margareta Jennische, Jonas Persson (Stockholm University), Michael Ullman (Brain and Language Laboratory, Georgetown University), Per Alm.

Linguistic knowledge is commonly conceptualized as being partly idiosyncratic and partly rule-governed. *Dual-system* accounts of the neurocognitive correlates of this distinction propose that idiosyncratic and rule-governed aspects of language are subserved by different cognitive systems. (In contrast, according to *single-system* accounts, the two types of computations are performed by a single cognitive system). According to one dual-system account – the *Declarative/Procedural* (DP) model of language – the distinction between idiosyncratic and rule-governed aspects of language can be tied to two distinctive neural systems for learning and memory, the declarative and procedural memory systems. Idiosyncratic knowledge, which includes sound-meaning associations and word specific information, is thought to be memorized in a mental lexicon, closely associated with the

declarative memory system. Rule-governed knowledge, which is the knowledge of how to combine´words and parts of words into phrases, sentences and complex words, is subserved by a distinct mental grammar that is hypothesized to be subserved largely by the procedural memory system. It is further hypothesized that the symptoms displayed by children with SLI and children with Dyslexia are largely due to abnormalities of brain structures of the procedural memory, specifically the basal ganglia and prefrontal cortex. Importantly, declarative memory is hypothesized to be intact in these disorders and potentially constitute a source of compensatory mechanisms.

The specific aims of this project are a) To test, and potentially falsify, the Procedural Deficit Hypothesis for SLI and Dyslexia b) To investigate the neurocognitive mechanisms underlying the acquisition of both language and non-language knowledge dependent upon the declarative and the procedural memory systems in children with SLI and children with Dyslexia, and c) To provide novel neurocognitive data on compensatory mechanisms in SLI and Dyslexia in order to encourage the development of innovative, theoretically motivated intervention programs designed to support such compensation.

***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. Aided language development is the acquisition of aided language forms, that is, graphic systems used with communication boards or technological aids. Children's development of aided communication forms does not only suggest deficits (in spoken language), but also achievements. The children's functioning abilities are reflected both in the failure to acquire spoken language and the ability to learn aided communication modes.

The acquisition of aided communication may also 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. The goal is to obtain a large corpus of utterances produced with communication aids by children aged 5-15 years, covering a large range of topics and produced in a variety of situations for different purposes, as well as systematic knowledge of how the children interpret utterances produced by others in their own communication form. By providing this information, the present study will be a much needed reference study for research on aided communication development.

***Project 3: The neurobiological basis of fluency disorders (stuttering and cluttering)***

**Participant:** Per Alm

The causal background of speech fluency disorders such as stuttering and cluttering has long been poorly understood. This project aims to clarify the underlying causal mechanisms, to enable development of more effective methods of treatment. The work proceeds through two types of activities: (a) critical review and theoretical integration of published research data, and (b) empirical studies of stuttering and cluttering, especially focusing on neurophysiological aspects. The previous studies in this project have focused on biochemical variables, sensory gating, auditory feedback mechanisms, neuromuscular reactivity, and morphological analysis of relevant brain structures. The main focus of ongoing studies is detailed analysis of the symptomatology of stuttering, with EMG recordings and high speed video, in combination with motor threshold measurement using TMS (transcranial magnetic stimulation).

The current working hypothesis is that stuttering and cluttering are speech motor sequencing disorders, on the premotor level, affecting the ability to correctly initiate speech motor activity. The functional impairment is suggested to be related to the automatization of speech sequencing, involving the circuits from the basal ganglia to the SMA (the supplementary motor area). A possible mechanism in stuttering is that hypofunction of the left frontal lobe speech network results in compensatory right hemisphere activity. As a result, the basal ganglia contribution to speech sequencing may become bilateral, with a risk for asynchronous and dysfunctional bilateral signaling from the basal ganglia to the SMA.

***Project 4: Brain correlates of speech and language deficits in neurodegenerative disorders***

**Participants**: Per Östberg in cooperation with Jeffrey Looi (Australian National University Medical School, Canberra) and Raffaella Crinelli, Lars-Olof Wahlund, Vesna Jelić, Nenad Bogdanović, Olof Lindberg (Department of Neurobiology, Care Sciences and Society, Karolinska Institutet)

Neurodegenerative disorders such as Alzheimer's disease and frontotemporal lobar degeneration affect behaviour and cognition profoundly. Speech and language abilities are not exempted. Part of the project concerns the neural correlates of frontotemporal lobar degeneration syndromes such as semantic dementia and progressive nonfluent aphasia. The relations between linguistic phenotypes of these disorders and MRI volumetry, global EEG synchronization, and neuropathological findings are explored. A related aim is to develop reliable linguistic measures and rating scales that can be used by speech-language pathologists in the assessment of patients with different forms of cognitive disorders and dementia.

***Project 5: Neuromodulation through transcranial current simulation: possibilities to facilitate rehabilitation?***

**Participants**: Per Alm, collaboration with Rehabilitation medicine and the Pain Centre, Uppsala University Hospital

A range of clinical conditions may be related to reduced neuronal activity in parts of the nervous system. In speech-language pathology this may be the case for disorders such as stuttering, dyspraxia, and aphasia. In this project the potential clinical use of the novel technique transcranial current stimulation (tRNS/tDCS) is explored, starting with a trial focusing on central neuropathic pain, in collaboaration with Rehabilitation Medicine. The intital tests indicate clinical long-term usefulness in some cases of central pain.

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6. Norén, N. Pronominella returfrågor i tre vardagliga svenska samtal. *Språk och interaktion 2* (Nordica Helsingensia 19). 2010;29-71.

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**Agencies that support the work/ Funding**

FAS Forskningsrådet för Arbetsliv och Socialvetenskap
Stiftelsen Sunnerdahls Handikappfond
Jerringfonden
The Swedish Research Council
Linnéa och Josef Carlssons stiftelse
Majblommans Riksförbund

## Medicinal History

**Group leader**: Kerstin Hulter Åsberg, adj. senior lecturer, ass. professor

**Members of the group during 2012**

Eva Ahlsten, BA, adj. Lecturer
Gunnar Boman, prof.em.
Anders Öckerman, adj. lecturer, med.student
Liselotte Englund, PhD, media researcher
Sara Kamilla Wik, architect.student
Arvid Puranen, med.student
Hampus Yngwe, med.student

**External collaborators:**

Museum of Medical History in Uppsala
University museum Gustavianum
Trondheim University
Paul Stradins Medical History Museum, Riga, Latvia

The aim is to disseminate knowledge about 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. Examples of these three aims are given in the following projects.

***Project 1: Elective course in Medicinal history***

The third course in Medicinal History was performed during spring 2012. The teachers were all senior researchers and academic teachers.

***Project 2: The History of the Biomedical Center (BMC) in Uppsala.***

A Swedish student in architecture at Trondheim University, Sara Kamilla Wik, has been guided and tutored in the archives of BMC by Gustavo Gonzales-Wall and Kerstin Hulter Åsberg for her examination report about the architectural history of the BMC *("BMC Biomedicinska Centrum: Då, nu och mot framtiden").*

***Project 3: The Thalidomide Catastrophy 50 years ago***

Liselotte Englund has performed a review of Swedish newspaper reports on Thalidomide 50 years ago with grants from Läkemedelsförsäkringen. The results will be published in 2013.

***Project 4: Animals in Medicine***

Dr Juris Salaks, head of Riga Medical History Museum, has issued an invitation to a planning seminar for a common exhibition at the university museums to be. The role of animals in medicine in the 1800$^{th}$ century will be focused.

***Project 5: Education in Professional Development***

Arvid Puranen has initiated a study concerning Professional development as an important part of the university education in medicine during the last 50 years.

***Project 6: Diagnoses of Schizophrenia during the 2000$^{th}$ century***

Hampus Yngwe has initiated a study concerning the changing description of the diagnosis of schizophrenia during the last century.

***Project 7: History of Tuberculosis in Sweden***

Gunnar Boman, Eva Ahlsten and Kerstin Hulter Åsberg have performed an exhibition at the Medicla History Museum in Uppsala with lectures and written stories about the history of tuberculosis in Sweden.

**Agencies that support the work/ Funding**

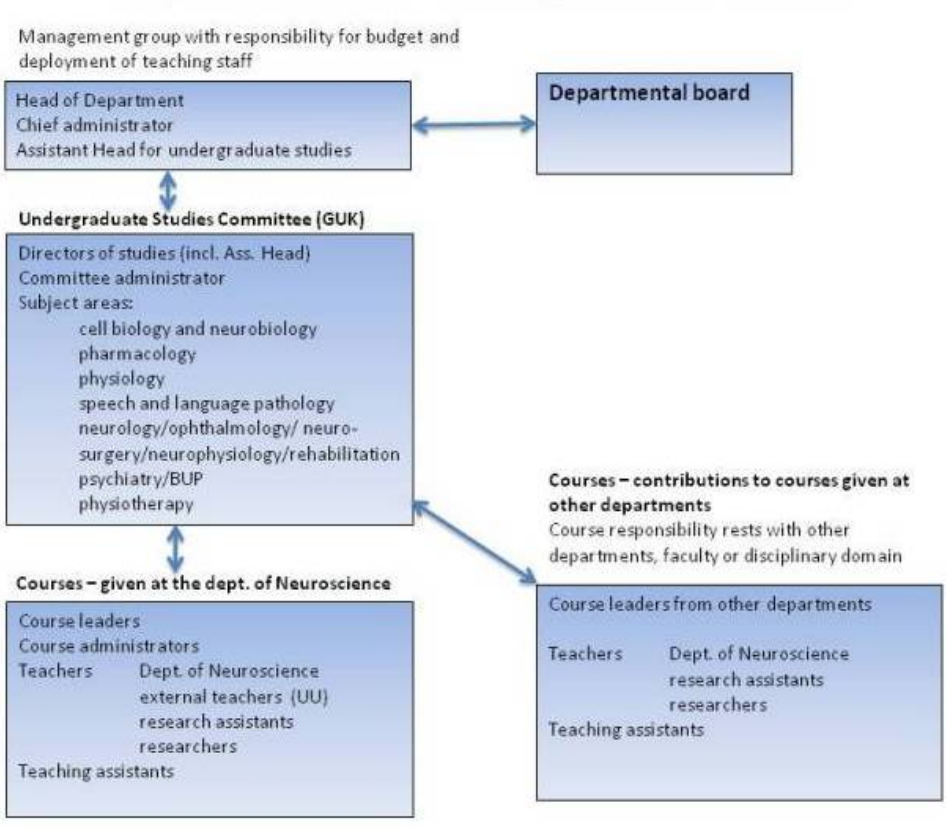
The Swedish Heart-Lung Foundation

# UNDERGRADUATE STUDIES 2012

*Case-based seminar “Såret som inte läker” in the medicine programme. T2, Course: "Tillväxt och regeneration". Students: Katriina Kuuti (close to the camera), Sofia Karlsson, Erik Öhlen, Kristoffer Svensson, Axel Lifvergren, Linnea Nyberg, Patrik Tufvesson, Arash Jangali (at the whiteboard) and Caroline Garph. Supervisor: Charlotte Israelsson (Developmental Neuroscience, standing to the left).*

## *Organization of Undergraduate studies at the Department*

During 2011-2012 the organizational structure the Departments´s educational efforts at undergraduate level was revised. The tasks of the directors of studies (studierektorer), course leaders, teachers and course administrators were more clearly defined in order to promote a more efficient pedagogical leadership within all levels of undergraduate teaching at the department. This revision was initiated and performed by the committee for undergraduate studies (Grundutbildningskommitteen, GUK) at the department of Neuroscience and was headed by Finn Hallböök.




Our leadership organization for undergraduate studies is described in the figure above. The main organ for pedagogical leadership is the committee for undergraduate studies. The membership of the committee consists in the directors of studies and one administrator. The directors of studies represent seven major subject areas, as shown in the illustration above. Each sector covers several courses, and a course may fall under more than one director of studies depending on the content of its syllabus.

**Members of the undergraduate studies committee:**

7 major subject areas with director of studies
- Cell biology and neurobiology (C&N)
  Finn Hallböök (convenor)
- Pharmacology (FA)
  Robert Fredriksson
- Physiology (FY)
  Olle Nylander
- Speech and language pathology (LOG)
  Monica Blom-Johansson
- Neurology/opthalm./n-surgery/n-physiol./rehab. (NEUR)
  *Vacant*
- Psychiatry/Child and adolescent psychiatry/ nursing pr. (PSYK)
  Mia Ramklint
  (Lisa Ekselius - Nursing and medium-length healthcare pr.)
- Physiotherapy (SJG)

Neil Ormerod (administrator)

The committee meets regularly, on at least two occasions per semester. In addition, in 2012 a half-day seminar was held, with in-depth discussion of examination and how we estimate and evaluate the various tasks involved in teaching: lectures, supervision and correcting exams etc.

**Director of studies, course leader and course administrator**

- Director of studies:
  - Long-term 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.

As a result of the organizational review, the various tasks of directors, course leaders and administrative staff were more clearly defined. The table above presents a brief summary of the tasks for director of studies, course leader and course administrator.

# *List of Courses given by the Dept of Neuroscience*

| Programme/ Course | Course code/ course part | Course Leader | Course administrator |
|---|---|---|---|
| **Within the faculty of medicine** | | | |
| **Medicine** | | | |
| KNEP Communication and the Nervous System | 3NR113 | Håkan Aldskogius | Stefan Petersson |
| NHoI, Neurobiology, Homeostas and Intervention | 3NR137 | Madeleine Le Greves | Neil Ormerod |
| Clinical Medicine V | 3NR008 | Katarina Laurell | Sari Thunberg |
| | *Neurology* | Erik Lundström/Anja Smits | Gun Schönnings |
| | *Psychiatry* | Mia Ramklint | Lena Bohlin |
| | *Ophthalmology* | Gerd Holmström | Gunneli Ekberg/ Birgit Andersson |
| Communication and verbal communicative skills | *3FV259* | Maria Holstad/ Mimmie Willebrand | Lena Bohlin |
| **Biomedicine** | | | |
| CMB - Cell Biology with Biochemistry | 3MU121 | Finn Hallböök | Karin Nygren |
| VBE - Tissue Biology with Embryology | 2MU122 | Finn Hallböök | Karin Nygren |
| Neurobiology with pharmacology | 3MU131 | Åsa Mackenzie | Neil Ormerod |
| Comparative medicine | 3MU142 | Madeleine Le Greves | Neil Ormerod |
| **Master's programme in biomedicine** | | | |
| Avancerad neurobiologi med hjärnans sjukdomar | 3NR600, | Bryndis Birnir / Zhe Jin | Karin Nygren |
| Nya mål för läkemedel - identifiering och utvärdering | 3NR380 | Helgi Schiöth | Karin Nygren |
| Masterprojekt i biomedicin | 3MU215 | *Erik Fries (IMBIM)* | Karin Nygren |
| Forskningspraktik i biomedicin med försöksdjursvetenskap | 3NR730 | Madeleine Le Greves | Neil Ormerod |
| Masterprojekt i biomedicin | 3MU230 | Erik Fries (IMBIM) | Karin Nygren |
| **Nursing** | | | |
| Omvårdnad och medicinsk vetenskap inom psykiatrisk vård | 3PS040 | Josefin Bäckström | Lena Bohlin |
| **Specialist nursing** | | | |
| Psykiatri | 3PS300 | Kristina Haglund | Lena Bohlin |
| Omvårdnad I | 3PS301 | Kristina Haglund | Lena Bohlin |
| Omvårdnad II | 3PS302 | Kristina Haglund | Lena Bohlin |
| Fördjupning | 3PS303 | Kristina Haglund | Lena Bohlin |
| Examnsarbete spec ssk | 3PS304 | Kristina Haglund | Lena Bohlin |
| **Speech and language pathology** | | | |
| Anatomi, fysiologi, patofysiologi | 3LG020 | Håkan Aldskogius | Anki Gustafsson |
| Logopedens yrkesroll I | 3LG110 | Margareta Jennische | Anki Gustafsson |
| Logopedens yrkesroll II. Rösten. Terapeutiskt förhållningssätt. | 3LG111 | Sofia Ögefeldt | Anki Gustafsson |
| Barnlogopedi I, Störningar i tal-, språk- och kommunikationsutveckling | 3LG210 | Maria Krüger-Vahlquist | Anki Gustafsson |
| Klinisk barnlogopedi I. Avvikande tal- och språkutveckling, | 3LG610 | Maria Krüger-Vahlquist | Anki Gustafsson |
| Barnlogopedi II. Pedagogik vid språkstörning. Läs- och skrivsvårigheter, | 3LG211 | Margareta Jennische | Anki Gustafsson |
| Klinisk barnlogopedi II. Läs- och skrivutredning, | 3LG611 | Maria Krüger-Vahlquist | Anki Gustafsson |
| Barnlogopedi III. Habilitering och alternativa kommunikationssätt, | 3LG008 | Margareta Jennische | Anki Gustafsson |
| Klinisk barnlogopedi III. Habilitering, | 3LG000 | Maria Krüger-Vahlquist | Anki Gustafsson |
| Funktionella och organiska röststörningar hos vuxna och barn, | 3LG213 | Sofia Ögefeldt | Anki Gustafsson |
| Klinisk röstlogopedi. Funktionella och organiska röststörningar, | 3LG613 | Maria Krüger-Vahlquist | Anki Gustafsson |
| Nervsystemets sjukdomar och skador hos vuxna | 3LG024 | Per Alm | Anki Gustafsson |
| Talavvikelser. Stamning. Laryn. Dövas och hörselskadades tal | 3LG401 | Per Alm, Sofia Ögefeldt, | Anki Gustafsson |
| Logopedi vid nervsystemets sjukdomar och skador hos vuxna, | 3LG301 | Per Östberg | Anki Gustafsson |
| Klinisk logopedi vid nervsystemets sjukdomar och skador hos vuxna | 3LG614 | Maria Krüger-Vahlquist | Anki Gustafsson |

| | | | |
|---|---|---|---|
| Logopedens yrkesroll III. Muntlig presentation. Terapeutiskt förhållningssätt | 3LG112 | Margareta Jennische | Anki Gustafsson |
| Forskningsmetodik | 3LG501 | *Simon Liljeström (Psychology)* | Anki Gustafsson |
| Klinisk kurs, talavvikelser. Stamning | 3LG615 | Maria Krüger-Vahlquist | Anki Gustafsson |
| Logopedens yrkesroll IV. Logopedens roll i vården. Juridik | 3LG113 | Margareta Jennische | Anki Gustafsson |
| Examensarbete i logopedi - magisternivå | 3LG503 | Gabriella Persdotter | Anki Gustafsson |
| Klinisk fördjupning | 3LG616 | Margareta Jennische/ Maria Krüger-Vahlquist | Anki Gustafsson |
| **Physiotherapy** | | | |
| Prof | 3SG028 | Ann Sundbom | Stefan Petersson |
| Anatomi | 3SG038 | Ann Månsson | Stefan Petersson |
| N motorik | 3SG075 | Ewa Wenngren | Stefan Petersson |
| Fys akt/inakt | 3SG076 | Susanna Tuvemo Johnson | Stefan Petersson |
| Biomek/funk | 3SG039 | Jonas Olsén | Stefan Petersson |
| Smärta | 3SG037 | Cecilia Norrbrink | Stefan Petersson |
| Neurologi | 3SG069 | Dag Nyholm | Sari Thunberg |
| Sjukgymnastik inkl vfu neurologiska funktionsstörningar | 3SG036 | Charlotte de Belder Tesséus | Stefan Petersson |
| Pediatrik | 3SG086 | Sara Holm | Stefan Petersson |
| Somatisk (med vfu) | 3SG027 | Johanna Holmbäck | Stefan Petersson |
| Rehab | 3SG046 | Helena Igelström | Stefan Petersson |
| Vet met I | 3SG087 | Anna Ullenhag | Stefan Petersson |
| Primärvård | 3SG073 | Christina Emilsson | Stefan Petersson |
| Vet met II | 3SG091 | Mikael Andersson | Stefan Petersson |
| Hälsa | 3SG072 | Ann Månsson | Stefan Petersson |
| Äldrevård | 3SG068 | Marie Sandström | Stefan Petersson |
| Fördjupning neuro | 3SG088 | Signe Lind | Stefan Petersson |
| Uppsats | 3SG090 | Charlotte Urell | Stefan Petersson |
| Magister/teori | 3SG018 | | |
| Magister/uppsats | 3SG079 | | |

**Within the faculty of pharmacy**

| | | | |
|---|---|---|---|
| **Pharmacy (bachelor´s programme)** | | | |
| Fysiologi | 3FF112 | Olof Nylander | Stefan Petersson |

**Within the disciplinary domain of science and technology**

| | | | |
|---|---|---|---|
| **Bioloyi/Molecular biology** | | | |
| Neurobiology | 1BG207 | Dan Larhammar | (IBG) |
| **Civil engineer chemistry/technology** | | | |
| Fysioi&mol. cellbiol | 3FF158 | Olof Nylander | Stefan Petersson |

**Elective courses**

**Within the faculty of medicine**

| | | | |
|---|---|---|---|
| Psykotraumatologi | 3PS038 | Per-Olof Michel | Lena Bohlin |
| Medicinens historia | 3NR501 | Kerstin Hulter Åsberg | Stefan Petersson |
| Försöksdjursvetenskap | 3FD130 | Madeleine Le Greves | Neil Ormerod |
| Hjärnan - funktioner, sjukdomar och mysterier I | 3NR201 | Klas Kullander | Stefan Petersson |
| Hjärnan - funktioner, sjukdomar och mysterier II | 3NR202 | Klas Kullander | Stefan Petersson |
| Psykiatri | 3PS050 | Caisa Öster | Lena Bohlin |
| Barn, unga och trauma | 3PS051 | Per-Olof Michel | Lena Bohlin |
| Fördjupningskurs inom neurosjukvård | 3NR009 | Karin Skoglund | Sari Thunberg |
| Projektarbete i logopedi | 3LG511 | Gabriella Persdotter | Anki Gustafsson |

| | | | |
|---|---|---|---|
| Examensarbete i logopedi - magisternivå | 3LG512 | Gabriella Persdotter | Anki Gustafsson |
| Examensarbete i logopedi - masternivå | 3LG513 | Gabriella Persdotter | Anki Gustafsson |
| Fördjupningsprojekt i logopedi | 3LG515 | Gabriella Persdotter | Anki Gustafsson |
| Fördjupningsprojekt i logopedi | 3LG514 | Gabriella Persdotter | Anki Gustafsson |
| Stamning och skenande tal | 3LG937 | Per Alm | Anki Gustafsson |
| Evaluation of Scientific Reports, Methods and Statistics | 3LG516 | Gabriella Persdotter | Anki Gustafsson |
| Klinisk handledning | Several | Margareta Jennische | Anki Gustafsson |
| Kommunikation i mångkultur | 3LG942 | Berna Gerber (South Africa) | Anki Gustafsson |
| Tidiga insatser för barn med funktionsnedsättning, ett mångkulturellt perspektiv | 3LG938 | Cornelia Strydom (South Africa) | Anki Gustafsson |
| Dysfagi | 3LG932 | Margareta Jennische | Anki Gustafsson |
| Dyskalkyli | 3LG936 | Margareta Jennische | Anki Gustafsson |
| Blissymbolics | 3LG941 | Margareta Jennische | Anki Gustafsson |
| Beteendemedicin | 3SG048 | Pernilla Åsenlöf | Stefan Petersson |
| Idrottsmed | 3SG007 | Charlotte de Belder Tesséus | Stefan Petersson |
| VFU | 3SG048 | Signe Lind | Stefan Petersson |
| Äldre | 3SG024 | Karin Hellström | Stefan Petersson |
| Fysisk träning | 3SG047 | Margareta Emtner | Stefan Petersson |
| Rehabiliteringsmedicin | 3NR401 | Staffan Stenson, psykolog | Gun Schönnings |

**Within the faculty of pharmacy**

| | | | |
|---|---|---|---|
| Humanfysiologi | 3FF117 | Markus Sjöblom | Stefan Petersson |

**Laboratory courses**

| | | | |
|---|---|---|---|
| Fördjupningskurs i genetisk utvecklingsbiologi | Several | | Karin Nygren |
| Fördjupningskurs i neurofarmakolog | Several | | Karin Nygren |
| Fördjupningskurs i neurovetenskap | Several | | Karin Nygren |

## *Programmes at the Dept of Neuroscience*

## Programme in Biomedicine

The Bachelor programme in Biomedicine (Kandidatprogrammet i Biomedicin) has 45 students per year with a total of 135 over the three years. The Bachelors program generated approximately 124 FTE of which 30.5 were produced at the Dept of Neuroscience.

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 heath and in disease. Four courses in the Bachelor's program are given from our department: Cell Biology with Biochemistry (CMB) (22.5 hp), Tissue Biology with Embryology (VBE) (15 hp), Neurobiology with Pharmacology (15 hp) and the course on experimental animal welfare (3 hp). The department also participates in the physiology course.

### 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. For example, the syllabuses for the courses

Bioinformatics with Statistics, Comparative Medicine and Medical Physiology have been revised. 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 will be discussed, and advice from the Pedagogic Unit will be sought, in order to ensure that it meets the criteria for HSV 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. Karin Nordström has lead this training programme. 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 and was conceived and planned by the Programme Committee of the Biomedicine Programme. Lina Thorvaldson, from the Department of Medical Cell Biology, is programme coordinator. The courses in the first year are given by several different departments in the medical and pharmaceutical faculties. During the second year students can choose freely from other courses, and are able to specialize in their field of interest. They also complete a master's project in their chosen specialty. The most popular options for the second year are the Uppsala Graduate School for Biomedical Research (UGSBR) or the Clinical Drug Development course. It is also common for students to do independent laboratory projects during this period.
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. In the first year 32 students were admitted, and so far 22 have graduated. Two students dropped out during the first course in

order to pursue PhD studies; and a further seven have been granted study breaks either to perform laboratory projects or for personal reasons.
Twenty-six students were registered with the programme in the autumn of 2011 and one dropped out during the first course and one started the medical programme in the spring semester 2011. Tuition fees for overseas students were introduced this semester and this probably accounts for the fall in applications. Five of these students are fee payers. As of now, six students have already graduated with one-year or two-year Master's degree; and 15 are currently engaged in their Master's projects and will graduate in June.
In the autumn of 2012, 31 new students were registered with the programme. To date, all have stayed with the programme. Three students are planning to graduate with a one-year master in June.
Of the students that have graduated so far, many have begun post-graduate studies.

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 two courses; Advanced Neuroscience (15 credits) headed by Bryndis Birnir in the Physiology unit and Drug Target Identification and Evaluation (15 credits) given by the Functional Pharmacology unit. Other courses in the first year are Major Diseases – homeostasis and endocrine diseases (15 credits) from the Department of Cell Biology, 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 programme provides in-depth knowledge of some of our major diseases, as well as concerning the brain; in health and in disease. Students follow the process of developing new drugs, from finding new targets to developing the final product. The theme of the programme is: “From the ailing body and the ailing brain to the discovery and development of new drugs”. The focus of the programme is placed on research-oriented questions for application in academic research and in pharmaceutical and biotechnological industry. The curriculum includes scheduled lectures, laboratory practicals, seminars, problem-oriented group assignments, demonstrations and study visits.

**Assurance of quality**
Course- and programme syllabus are continuously revised. Course evaluations are discussed in the programme meetings as well as in meetings between the students and the programme coordinator and meetings between the course leaders and the programme coordinator.

**Development of teaching and learning**
Our teachers are recruited from amongst the teaching staff and specialists at 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.

Over the course of the programme, some measures have been made to counteract the tendency for students to leave the programme during the second semester to pursue other studies. First of all, laboratory project courses within the programme were instigated so that students wishing to get more experimental experience did not have to take a study break, but had the opportunity to gain this experience so within the framework of the programme. These courses

are also popular options during the elective period in the third semester.
Another measure was to introduce the option to study immunology during the first part of the second semester. Since many students came from a pharmaceutical background, they found that the course content of the programme during the second semester tended to overlap with courses they had already taken. The immunology course became a popular alternative, and almost half of the students chose this option in the spring of 2013.
Students from other universities had often not taken any course in laboratory animal science, which caused problems for those wishing to complete master projects that include animal research. The university has a 4,5 credit course in Laboratory Animal Science, but that is difficult to combine with other courses - especially for the fee-paying students who are forced to pay extra, if room could not be found in the 30 credits for which they have already paid. The solution was to establish a 15 credit course, in which the Laboratory Animal Science elements are combined with a laboratory project that can be taken during the elective period of the third semester.

**Internationalization**
The proportion of students with an international background has decreased with the introduction of the tuition fees, but remains significant. 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. Five tuition-fee paying students were accepted this year. Among the 31 students registered in 2012, only six were international with one fee payer. Part of this decrease is explained by a fall in the number of international applications, and in difficulties for fee-paying students in raising funds for their studies due to the lack of scholarships available to them. Another explanation is also that we now have more applications from the Bachelor programme, and these students are given priority.

Our international students come from various countries. Among the students registered in 2010, one third came from China and one third from Sweden. The others came from India, Pakistan, Iran and other countries. No European students were registered that year.
Of the nine international students registered in 2011, two came from India, two from China and the others from various countries. Two European students (from Iceland and Great Britain) were registered.
The six international students registered in 2012 came from very different backgrounds; Costa Rica, Colombia, Iraq, USA, India and Greece.

## The Speech and Language Pathology Programme

The fourth class (LK08) of speech and language pathologist (SLP) (28 students) graduated in January and thirty-four new students were admitted to the program in the spring semester (32 females and 2 males).

Some smaller adjustments in programme course syllabuses have been made during the year. In addition to regular courses, three courses at advanced level were given during 2012. These elective courses were offered to students and active clinicians, mostly speech and language pathologists. The diversity in background and experience among participants contributed to fruitful discussions.

- Early intervention, a multicultural perspective (7,5 hp), was given by Faiza Bardien from Stellenbosch University, South Africa.

- Dysphagia in neurological diseases (7,5hp)

Furthermore a new course in Clinical supervision (7,5 hp) was given for the first time and attracted a large group of SLPs who will in the future serve as supervisors for the students of the programme.

In connection to the dysphagia course a symposium on Dysphagia treatment was given with Dr Maggie Lee Huckabee , Dr in Speech Pathology , from the department of Communication Disorders, University of Canterbury, Christchurch, New Zeeland as invited speaker. The symposium was well attended by about 60 clinicians and students

**Assurance of quality**

The National Agency for Higher Education's evaluation of the programme, which began in the autumn 2011, continued during the spring semester of 2012. The objective of the evaluation exercise was to determine to what extent the students achieved learning outcomes corresponding to the goals for the SLP program in the Higher Education Ordinance. Previous student degree projects (second cycle) and a thorough time-consuming self-evaluation had been submitted to the agency. A survey conducted by the Swedish National Agency for Higher Education among alumni showed a high degree of satisfaction among former students. Nine goals of the SLP program were evaluated. In the report the overall assessment was given that the programme displays a high level of quality. The programme was judged to be of very high quality in relation to four of the goals; resulting in a joint second place in the ranking of SLP programmes in Sweden. Those four goals were enhancement of the scientific base for the teaching at the programme; the clinical, educational and therapeutic knowledge of the students in the various domains of speech pathology; the ability of the students to critically discuss and review facts and phenomena as contribution to professional development: and, finally, the students ability to make plans for therapy and rehabilitation integrating scientific, social and ethical aspects with respect to the overall situation of the patients and Human Rights.

**Development of teaching and learning**

The National meeting for education in speech and language pathology in 2012 was hosted in Gothenburg with participants, teachers and students from all Speech and language pathology programmes in Sweden. The meeting discussed common problems and possible collaborations. The self-teaching course in law for SLP students, which had earlier been developed in this collaboration, was given for the fourth year in 2012.

Regarding general and subject-based professional development in teaching and learning, our teachers have attended courses 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. The theme for this year was "Research related learning in clinical practice. How can we stimulate the students to relate theory and practice in a scientific way?" and about 65 clinical teachers attended the meeting.

**Internationalization**

The final exchange within the Linnaeus - Palme exchange program was performed in spring 2012 when Margareta Jennische, programme director at the Uppsala programme, taught

Augmentative and Alternative communication with focus on Blissymbolics to students at the Stellenbosch programme in March, and lecturer Faiza Bardien, from the Stellenbosch programme, taught Early intervention with a multicultural perspective to Uppsala students in April. The programme also participated in Nordic meeting of the collaborative project NordSpeech (within the framework of NordPlus). Unfortunately no funds for exchange of teachers and students during the year were received. Margareta Jennische is external sensor at the SLP program at Bergen.

**Broadened recruitment**

The programme has a strong over-representation of female students. To increase the male recruitment to the programme, a male student participated at the SACO educational fair in Stockholm. Speech and language pathology is a relatively unknown to the general public.

**Grants & Awards**

For the third time, a Linnaeus-Palme grant was received in 2011 which enabled teacher exchange with Stellenbosch University, South Africa during spring 2012.

A grant was received from the Faculty of Medicine to evaluate and further develop the teaching of scientific approach to the students during spring 2012

The SLP students' pedagogical award 2012 was given to Per Alm, lecturer in fluency disorders and neurological disorders.

## The Medicine Programme

A new medical curriculum was introduced in spring 2006. The Department played a major role in the discussions and preparations for the new curriculum..

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. Håkan Aldskogius at the Department of Neuroscience has been head of Stage III council since its establishment in the early years of the new curriculum. In this function he has also been a faculty member of the executive program committee for the medical curriculum. Håkan has stepped down from this position and we express appreciation for his efforts during these years.

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 below in more detail. In brief, the Department is responsible for an introductory neuroscience course *(Communication, Nerves and Psyche)*, semester 1, has major roles in the

courses *Growth and Development* and *Homeostasis and Endocrinology*, semester 2, is responsible for *Neurobiology, Homeostasis and Intervention*, semester 3, and has an overall administrative responsibility for *Clinical Medicine V*, semester 8-9.

The Department's teaching commitments in *Clinical Medicine* V includes integrated preclinical-clinical neuroscience, neurology, neurosurgery, clinical neurophysiology, rehabilitation medicine, psychiatry and ophtalmology. The Department has distinctive activities also in *Clinical Medicine VI* as being responsible for an integration period with focuses on reproduction endocrinology and neuroendocrine mechanisms in gender biology, as well as a clinical course in child and adolescent psychiatry. Finally, the Department's teachers make significant contributions to several other courses through lectures and as tutors in problem based learning sessions, laboratory classes, and independent project work.

## The Physiotherapy Programme

Fifty students were admitted to the programme in the spring and autumn semesters of 2012. Fifty-five students graduated in the spring and thirty-five students in the autumn.
Our on-going efforts to decrease the attrition rate have continued during 2012, mainly in the first introduction course. The introduction course includes early minor field-studies with the aim of giving the students a deeper insight into the profession of physiotherapy. However, more students have graduated from the physiotherapy programme during 2012, due to excessive intake of students and an increase in students' opportunities for individual curriculums.
Fourteen students were registered to write the thesis of 15 credits at the one-year Master Programme.

Some students had the opportunity to take part in a student-run interdisciplinary health clinic for older people, situated at BMC, during their last semester in the programme. In meeting with the individuals at the clinic, the students practiced a motivational interviewing approach and applied their knowledge of factors promoting health. This activity promotes links between departments at Uppsala University and between students and teachers.

The course "Interaction and communication", 7,5 credits, was revised and accepted by the programme committee for the Physiotherapy programme so that motivational interviewing has become its main component.

### Assurance of quality

During 2012 the staff and the teachers at the unit were involved in The National Agency's evaluation of Swedish physiotherapy programmes. The evaluation examined the extent to which the students' actual academic performances met the expected learning outcomes. The evaluation was based on the students ' independent work (thesis), the programme's self-assessments, and surveys of former students as well as students' perceptions of educational performance in relation to the educational objectives of the degree in physiotherapy. Students' independent work and training results were reported in a self-evaluation form as the main basis for a comprehensive review. We wrote three self-evaluations, as the unit is responsible for three qualifications: vocational qualification, Bachelor's degree and Master's degree. The self-evaluations not only constituted an important basis for the National Agency's assessment but also served as an important instrument in the unit´s own quality assurance in respect of the program.

Continued efforts towards the assurance of quality in the physiotherapy programme include theoretical and clinical activities, evaluation of clinical training and self-evaluations. The self-evaluation is done every two years of all courses in the program. The results are compiled so strengths, weaknesses and need for change in the programme emerge.

### Development of teaching and learning

During 2012 a process of creating a new curriculum for the whole programme started with the aim of implementing a clear behavioural medicine profile in the courses. The working process is 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, guarantees the progress of the work in three phases. Phase 1 matches a period of "planning and professional development"; phase 2 "development of curriculum"; and, phase 3 "implementation of the curriculum". During 2012 phase 1 was completed and phase 2 is near completion.

Six teachers at the programme attended a course in Behavioural Medicine, 7.5 credits, during the spring semester in order to enhance their own skills. Teachers in the programme were also invited to attend the educational courses, seminars and workshops offered by the Division for Development of Teaching and Learning.

### Clinical training

Finding trainee posts for clinical practice for our students has been one of the major accomplishments of our staff and the steering group this year. Effort and funding for finding new trainee posts has been a priority. Teachers have also travelled to different regions (Gävleborg, Dalarna, Värmland and Gotland) as well as visited trainee posts in Uppsala, to motivate and inspire clinical physiotherapists, as well as inform about supervising, with the objective of securing additional trainee posts. A clinical supervisor course and annual meetings for clinical supervisors form part of our ongoing efforts to maintain a high level of quality as regards trainee posts.

We arranged a meeting for all clinical supervisors in the autumn semester with the theme "Physical activity, physical capacity and physical training". The aim was partly to raise the competence of clinical supervisors, and partly to inform them of the content of, and topics covered by students of, our programme.

We feel that the general teaching quality in the clinics has been guaranteed. However, it has been a great burden on the programme to find enough trainee posts given a throughput of almost 50 students per semester.

### Internationalization

Teachers and students from the programme were active as members of the "Joint Physiotherapy Education in Bachelor Thesis", a Nordplus activity, during spring 2012. This scheme is an international collaboration between the Nordic and Baltic countries with the aim of giving students and teachers an opportunity to gain real international experience. Teachers and students involved in the Nordplus activity visited Haapsalu in Estonia in the spring semester.

### Broader recruitment

The programme has about 40% male students. The recruitment should be extended to students with immigrant backgrounds to reflect the patient base physiotherapists meet in clinic. Our study adviser and director of studies are continuously engaged in information activities, such as those directed at high-school students.

**Grants and awards**Henrik Johansson, teacher and PhD student at the unit, was awarded the Pedagogical Award of Uppsala University in 2012, for his outstanding contributions within education at basic level at the Physiotherapy programme.

Julian Norberg from Ludvika hospital and Britta Eriksson from Uppsala County were awarded with the programme's annual award granted to two excellent clinical teachers.

The programme received grants from the Faculty of Medicine at Uppsala University (KrUUT) for a project dealing with outcome criteria for Bachelor and Master Thesis. The project was closed and reported during 2012.

## The Specialist Nursing Programme

The Specialist Nursing programme admits a total of 130 students per year, of which 7 students were in the Programme in Psychiatric Care, based at the Dept. of Neuroscience, in the spring of 2012 and, 13 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

During 2012 lecturers and seminars were arranged for the teachers at the unit and clinicians in the hospital involved with, and teaching in, the programmes at the unit. This was done together with the Division for Development of Teaching and Learning. Focus was on curriculum, course syllabus, learning outcomes, examinations, assessments and pedagogical discussions. This was highly valued, especially among the clinical teachers. 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. The results of evaluation are further discussed in the programme committee. Course leaders and teachers are involved in a National network with teachers in the Specialist Programme in Psychiatric Care from different universities. In the network, experiences are exchanged and new ideas can be brought home.

### Development of teaching and learning

Clinical examinations (OSCE's) of professional competence in nursing, at an advanced level, have been used in the programme for seven years. During 2012 we have developed a more standardized approach in the station-based examination. Focus is on assessment of communication skills, as this is one of the most central competences in psychiatric nursing. Assessment measures and checklists were re-designed in order to facilitate and get a more reliable assessment of the learning outcomes of the programme. In addition, the group remodelled and developed scenarios with the intention to create pedagogical models with two different levels and different complexities in the examination (semester I and II).

### Clinical training

Trainee posts for clinical practice for the students have been arranged, with a preference for placements in the region of Uppsala. Students perform 10 weeks of clinical practice during the programme. 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

All teachers are continuously engaged in information activities directed to nurses at a basic level in clinical practice. The programme in Psychiatric Care has in 2012 taken in students from the whole region of Mälaren and Gävleborg.

### Grants and awards

The programme received grants from the Grundutbildningskommitéen (GRUNK) for a project for quality assurance and development of clinical examination OSCE. The project was reported during 2012 and, is now on-going as a routine in the programme.

## The Nursing Programme

The Nursing programme admits a total of 200 students per year of which the course *"Omvårdnad och medicinsk vetenskap inom psykiatrisk vård 7.5 hp"* generated 21.5 HST to the dept Neuroscience 2012.

The programme provides knowledge of psychiatry and mental health in medical as well as caring sciences. The focus of the programme 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

During 2012 lecturers and seminars were arranged for the teachers at the unit and clinicians in the hospital involved with, and teaching in, the programmes at the unit. This was done together with the Division for Development of Teaching and Learning. Focus was on curriculum, course syllabus, learning outcomes, examinations, assessments and pedagogical discussions. This was highly valued, especially among the clinical teachers. 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. The results of evaluation are further discussed in the programme committee. The course has, over several years, been one of the highest rated in the Nursing Programme. 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**
It is a challenge to acquaint students with psychiatry and psychiatric care in the short time available. There are two examinations relating to the theoretical education and one of them, an oral individual examination has been further improved during 2012. A more stringent assessment guide for teachers, and a detailed reading guide for students are now in use.

**Clinical training**
Students undertake two weeks 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 2012, touching on topics ranging from Laboratory animal science to Medical history as well as Neuroscience, Drug targeting and development and Physiology. English was the language of instruction for some of these courses, including Laboratory animal science and 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.

Noteworthy for 2012 was the introduction of several new elective courses in psychiatry aimed at professionals working in related disciplines, such as social work. These included Children, Adolescents and Trauma; Psychotraumatology; and, an internet-based distance course in Psychiatry. These courses are greatly valued by professionals working in the field and the distance course proved to be very popular, attracting over 80 participants.

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

During the past year the following lecturers and PhD students have participated in the teaching of neurobiology for biomedical, biology and pharmacy students:

***Lecturers*:** Klas Kullander, Malin Lagerström, Martin Larhammar, Katarina Leao, Richardson Leao, Åsa Mackenzie, Katarzyna Rogoz, Johan Zelano, Emma Arvidsson
***Supervisors of practicals and seminars:*** Bejan Aresh, Emma Arvidsson, Nadine Schweizer, Thomas Viereckel

Staff at the Unit have course leader responsibility for the following courses:

***Neurobiology with pharmacology, 15 hp, the Biomedicine Programme:*** The course is given once per year (second period of fall semester) as an integrated part of the Biomedicine programme. 35-45 students attends the course on each occasion. The course is given in Swedish with Åsa Mackenzie as course leader. The course consists of lectures, case-based studies, demonstrations, lab practicals, oral and written exams 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 20-30 students. The course is given in English and approximately one third of the students are usually exchange students. Malin Lagerström is the main organizer of the course. 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 is responsible for this popular evening course.

Several lectures are given in other courses such as Laboratory Animal Science (pain and lab animal handling), Cell and Molecular Biology at the Biomedicine Programme, and Physiology for Pharmacy students (neurobiology)

Lectures are also given at the Advanced Neurobiology master´s course.

## Developmental Neuroscience

The undergraduate teaching by staff at the unit for Developmental Neuroscience (Hallböök and Ebendal research groups and their collaborators) occurs mainly within the courses: Growth and degeneration (ToD, T2) Medicine programme 2nd semester, medical embryology section (3 weeks 100% 95 students, approx 7 FTE). Cell biology with Biochemistry (CMB 22,5 hsp, T2) Biomedicine programme, 2nd semester (course responsibility, 11 weeks 100% 55 students, approx 14,75 FTE). Tissue biology with Embryology (VBE 15 hsp, T3) Biomedicine programme, 3rd semester (course responsibility, 6 weeks 100% 50 students, approx 7 FTE).

Course responsibility (Hallböök) is for courses in the *Biomedicine bachelor's programme*. The full courses are 22.5hp (15 weeks) and 15hp (10 weeks) and are given once a year in the

programme. Both courses are 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.

Ebendal is responsible for a block in Human embryology within the ToD–course in the *Medicine programme*. The block span 2.5 weeks and covers human embryology and basic mechanisms of developmental biology. The course is given twice a year and there were around 90 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, we exercise supervision responsibility for 3 seminars and six case-based seminar groups per semester.

Several lectures are given in other courses such as Experimental Animal research, Neurobiology for both the biomedicine programme and the medicine program, and the Masters course in Neurobiology.

Elective courses - Advanced course in Neuroscience 7,5hsp, 15hsp, 30hsp, 60hsp.
Two students have had their program theses supervised within the unit. Four more students took the elective Advanced course in Neuroscience.

**Assurance of quality:**
Biomedicine programme courses are subject to a web-based student course evaluation. The student evaluations were very positive with overall scores for CMB of 4,7(6) and for VBE of 4,9(6). 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 leads the course while Robert Fredriksson is director of undergraduate studies in pharmacology. This course is given twice a year with around 90 students each time. Teachers based at the unit give lectures in pain and analgesia, as well as vascular pharmacology. We are also involved in organising PBL cases, seminars, and examinations.

In addition, we participate in the following courses: Communication and the Nervous System (T1, 5 hp), Nutrients, Energy and Fuel Metabolism (T1 9,5 hp), Homeostasis and Endocrine Regulation (T2, 8.5 hp). For these courses we are responsible for PBL cases and seminars. We are also involved in the course Integration VII (4.5 hp, T8), for which we have responsibility for the preclinical parts of the course, including lectures, PBL cases and seminars.

***Biomedicine Programme:*** In the Master Programme in Biomedicine (second-cycle) we are responsible for the course Drug Target Identification and Evaluation in Neuroscience (15hp), with Helgi Schiöth as course leader. This course is run entirely within the unit with a few invited lecturers.
Further, we are responsible for the course Research Training in Biomedicine and Laboratory Animal Science (15hp), which is an elective course within the Master Programmes in Medicine/Pharmacy at Uppsala University, course leader: Madeleine Le Grevès.

In the Biomedicine program (first-cycle), we are responsible for the course Comparative Medicine (3,5hp), with Madeleine Le Grevès as course leader. The course is given annually for approximately 40 students, and provides theoretical knowledge and practical skills in laboratory animal science. The course teaches 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 to using laboratory animals. Handling and common invasive techniques of rats and mice is mandatory.

We also teach in the course Neurobiology with Pharmacology (15 hp), for which we give lectures on ion channels and electrophysiology, neuropeptides, pain and analgesia as well as with supervision for PBL cases and laboratory practicals. This course is run once every year.

We contribute lectures on G Protein Coupled Receptors and vascular pharmacology in other courses in the programme.

***Other Programmes:*** We are co-organizers of the faculty of Natural Sciences and Technology course Genes, Brain and Behavior, with Prof Elena Jazin. We are responsible for the neurobiology part of this course, which is organized by Robert Fredriksson. Here, we teach various subjects such as neuronal transmission, transgenic mice techniques, bioinformatics, pharmacology, electrophysiology, QTL genetics, association genetics, and behaviour.

We also contribute lectures (electrophysiology, synapse biology and ion channels) and laboratory practicals to the Neurobiology course for biologists.

## 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, 20.5 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.

Numerous lectures are given in other courses (including other faculties) at undergraduate and graduate level, particularly lectures concerning the distinction between science and pseudoscience but also various aspects of neurobiology.

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, Karin Nordström, Olof Nylander, Göran Sperber, Markus Sjöblom and Svante Winberg.
Ph.D. Students: John Sedin, Hanna Olsén, Josefin Dahlbom, Anna Sommansson, Suresh Mendu and Yang Jin.

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: Membrain potential (T1), ergometry test on bicycle (T1), audiometry (T3), refraction (T3), nystagmus (T3), neurological examination (T3) and temperature regulation (T6).

In the ***Biomedicine Programme*** we teach cardiovascular and gastrointestinal physiology. We have responsibility for the following student laboratory subject: Ergometry test on bicycle and temperature regulation.

For ***Pharmacy students***, 180 + 90 per year, Master of Science programme in pharmacy (12 hp): 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 sheep 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

Course leader of Advanced course in human physiology (15 hp), 70-80 students per years. We teach sensory and basic neural physiology, cardiovascular, respiratory, endocrine and gastrointestinal physiology. This course contains 5 cases and the following laboratory subjects: neurological examination, nystagmus and temperature regulation.

## Neuroanatomy

Functional Neuroanatomy for ***the Medicine programme,*** 200 students per year: The unit is responsible for the Introductory Neuroscience course (T1, 5 hp), including lectures, microscopy classes and demonstrations in human brain anatomy. The unit is also responsible for the development and revisions of two PBL cases during this course. The unit participates with lectures in functional neuroanatomy, and as PBL tutors, in Neurobiology, Homeostasis and Intervention (T3, 19,5 hp) and Clinical Medicine V (T8, 25,5 hp). The unit is also responsible for demonstrations in human brain anatomy (T3) and for the development and revisions of two PBL cases during the course Neurobiology, Homeostasis and Intervention.

***Speech and Language Pathology programme***: The unit is responsible for an integrated course in Anatomy and Physiology (T1, 6 hp) ca 30 students per year,. The focus of the course is in neuroscience, and the unit is responsible for lectures and for demonstrations in human brain anatomy.

***Physiotherapy programme:*** The unit participates with lectures and group teaching in neuroanatomy, ca 100 students/year, during their first year course in Basic Anatomy.

***Additional teaching***: The unit gives lectures on functional neuroanatomy in various independent courses: Neurobiology (ca 20 students per year, 15 hp), Human Physiology (ca 30-40 students per year, 15 hp), and Pediatric Swallowing and Feeding.. The unit also gives lectures on neural transplantation in the independent course Transplantation Biology (ca 70-80 students per year, 7,5 hp), and in regenerative neurobiology in the master program course Advanced Neurobiology with Diseases of the Brain (ca 30 student, 15 hp). In the latter, the unit organized and taught an extensive laboratory class in methods for Neural Stem Cell Culture.

## Clinical Neuroscience Units

### *(Neurology, Neurosurgery, Neurophysiology and Rehabilitation Medicine)*

Education in clinical neurosciences is introduced in the early stages of the Medicine Programme and is integrated with preclinical neuroscience. Teaching is given as a combination of lectures, discussions of clinical cases in groups of 8-10 students, seminars and individual supervision of students. In general, the transition of pedagogy to problem-based learning has been beneficial in terms of capturing the students' interest for neurosciences at early stages of their education. On the other hand, the system has challenged the limited resources and teaching capacities of the clinical units.

The course leader of the neurology unit (Anja Smits) has collaborated at a national level with teacher representatives from other teaching hospitals in Sweden to discuss national guidelines and a core curriculum of clinical neurosciences. Recently, academic teachers in neurology have been recruited to a number of regional hospitals in Sweden (Helsingborg, Östersund), and teaching of medical students is becoming more decentralized from university hospitals. In the Uppsala region there are no positions available yet for academic teachers in neurology other than at the Uppsala university hospital, while students are frequently located at regional hospitals for their clinical training. This has required close collaboration with clinical neurologists colleagues at hospitals in the region and increased administrative duties.

***Undergraduate education with course leader responsibilities***

***1) Clinical neuroscience for Medical students, 180 students per year***
The main teachings activities take place in T8/T9, in which period is offered an integrated course in clinical neurosciences (neurology, neurosurgery, clinical neurophysiology and rehabilitation medicine), ophthalmology, psychiatry and otorhinolaryngology, comprising 25,5 hp. Katarina Laurell (neurology) has been responsible for the integration of the course until September 2012 and has now been replaced by Adriana Ramirez (psychiatry).
Course leaders: have included: for the integrated course; Katarina Laurell (Director of studies), until September 2012, for Neurology; Anja Smits and Erik Lundström, for Neurosurgery; Per Enblad, for Clinical neurophysiology; Kristin Elf, for Rehabilitation Medicine; Krister Tengvar.

***2) Neurology for students in Physiotherapy, 40-50 students per year***
Dag Nyholm is course leader for this two week- course (3 hp) which is given twice per year.

***Undergraduate education with no course leader responsibility***

We are involved in teaching for courses in the following programmes: *Medicine programme (T3, T6, T9, 180 students per year),*lectures on "Muddy Points", "Neurological Examination", "Acute Neurology" etc are given by Håkan Askmark, Eva Kumlien, Johan Zelano, Jimmy Sundblom; *Speech and Language Pathology programme (30 students per year),* Erik Lundström taught neurology for a two-week course (3hp); *Biomedicine programme,* Johan Zelano lectured on neurology*; Nursing programme,* Erik Lundström lectured on neurology. Erik Lundström also taught neurology for residents (AT-läkare).

**Awards 2012**

Atle Melberg, neurology; Pedagogical Rose from the Medical Student Association

## Ophthalmology

***The Medicine programme:*** Ophthalmology is taught in an integrated course, Clinical medicine V, covering ophthalmology, ear-nose-throat, psychiatry, and neurology, neurosurgery and neurophysiology.
Teaching in ophthalmology includes lectures, seminars and clinical training/practice. To assure a rich clinical exposure for students, clinical training is organized at the ophthalmology clinic at the Uppsala university hospital and additionally at ophthalmology clinics in regional hospitals. During clinical training, the student cycles through a 1.5 week clinical rotation including auscultation with a consulting senior ophthalmologist, auscultation in vitreoretinal surgery, auscultation in cataract surgery and student consultation under the supervision of a qualified specialist in ophthalmology. 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.

***The Biomedicine Programme***: Ophthalmology is taught during one day. The teaching includes lectures as well as demonstrations.
***SK-courses:*** SK-courses are national courses, constituting a mandatory part of the national curriculum for specialist training in Sweden with participants from all specialist clinics in Sweden. Ophthalmology at Uppsala university contributes to national Ophthalmology training with the SK-courses Practical optics, Paediatric ophthalmology, and Corneal diseases.
*Practical Optics:* The course covers physical characteristics of light, effects of light and laser on the eye, geometrical optics and ophthalmic instruments. Thirty-seven lectures are scheduled over the course of one week. The course includes practical training with optical instruments used in clinical ophthalmology in three half-day sessions. At the end of the course, there is an examination seminar.
*Paediatric ophthalmology and strabismus:* The course covers aetiology, diagnosis and treatment of diseases in paediatric ophthalmology, as well as strabismus in adults and children. There are several seminars and case presentations, in addition to traditional lectures. There is also practical training of students with patients.
*Corneal diseases:* The course covers aetiology, diagnosis and treatment of corneal disease. The course is structured in lectures and seminars.

### 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

The SK-courses are evaluated by the national evaluation scheme required by the national Swedish residents' educational organisation, IPULS, and by specific evaluation that covers the content and the teaching of each lecture.

### Additional teaching

Ophthalmology also contributes with lectures on specific topics in the nurse specialist nursing programme, the orthoptist education and the masters program at the Department of Neuroscience.

## Psychiatry

### *(Psychiatry and Child and Adolescent Psychiatry)*

***Medicine programme:*** The unit of psychiatry have course leader responsibility for teaching psychiatry for the course *Clinical Medicine V*, in semesters 8-9, and course leader responsibility for teaching child and adolescent psychiatry for the course *Clinical Medicine VI*, in semesters 9-10. We also teach the subjects communication skills and medical psychology. These subjects are part of the course *Professional Skills and Communication*, that continues through the whole programme. Within this course we give lectures and provide practical training in semesters 1, 3, 4 and 10. Finally, we give solitary lectures for different courses, such as on neurotrauma for the introductory neuroscience course *(Communication, Nerves and Psyche*, at semester 1, and on neuropsychological development, for the course *Growth and Development* and *Homeostasis and Endocrinology* in the second semester, and on emergency psychiatry for *Emergency Treatment II*, in semester 11.

***Nursing programme:*** The unit for Psychiatry is responsible for the course "Nursing and Medical Science within Psychiatric Care, 7.5 credits", a mandatory course within the **"Nursing programme"** (180 credits). The course is a part of semester 4 and the fields of study are Medical science (4 credits) and Caring sciences (3.5 credits). The course integrates theoretical (4.5 credits) and practical training (3 credits).

***Specialist nursing programme in psychiatric care:*** The University offer a specialist-nursing programme with 10 different specializations. The specialization in *Psychiatric care*, 60 credits, is given by the unit for Psychiatry. The courses *Nursing in psychiatry/mental health I* and *Psychiatry* are given in semester 1. In semester 2 the course named *Nursing in Psychiatry/Mental Health II* is given. For the final part of the programme, the students can chose between *Advanced Nursing Study within Psychiatric Care* and a *Degree Project* of 7,5 credits or a *Degree Project* of 15 credits.

***Physiotherapy programme:*** During one week we give a course of 1,5 credits where we give lectures on common psychiatric disorders and evidence-based treatments.

***Biomedicine programme:*** During the course *Diseases – Clinical Survey* we teach psychiatry during one week each year.

***Speech and Language Pathology Programme:*** During the course *Nervous System Disorders in Adults* we teach psychiatry during one week each year

The unit also carried out one national ST-course on diagnostics in psychiatry. The course was arranged within the METIS format (http://metisprojektet.se/) , for doctors during their residency training. Together with the Karolinska Institute the unit also carried out the first Research school in Clinical

psychiatry (http://ki.se/ki/jsp/polopoly.jsp?d=35264&l=sv.html; 30 credits). The aims of the school are to improve PhD eduction, increase quality and to attract more PhD students. It has, so far, turned out very well.

### 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. We use student evaluations as a basis for revising and developing our courses and pedagogical methods.

### Development of teaching and learning

During the 2012 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
- Working with examination forms, introducing new approaches
- Development of a new curriculum for the course *Communication Skills (within Professional Skills and Communication)*
- One representative from the unit is part of the group developing the curriculum for the course *Diseases – Clinical Survey* at the Biomedicine programme

### Clinical training

Medical and nursing students had their clinical training at the University hospital, Division of psychiatry.

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Kph, Tryckaktiebolaget AB, Uppsala 2013