Department of Immunology, Genetics and Pathology
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Department of Immunology, Genetics and Pathology
Uppsala University

www.igp.uu.se
Welcome to the Department of Immunology, Genetics and Pathology (IGP) at Uppsala University. We invite you to read about research and education carried out at the department. Our research groups present their important work on molecular technologies, basic biology, and specific diseases. Tight collaboration between experimentally and clinically active researchers bridges our experimental research to health care.

IGP researchers have strong national and international networks. More than half our scientific publications have international co-authorship. Researchers at IGP have excellent track records as recipients of external grants. Recruitment of young investigators with externally funded positions and young PIs already at IGP promise a future faculty with the capacity to further advance our successful work.

We have an important mission to train the next generation of scientists. Undergraduate education at IGP includes three Master’s programs with the highest score in a national evaluation. We also train more than 100 PhD students for future careers in academy, hospitals, industry, or government.

IGP hosts eight service infrastructures and we played a central role in establishing SciLifeLab as a national resource in molecular biosciences. Many researchers at IGP start companies and collaborate with partners in the business community. Several are also involved in clinical trials.

We are proud of our achievements. There are many ways to connect with IGP. The Rudbeck Seminar series is open to all, and doctoral dissertations are public events. On our website, you can find recent scientific publications, read about grants and awards, media coverage, and the IGP Newsletter. Community building is key to our work at IGP.

Karin Forsberg Nilsson,
Head of Department
"IGP is an excellent environment. The quality of science is the principal motivation, and unpublished data and hypotheses are discussed in a friendly atmosphere."

E. Dejana

IGP hosts eight service facilities.

IGP has an extensive postgraduate education, with more than 100 enrolled students.
The department successfully conducts and disseminates research with the aim to increase biological understanding of development and disease, and improve diagnostics and treatment. The overarching goal is translational medicine in disease areas such as cancer, autoimmunity, degenerative and other genetic diseases. The research carried out is linked to relevant clinical problems with a clear aim to shorten the delay between scientific discovery and health gain. Our work is strengthened by the five associated clinics. Integration with the University Hospital underpins IGP’s role in translational research. We see several fruitful examples of this, e.g. cross-collaborative cancer biobanking and transferring genomic methods to health care.

EDUCATION
The Department participates in teaching in several undergraduate programs and we have an extensive postgraduate teaching programme. We also host four international master programs with strong links to ongoing research at the department, and also to society outside academia.

SUCCESSFUL FUSIONS
IGP was originally created by the fusion of Medical Genetics and Pathology, aiming to promote translational efforts by combining emerging technologies in genetics with profound knowledge of disease biology. Translational efforts are promoted by the affiliation with hospital clinics.

INTERACTION WITH COMPANIES
Researchers at IGP are following the prominent Uppsala tradition of technology development for molecular analysis. They file numerous patents, start companies and license their technologies to world-leading companies.

INTERNATIONAL RELATIONS
IGP is an international workplace with researchers and students from all over the world. We have a strong ambition to establish scientific and teaching contacts across borders because international collaboration is often the most successful way of addressing the grand challenges to human health.

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**Undergraduate education**

IGP offers highly competitive undergraduate education and Master programmes, with courses in our fields of interest. We strive to attract ambitious and talented students, and to stimulate their academic development. The Department takes part in teaching in several undergraduate programmes and we give a large number of single subject courses. We organize three Master programmes; Forensic Science, Molecular Medicine and Medical Nuclide Techniques. We are also one of the partners in the Erasmus+ programme International Master in Innovative Medicine (IMIM).

**Many International Students**

Several undergraduate courses and all master programmes are available in English. As a result our Master’s programmes have students from more than 20 different countries. Our research-integrated programmes thereby educate Master’s students who are internationally competitive on a global job market, which can open possibilities for teaching in different countries.

**High Quality Score**

IGP constantly evaluates and develops its educational programmes. An effect of our efforts to this end is the EIT Label that the IMIM programme recently received from the European Institute of Technology. A few years previously, the Swedish Higher Education Authority (UKÄ) evaluated fifteen educational programmes at the medical faculty at Uppsala University. Three out of the fifteen programmes received the highest score, Very high quality. All these three programmes are Master’s programmes at IGP.

**Strong Link Between Education and Research**

Our Master programmes have a strong connection to research and to society outside academia, which was also emphasized as a strength in the evaluation. The teaching is tightly linked to on-going research activities. In the IGP and UppsalaLifeLab students learn about research quality through lectures about e.g. ethics, biostatistics, bioinformatics, research planning, and how to counteract scientific misconduct. Furthermore, students are performing graduation projects where they work within a research group to learn scientific strategies and project management. After completion of the project, the degree report is often written as a scientific article.

**A Master Programme Student Who Likes Research**

Fredrik Lyngskog is presently doing his degree project in the Biomedicine programme at Uppsala University. During my basic level studies in bio-medicine I became interested in genomics and bioinformatics and I chose to continue my education in the Molecular Medicine programme”, he says.

Fredrik is very pleased with the programme. He thinks that all courses have been relevant and he has enjoyed the atmosphere among the students.

“Around two thirds of the students have a basic level education from a foreign university and we have had many interesting discussions comparing exams and ways of teaching in different countries. We have also had many social events such as a Christmas party with food from all parts of the world.

After finishing his degree project Fredrik is interested in continuing with postgraduate studies and he thinks his education makes him well prepared for this.

“Both the course content and the teachers have focused on research relevance. It’s been very inspiring to have such committed and involved teachers,” he says.

**A Broad Education in Human Biology**

Amanda Lindberg is studying the fourth semester in the Biomedicine programme. “I really appreciate the programme, she says. “The courses are interesting and fun, and the teachers are active researchers that are very familiar with their subjects. This means that we are often presented the very latest research findings.”

One of Amanda’s favourite courses so far was Medical Genetics, given by IGP, where the students for instance had the opportunity to test how forensic analyses are done in real life. She also appreciated the bacteriology and metabolism courses.

“The programme is very broad, which I think is good. Sometimes I would like to learn more about a certain topic, but on the other hand I guess there is not time within the programme’s three years to both study many different subjects and focus more on some of them.”

However, before graduation Amanda will have the opportunity to further explore a specific area when she does her degree project. After this she will most likely apply for a Master programme.

“Our education provides a good basis for many Master programmes and most of my friends in the programme will continue with a Master. I have started looking at possible programmes here in Uppsala but I still have some time before I have to decide what to do next,” she concludes.
Postgraduate education

IGP has an extensive postgraduate education, with more than 100 enrolled students.

Our goal is to provide postgraduate training of the highest international standing, preparing the doctoral students for future careers in academia, industry or government.

A BLEND OF DOCTORAL STUDENTS
The Department attracts postgraduate students from a variety of undergraduate backgrounds. In the research programs focusing on basic biological and medical research, many students have previously studied biology or bio-medicine, or have a degree as engineers. Doctoral students in the translational and clinical research programs are often qualified physicians or students in the medicine program.

This valuable mix of experiences is also enhanced by the international contribution to our postgraduate student community. Around one half of the students have an undergraduate degree (Bachelor or Master) from a university outside Sweden. The combination of students with different backgrounds, and likely different career goals, promotes a lively and productive educational research environment both in the research groups and in the Department as a whole.

SCIENTIFIC WORK AND COURSES
Postgraduate education at IGP is mainly performed as scientific work in a research group, under the guidance of a supervisor. This often includes experiments in the lab, data analyses and other hands-on investigations. In addition, our PhD students are required to attend postgraduate courses and the Department has allocated funds from which students can apply to participate in international courses, or to visit research laboratories to learn techniques required for their research projects.

The PhD student council at IGP annually arranges a conference where the PhD students present their work to their fellow students. This is a great opportunity for the students to learn about their colleagues’ work and to practice their presentation skills.

SUBSEQUENT PROFESSIONS
Doctoral students who get a PhD at IGP have very diverse subsequent careers. Many stay on in the academia, eventually establishing their own research groups. Others go on to work in national or international science companies. Doctoral candidates with a medical background often continue to conduct research, in combination with work as physicians.

TWO PhD STUDENTS AIMING FOR RESEARCH CAREERS
Verónica Rendo and Ross Smith are two PhD students aiming for research careers. Verónica Rendo and Ross Smith are in the last year of their postgraduate education at IGP and they both have an international background.

“My studies here have given me the tools to develop as a researcher.”

“Since IGP’s research groups are located in different premises some interactions are more limited.”

“I fell in love with science again”

“They both enjoy the atmosphere at IGP and in their research groups and think that the department provides great opportunities to do research.

“There are so many competences gathered and it’s very easy to meet people to discuss your results or get advice on technologies, also if they are in another research field. Many are willing to share knowledge and I believe that my studies here have given me the tools to develop as a researcher,” Verónica says.

“Sometimes I have felt like an imposter – like ‘What am I doing here?’ – but there is always someone to ask and I have been learning a lot. Now others even come to me for advice. It’s really an advantage to have experts in so many fields close by and there is a lot of cross communication and interactions between the groups.”

“Ross also has an undergraduate degree in biology, in his case from the United States. However, he joined IGP when he started working as a technician.

“I wanted to move to Sweden to pursue my interest in orienteering and was recruited to IGP by my present supervisor. This was based on my experience in animal work and I spent the first year or so in the lab as an animal technician. But then I fell in love with science again and wanting to do more challenging work I decided to go for a PhD degree.”

“They both enjoy the atmosphere at IGP and in their research groups and think that the department provides great opportunities to do research.

“There are so many competences gathered and it’s very easy to meet people to discuss your results or get advice on technologies, also if they are in another research field. Many are willing to share knowledge and I believe that my studies here have given me the tools to develop as a researcher,” Verónica says.

“I fell in love with science again”

“This is one thing that could be improved though,” Verónica says. “Since IGP’s research groups are located in different premises some interactions are more limited.”

“Ross will likely defend his thesis by the end of the year and he wants to stay both in science and in Sweden. When Verónica graduates she is interested in continuing with research and hopefully translate her findings into help solve clinical needs.

“I would be great to see that people can benefit from what I do,” she says.
Translational research

Research at IGP is linked to relevant clinical problems with a clear aim to shorten the delay between scientific discovery and health gain.

One of the major aims at the Department is to perform translational research, bridging basic experimental research and modern diagnostics and therapy. Translational research is promoted by tight collaborations between experimentally and clinically active researchers and the relationship with our affiliated hospital clinics provides excellent conditions for success.

**CLINICAL IMMUNOLOGY AND TRANSFUSION MEDICINE**
Research at the clinic focuses on diabetes and other autoimmune diseases, immunological reactions after transplantations and development of immune therapy for cancer.

**CLINICAL PATHOLOGY**
The hospital unit for clinical pathology has a dedicated research and development group that provides services for internal and external clients. These include handling requests for withdrawal of patient samples and microscopic or molecular analyses. The unit has a well-functioning collaboration with IGP researchers and with the strategic research project U-CAN.

**ONCOLOGY**
At the oncology clinic patients with cancer receive their treatment and many doctors at the clinic perform research on tumour diseases and cancer therapies. An important part of the clinic is the clinical research and development unit that provides assistance and knowledge in clinical drug trials of and other clinical studies.

**HOSPITAL PHYSICS**
Researchers at the unit for hospital physics study the physical and technical aspects of using radiation in cancer therapy.

**BEING BOTH RESEARCHER AND CLINICIAN**
Our translational and clinical research is conducted by scientists that are affiliated in different ways to the Department. Several group leaders are active physicians with positions at IGP. In addition, there are a number of researchers that are employed at the University Hospital and have adjunct positions at IGP as professors or senior lecturers.

Furthermore, three new PhD students are annually enrolled in the Early Doctorate Programme for medical students affiliated with the Faculty of Medicine. In this programme medical student are registered as PhD students in parallel with their medical education.

**NIKLAS DAHL**
A professor at IGP and senior physician in clinical genetics. He appreciates the translational approach at the Department.

"It is a great privilege to work as a clinical geneticist in the environment in and around IGP," he says. "Clinical genetics is a rapidly expanding discipline driven by novel technologies, not the least next generation sequencing. We need to meet the increasing demands from the community and patients by being at the edge of clinical research and by implementation of new findings in our health care system. This is a continuous process that requires factors such as established infrastructures, innovative environments and interactions with scientists in adjacent fields in addition to a strong clinical anchoring."

The translational research setting at IGP has also been an advantage. The presence of both frontline research and active clinicians creates a dynamic and inspiring environment. "IGP has been great place to do my PhD. I have acquired a robust research education where I’ve been part of exciting projects and I now hope to be able to bring ‘research thinking’ into the clinic," Niklas finishes.

**STUDY OF RASOMIMIC ADENOVIRUS ADV-05 VAX IN PATIENTS WITH NEUROENDOCRINE TUMORS: SAFETY AND EFFICACY (RADNET)**
NCT03274931 (on-going)

**CD19-TARGETING, 3RD GENERATION CAR T CELLS FOR REFRACTORY B CELL MALIGNANCY** - A Phase Ii Trial, NCT02132624 (on-going)

"The scientific environment attracted me and I was captured by genetics and its importance for disease during my internship in pediatrics. For my thesis, I combined experimental work in a laboratory with on duty in the pediatric clinic during the weekends. This laid the foundation for my insights into translational research and its critical importance for improved care and treatment of patients."

"Since I’m interested in both research and helping patients this has been a great opportunity for me."
SciLifeLab and service facilities at IGP

SciLifeLab is a national infrastructure resource focusing on health and environmental research. It is a joint effort between four universities: Karolinska Institutet, KTH Royal Institute of Technology, Stockholm University and Uppsala University. The centre offers services and know-how to the Swedish research community but also to external users such as companies, healthcare institutions and governmental agencies.

SciLifeLab services are organised in 42 facilities, located at several Swedish universities. There are also a number of pilot facilities that have been established with the aim to be included as national service facilities in the future.

Seven SciLifeLab facilities are hosted by IGP, which means that they are managed and run by IGP staff. In addition, IGP hosts the BioVis core facility, funded by the Medical and Pharmaceutical Disciplines.

### SciLifeLab Facilities at IGP

**Uppsala Genome Center** is one node of the National Genomics Infrastructure. The facility is open to academic research groups in Sweden on a non-profit basis. We provide tailor-made, cost-effective and expedient solutions for all types of genetic/genomic projects using e.g. massively parallel sequencing technologies, Sanger sequencing and STR typing.

The facility **Clinical Genomics Uppsala** provides high-throughput genomic services for late-stage, translational research projects and develops new genetic tests for clinical diagnostics within health-care. The focus is on developing genetic tests for various cancer forms and inherited diseases using state-of-the-art next-generation sequencing and bioinformatics.

The **PLA Proteomics** facility aims to serve the national and international scientific communities with advanced molecular techniques directly, or by making these available via other SciLifeLab facilities. We offer analyses of individual proteins, protein-protein interactions and post-translational modifications in single- and multiplex manners using technologies such as in situ PLA, solid-phase PLA, PLARCA, PLA via flow cytometry, PLA-WB, etc.

The **Tissue Profiling Facility** provides service and consultation for external research groups with focus on histopathological analysis in tissue samples. Special emphasis is put on tissue microarray production, immunohistochemistry, antibody validation and digital slide scanning.

The Preclinical Cancer Treatment (PCT) facility is a SciLifeLab and Uppsala University sponsored pilot facility opening in 2017. The PCT centre will provide service for preclinical and clinical researchers that are evaluating novel drugs in combination with standard treatments in vivo or that conduct controlled studies for refining current cancer therapies in vivo.

The **BioVis facility** provides technology and know-how for multimodal biological visualization at the tissue, cell, and sub-cellular levels, including supporting analytical and preparative technologies. Our technologies include light microscopy, flow cytometry and image analysis.

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**Bioimaging provides the means to place genomic and proteomic information in a cellular or tissue context. At BioVis we offer advice regarding methods and visualization-related problems as well as access to state-of-the-art instruments.”**

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Most of the SciLifeLab facilities hosted by IGP are located at Navet in BMC.
U-CAN is a unique project, hosted by IGP, in which frozen tissue and blood samples are collected in a standardized way from cancer patients before, during and after treatment. Patient data and radiological images are also collected. The material is used in research projects with the ultimate goal to improve treatment and disease outcome for cancer patients. This includes developing methods to fine tune diagnoses and better characterize different tumours, and to improve the possibilities to choose an optimal therapy for the individual patient.

MORE THAN 12,000 CANCER PATIENTS HAVE BEEN INCLUDED
The project was initiated in 2010, after receiving governmental funding for strategic research projects. Since then samples and patient information have been collected from thousands of patients with nine different cancer diagnoses. Patients are included by hospital staff at Uppsala University Hospital, Umeå University Hospital and at county hospitals in the wider Uppsala-Orebro region.

SUCCESSFUL COLLABORATION
The project is headed by Associate Professor Tobias Sjöblom at IGP. He believes that the success of the project stems from the fruitful collaboration between the involved organisations.

“Our mission was to propel today’s research by collecting large amounts of data and biobank samples, and to make them easily accessible. No single company or university, anywhere in the world, can do this alone. Our long-term, and I think unique, relationship between the participating universities, university hospitals, county councils, biobanks, regional cancer and biobank centers, and Science for Life Laboratory has been the key to our success”, he says.

HIGH EVALUATION RATING
After the first five years the project was evaluated by the Swedish Research Council. In the evaluation summary of the international panels’ assessment U-CAN received the highest rating in the evaluated categories: performance, strategy, added value and research output.

“This was of course very rewarding for all of us involved in U-CAN. Going forward we will continue patient inclusion but further increase the emphasis on clinical data. We will also increase support to high quality research projects based on materials from U-CAN,” says Tobias Sjöblom.

INCREASED DEMAND FOR RESEARCH PROJECTS
Since the start, more than 35 research projects have been approved, half of which were submitted only last year. This rapid increase in project applications reflects the research community’s need for systematically collected samples with readily available long-term follow-up data. It is also a consequence of that most U-CAN collections are now reaching “research-maturity”.

As a department with an overall focus on translational research, IGP recognizes the need to efficiently communicate, disseminate and apply scientific results in industry and healthcare. Many of the researchers at IGP forge strong links with partners in the business community to ensure efficient interactions.

Appointments of adjunct lecturers and adjunct professors further strengthen contacts with companies in the biotech and life science sector. During 2016, IGP had ten industry-sponsored postdocs involved in both collaborative projects and commissioned research. IGP has also been able to support new start-ups by offering lab premises on commercial terms for incubating companies in association with their founding labs during initial stages.

"New molecular techniques are important drivers of progress in medical research and practice. As an effect of this we are witnessing profound changes in healthcare. To contribute to this development we need to form close interactions between academia and industry."

Ulf Landegren

COMPANIES FOUNDED BY IGP RESEARCHERS
A strong, long-term focus on developing enabling molecular technologies and resources has rendered IGP an important partner in the SciLifeLab organization. It has also resulted in filing of a large body of valuable patents for advanced analyses at levels of nucleic acids or proteins by the MoTools unit and other groups at the department.

These innovations have formed the basis for several successful companies, often with graduate students and postdocs at the department in key roles as CEOs, COOs, CSOs, CROs, etc. The companies include ParAllele, Olink Bioscience, Olink Proteomics, Halogenomics, Cray Innovation, ExScale Biospecimen Solutions, Q-Linea, Atlas Antibodies, Genagon Therapeutics, and Vanadis Diagnostics.

COMPANIES LICENSING IP BY IGP RESEARCHERS
Several of the companies that have been built on work at IGP have gone on to successful exits through acquisition by leading international biotech and diagnostic companies, while others are in a growth phase, maintaining close association with members of the department. In addition, technologies invented and developed at IGP have been licensed to many of the world’s leading life science companies, including Abbott, Affymetrix/Applied Biosystems/ThermoFisher, Agilent, Pharmacia Biotech/GE Healthcare, PerkinElmer, Leica, DuPont, and SigmaAldrich/Merck.

Uppsala University has a strong tradition of world-leading technology development for molecular separation and analysis, which has often been conducted in close collaboration with industry. This tradition is very much alive at IGP, whose researchers have filed numerous patents and started several successful companies.

At least ten companies have been founded by IGP researchers, based on innovations and patents from the Department.
Prizes and awards

In the last few years many IGP researchers have been endowed various kinds of national and international prizes and awards. Some of these are for specific scientific or entrepreneurial achievements, others for long-term contributions to science.

CANCER RESEARCHER OF THE YEAR
Lena Claesson-Welsh (2017)

OLF RUDHECK PRIZE
Bengt Glimeilius (2016)
Lena Claesson-Welsh (2014)
Bengt Westermark (2012)
Per Westermark (2010)

GUSTAF ADOLF MEDAL IN GOLD
Lena Claesson-Welsh (2016)

LEFOULON-DELAANDE GRAND PRIX
Elisaberta Dejana (2016)

ERIC KERNSTROMS SVENSKA PRIS
Tobias Sjöblom (2016)
Taja Mäkinen (2015)
Helena Åkerud (2013)
Lars Petuk (2012)

EARL P. BENDITT AWARD
Elisaberta Dejana (2016)

LENNART PHILIPSON PRIZE
Maria Ulvmar (2016)

FLORMANSKA BELÖNINGEN
Fredrik Johansson Swartling (2016)
Anna Dimberg (2013)

HEMATOLOGICAL THESIS OF THE YEAR
Panagiotis Bialiakas (2016)

HILDA AND ALFRED ERIKSSON PRIZE
Per Westermark (2005)

MARIE CURIE AWARD
Hadi Honavar (2013)

UPPSALA COUNTY COUNCIL RESEARCH PRIZE
Bo Nilsson (2015)
Richard Rosenquist Brandell (2013)
Olle Korsgren (2012)

HWASSER PRIZE FOR BEST PRE-CLINICAL PHD THESIS
Hannah Karlsson (2015)
Carl-Magnus Claussen (2014)

THE KING’S MEDAL OF THE 8TH SIZE
Bengt Westermark (2014)

ATHENA PRIZE
Alex Karlsson-Parra (2014)

UPPSALA UNIVERSITY’S INNOVATION PRIZE HJARNAPPLET
Ulf Landegren (2013)

ESTRO REGAUD-MEDALJ
Bengt Glimeilius (2013)

IGP is an efficient, transparent and service-minded organization. We have a well functioning administration that supports and facilitates the work of staff and students at the Department.

The administration deals with matters that concern human resources, finances, undergraduate and postgraduate education, and internal and external communication.

HUMAN RESOURCES
Camilla Nilsson coordinates the human resources work. She and her team support group leaders and other staff in matters concerning recruitments and employments.

“We handle announcements of positions, negotiations with the unions, employment contracts and similar matters,” she says. “In addition, we support the department’s personnel by assisting with issues regarding their employment such as parental leave, salary discussions and individual development conferences.”

FINANCES
Several financial officers are handling the department’s finances.

“In the financial administration we manage the finances for both the whole department and for individual research groups,” says Birgitta Gustafsson, financial coordinator at IGP. “This includes pursuing that grants from the university and from external grant agencies are used for the intended purposes, and to report to the grant agencies within the time frame that they have defined.”

UNDERGRADUATE EDUCATION ADMINISTRATION
The undergraduate student administration organizes IGP’s courses, in collaboration with the Head of undergraduate education, course leaders and teachers involved in the courses. They take care of room reservations, prepare course schedules, update course web sites, register students and examination results, and administer exam papers.

POSTGRADUATE EDUCATION ADMINISTRATION
The postgraduate education administrators handle matters that concern IGP’s more than 100 postgraduate students. They administer the admission of students, register their course work and take care of the administrative arrangements around the students’ thesis defense.

COMMUNICATIONS
The communications officer at IGP is responsible for the IGP web, which is used for both internal and external communication.

“Our administration supports and facilitates the work of staff and students at IGP.”

Camilla Nilsson
**About us**

IGP is located at the Rudbeck Laboratory, at the Biomedical Centre (BMC) and at the University Hospital.

**RESEARCH PROGRAMMES**
- Clinical and Experimental Pathology
- Clinical Immunology
- Experimental and Clinical Oncology
- Human Protein Atlas
- Medical Genetics and Genomics
- Medical Radiation Sciences
- Molecular Tools
- Neuro-oncology
- Vascular Biology

**SERVICE FACILITIES**
- Uppsala Genome Center
- PLa platform
- Tissue Profiling platform
- Clinical Sequencing facility
- Single Cell Proteomics Facility
- Preclinical Cancer Treatment Center
- SciLifeLab Data Office
- BioVis

**FINANCIAL TURNOVER 2016**

<table>
<thead>
<tr>
<th>Total: 375 MSEK</th>
<th>128 MSEK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research</td>
<td>219 MSEK</td>
</tr>
<tr>
<td>Government funding</td>
<td>219 MSEK</td>
</tr>
<tr>
<td>External funding</td>
<td>Sweden, EU, USA</td>
</tr>
</tbody>
</table>

**SOME PRESTIGIOUS GRANTS**
- ERC Starting grants
- Lars Feuk
- Lars Forsberg
- Fredrik Svanberg
- Consolidator grant
- Taija Mäkinen
- ERC Advanced grants
- Christer Betsholtz
- UF Landegren
- Knut and Alice Wallenberg Foundation project grants
- Bengt Westermark et al
- Christer Betsholtz et al
- Wallenberg academy fellow
- Linda Holmfeldt
- Wallenberg scholar
- Christer Betsholtz
- Lena Claesson-Welsh
- Wallenberg classical scholar
- Richard Rosenquist Brandell

**MAJOR FUNDING AGENCIES**
- AFA Insurance
- AstraZeneca
- Beijer Foundation
- Diabetes Wellness EU, FP; and Horizon2020
- ERC
- EU, IMI
- FORTE
- Göran Gustafson Stiftelse
- Juvenile Diabetes Research Foundation
- Knut and Alice Wallenberg Foundation
- Leducq Foundation
- National Institutes of Health
- Novo Nordiskfonden
- Olle Enqvist Byggmästare Foundation
- Ragnar Söderbergs Stiftelse
- SSMF
- Stiftelsen Onkologiska klinikens I Uppsala forskningsfond
- Swedish Cancer Society
- Swedish Childhood Cancer Foundation
- Swedish Crime Victim Compensation and Support Authority

**SOME HIGH IMPACT PAPERS**
- (2015) (with IGP researchers as first/last author)
- Times cited: 25, IF = 12
- Times cited: 10, IF = 10

- Times cited: 79, IF = 12
- Times cited: 20, IF = 11

**Research**
- Nils-Erik Heldin
- Financial coordinator
- Birgitta Gustafsson
- Personnel coordinator
- Camilla Nilsson

**Undergraduate education**
- 3 MSEK
- 500 people affiliated to IGP
- 150-200 thesis defences annually
- 105 postgraduate students
- 51 research groups
- 12 senior lecturers
- 34 professors
- 600 people affiliated to IGP

**Groups with specific responsibilities**
- Equal opportunity group
- Work environment group
- Equipment group
- Postgraduate education group
- Rudbeck seminar group

**Publications**

**Number of publications per year**

- 2010: 100
- 2011: 150
- 2012: 200
- 2013: 250

**Number of publications per year in journals with IF > 10**

- 2010: 5
- 2011: 10
- 2012: 15
- 2013: 20

**Swedish Foundation for Strategic Research**

**Swedish Radiation Safety Authority**

**Swedish Research Council**

**Torsten Söderbergs Stiftelse**

**Uppsala University Hospital (ALF funding)**

**Vinnova von Kanton Foundation**

**World Wide Cancer Research Åke Wibergs Stiftelse**

**Some prestigious grants**

- ERC Starting grants
- Lars Feuk
- Lars Forsberg
- Fredrik Svanberg
- Consolidator grant
- Taija Mäkinen
- ERC Advanced grants
- Christer Betsholtz
- UF Landegren
- Knut and Alice Wallenberg Foundation project grants
- Bengt Westermark et al
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- Wallenberg classical scholar
- Richard Rosenquist Brandell

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- Times cited: 25, IF = 12
- Times cited: 10, IF = 10

- Times cited: 79, IF = 12
- Times cited: 20, IF = 11

- Times cited: 6, IF = 12

**Baliakas P et al. Not all IGHV3-21 chronic lymphocytic leukemias are equal: prognostic considerations. Blood. 2015, 125(2):856-9.**
- Times cited: 14, IF = 11

- Times cited: 10, IF = 12
Clinical and experimental pathology

The programme focuses on disease-related alterations in human tissues.

Researchers in this programme study both morphological and molecular alterations in e.g. protein expression or at the levels of DNA or RNA. On-going projects include studies on tumours, inflammation, degeneration and amyloidosis in various organs.

**NEUROPATHOLOGY**
The group headed by Irina Alafuzoff focuses on various degenerative processes and diseases of the human brain. They use a range of techniques for studying tissues, for instance histology, immunohistochemistry, in situ hybridization, morphometry and tissue microarray strategy. The research approach can be described as being overall systemic, incorporating all fields of medicine.

**LYMPHOMAS**
Rose-Marie Aminis group studies different diagnostic, prognostic and predictive markers in malignant lymphomas by investigating different genetic events, important for lymphoma initiation and progression. They focus on the aggressive B-cell lymphomas and aggressive lymphomas affecting the central nervous system.

**LUNG CANCER**
Two research groups focus on lung cancer. Johan Botling’s group studies the molecular pathology of non-small cell lung cancer. They have identified specific aberrations on genomic and transcriptomic levels that are strongly associated with clinical outcome. A key effort of the group is to translate knowledge and established technology developed in research projects into routine diagnostics.

Patrick Micke and his team use human lung cancer tissue to perform molecular analyses based on the concert of different cell types in the in situ environment. In this integrative approach, they combine genomic information with clinical parameters to identify molecular interactions that can be utilized as biomarkers or new treatment targets.

**AMYLOID RESEARCH**
Per Westermark’s group has a broad interest in the nature, pathogenesis and impact of a number of amyloid diseases. The possible transmission of amyloid diseases by a prion-like mechanism is their of our main interests. They also perform amyloid diagnostic work in association with the University Hospital.

**AGING RELATED NEURODEGENERATION AND SYSTEMIC DISORDERS**

**IN ALZHEIMER’S DISEASE (AD)** lesion as hyperphosphorylated τ (HPτ) and β-amyloid (Aβ) are seen in the brain. Further alterations such as α-synuclein (αS) and transactive DNA binding protein 43 (TDP43) are common. We have studied these alterations in cognitively unimpaired and in idiopathic normal pressure hydrocephalus (iNPH), both settings are unique. HPτ was observed in 58 % (age range of 50-102 years) and the incidence of HPτ/ Aβ (i.e., Primary Age Related TDP43 (PART) and the Aging-Related Tau Astrogliopathy (ARTAG) was seen in 57 % of unimpaired aged subjects (manuscript under preparation). Other concommitant brain alteration also increased with aging, αS from 12 to 19 % and TDP43 from 21 to 36 %.

The causative mechanism for neuronal and glial degeneration is poorly understood, whereas there are suggestions that systemic disorders might be of significance. We have studied the brain in parallel with peripheral organs displaying alterations related to various systemic disorders. Currently we are studying the effect of cardiovascular disease on kidneys, heart and the aging brain. Recently we also noted a severe cell loss even in the late stage of neuro degeneration whereas the inflammation decreased.

**SEVERAL CLINICAL PATHOLOGISTS are also affiliated with the Department. Their research projects aim to improve diagnostics to make it more informative and to identify potential targets to be used for the development of new treatment strategies. The research is mainly based on analyses of disease related alterations in tissues obtained from biopsies, surgical specimens or autopsy studies. Studied diseases include pituitary adenoma, prostate cancer and lung cancer.”**
**Tumour-biological studies of malignant lymphomas**

**MALIGNANT LYMPHOMAS** comprise a heterogeneous group of about one hundred different disease entities and the diagnosis is made on formalin-fixed paraffin-embedded tissue material (FFPE). Since the introduction of core needle biopsies in lymphoma diagnostics, material available for research purposes is often insufficient and fresh frozen material is almost always lacking. Therefore, we need to develop the use of small amount of FFPE material to adapt to the new high-throughput molecular techniques.

We use different techniques in addition to morphology like immunophenotyping by flow cytometry and immunohistochemistry. FISH and in situ hybridisation in order to make sure of an adequate lymphoma classification. For the molecular studies we apply high-throughput technologies such as next-generation sequencing, microarrays and targeted functional analysis.

We study different diagnostic, prognostic and predictive markers in both aggressive B- and T-cell lymphomas and also indolent B-cell lymphomas by investigating different genetic events, important for lymphoma initiation and progression. Lately, new treatment modalities like targeting specific molecular pathways have been introduced in the lymphoma field and thus it is of importance to identify which genes are affected in each lymphoma category. In addition, new treatments targeting cells in the tumour stroma have been developed and we also study inflammatory cells in the stromal compartment.

**Diagnostic molecular tumour pathology**

**KNOWLEDGE OF THE LANDSCAPE** of driving mutations in unselected real-life patient populations is crucial for the implementation of modern precision oncology. We have characterised mutation patterns in tumour samples from a regional population-based lung cancer cohort, retrospectively in a large collection of surgical tissues, and prospectively in the U-CAN project with focus on advanced disease.

Molecular data in combination with clinical follow-up and cancer registry parameters form the base for diagnostic and predictive biomarker research. Complex mutation patterns are studied further with novel in situ techniques, and in a recent project we explore the role of tumour-associated macrophages in tissue compartments of lung cancer lesions. A key priority is to translate knowledge and established technology into routine pathology diagnostics. Our group leads the Solid Tumour Work Package in the national Clinical Sequencing Platform, Science for Life Laboratory. In house development of targeted next generation sequencing for formalin-fixed tissues and adapted bioinformatic pipelines have led to the introduction of multiplex diagnostic mutation assays for colon cancer, lung cancer, melanoma, GIST, and ovarian carcinoma. This year targeted sequencing diagnostics was launched for circulating tumour DNA in liquid biopsies. Ongoing work includes RNA-assays for fusion gene detection and global tumour profiling in prospective clinical trials.

**Amyloid in the pathogenesis of human diseases**

**WE STUDY THE NATURE**, pathogenesis and possible transmission of the diseases as well as amyloid deposits exert effects on cells. Both systemic forms, with amyloid deposited throughout the body, and local forms, limited to one organ or tissue are included.

Much of our work on systemic amyloidoses is presently focused on the diseases caused by aggregation of transthyretin (TTR). We have found that there is an interesting correlation between clinical manifestations and the constituents of the amyloid aggregates among Swedish patients with a hereditary form of the disease. Two distinct phenotypic groups can be found, in which the amyloid consists of mainly full-length TTR molecules in one type, while the other type predominantly consists of C-terminal TTR fragments. We are trying to determine how cleavage of TTR occurs and how amyloid formation from full-length and cleaved TTR differs. Together with groups at Uppsala University Hospital, we are also involved in the development of new diagnostic tools in systemic amyloidosis. In addition, we collaborate with many research groups on prion-like transmission of amyloid diseases.

Our work on localized amyloidoses is mainly focused on amyloid in the human aorta. We study aortic medial amyloid derived from the peptide medin, which we believe is important in the pathogenesis of aortic aneurysm, and with an, as yet not fully biochemically characterized form, that is associated with atherosclerosis.

**Integrative Lung Cancer Pathology**

**THE INTRODUCTION** of checkpoint inhibitors has revolutionized lung cancer therapy and has demonstrated that the immune system can control cancer growth. Since long lasting responses are observed only in a subgroup of patients, a better understanding of the underlying mechanisms that regulate anti-tumour responses are warranted.

Our research project integrates tissue pathology with data on different molecular levels and connects them with the individual patients’ outcome in two traits: (1) Retrospectively, by analyzing the immune profile of lung cancer patients (n=712), including analysis of global RNA expression (RNAseq), immune cell infiltrates and immune mediators. We use different techniques in addition to morphology like immunophenotyping by flow cytometry and immunohistochemistry. FISH and in situ hybridisation in order to make sure of an adequate lymphoma classification. For the molecular data in combination with clinical follow-up and cancer registry parameters form the base for diagnostic and predictive biomarker research. Complex mutation patterns are studied further with novel in situ techniques, and in a recent project we explore the role of tumour-associated macrophages in tissue compartments of lung cancer lesions. A key priority is to translate knowledge and established technology into routine pathology diagnostics. Our group leads the Solid Tumour Work Package in the national Clinical Sequencing Platform, Science for Life Laboratory. In house development of targeted next generation sequencing for formalin-fixed tissues and adapted bioinformatic pipelines have led to the introduction of multiplex diagnostic mutation assays for colon cancer, lung cancer, melanoma, GIST, and ovarian carcinoma. This year targeted sequencing diagnostics was launched for circulating tumour DNA in liquid biopsies. Ongoing work includes RNA-assays for fusion gene detection and global tumour profiling in prospective clinical trials.

(2) Prospectively, by analyzing patients treated with immunotherapy (anti-PD-L1, anti-PD-1 or CTLA4 inhibitors). Tumour tissue and blood samples are collected systematically within the U-CAN infrastructure and in parallel clinical information are reported into the central database. Available biopsies will be analyzed by targeted sequencing and immune markers will be determined by multiplexed gene expression measurements (nCounter). PBMCs isolated from blood will be analyzed by multiplexed FACs.

The aim is to systematically collect biomaterial and clinical data from patients treated with immunotherapy and by the combined analysis identify better predictors for therapy response.
Clinical immunology

The programme runs projects that span the complete immunological range from innate to adaptive immunity and the resulting effects on the host.

The Clinical Immunology research groups have a strong translational focus, supported by close interactions with Uppsala University Hospital.

**IMMUNOTHERAPY OF CANCER**
Magnus Essand’s research mainly concerns advancements of translational cancer immunotherapy, focusing on development of oncolytic viruses, CAR T-cells and dendritic cell based vaccines.

**DIABETES RESEARCH**
Research in Olle Korsgren’s group focuses on the cause of diabetes and on possibilities to prevent and cure the disease. The research has a broad multidisciplinary translational approach.

**IMMUNOSTIMULATORY GENE THERAPY**
Angelica Loskog and her team are inventing and evaluating novel cancer immunotherapies. The focus is on CAR T-cells and adenovirus-mediated immunostimulatory gene therapy.

**VASCULAR INTERACTIONS**
Peetra Magnusson investigates possibilities to protect the endothelium in disease and to improve organ transplantation.

**IMMUNO-ONCOLOGY**
The projects in Sara Mangsbo’s group aim to develop and validate new immune therapies that aim to both improve and renew the effector cells in the body, and also revert the immunosuppressive milieu.

**INNER IMMUNE RECOGNITION**
Bo Nilsson’s group studies the cascade systems of the blood, specifically the mechanisms behind thromboinflammation, which is triggered by the cascade systems.

**RHEUMATIC DISEASES**
Johan Rönnelid’s research focuses on functional and prognostic impact of immune complexes and immune complex-associated autoantibodies in rheumatic diseases.

**STROMAL CELL MEDIATED IMMUNE REGULATION**
Maria Ulvmar’s research group focuses on the specialized lymph node vasculature.

IMmunotherapy of cancer using engineered viruses and T-cells

**IMMUNOTHERAPY OF CANCER** has emerged as one of the most promising new developments in medicine. Checkpoint antibodies, which kill cancer cells through activation of anti-tumour cytotoxic T-cells have produced outstanding responses and cure of metastatic recurrent cancers. The same is true for patient-derived chimeric antigen receptor (CAR) T-cells when it comes to certain forms of blood cancer.

However, we have only just begun to understand how immune regulatory mechanisms in cancer can be exploited for treatment; there is clearly more to come.

Our research mainly concerns translational cancer immunotherapy, focusing on oncolytic cancer-killing viruses and CAR T-cells. Most work is preclinical and based on studies on patient samples and advanced mouse models but two oncolytic viruses developed in our laboratory are now being evaluated in clinical trials for neuroendocrine cancer and prostate cancer.

A current preclinical focus of ours is to develop neurotropic viruses for treatment of glioblastoma, the most aggressive form of brain cancer.

We are also involved in a clinical trial with CAR T-cells for blood cancer and a new expansion protocol for CAR T-cells, developed in our laboratory, is about to be evaluated in an upcoming clinical trial. Another preclinical effort is to develop next generation CAR T-cells that can modulate the tumour microenvironment and generate bystander killing of tumour cells not targeted by CAR T-cells for future treatment of solid tumours.
Type 1 Diabetes

In Sweden, more than 2 children per day are diagnosed with type 1 diabetes, reaching more than 800 patients every year.

Diabetes is a lifelong, incapacitating disease affecting multiple organs. Our research focuses on the cause of diabetes and on possibilities to prevent and cure the disease. The research has a broad multidisciplinary translational approach, which integrates genetics, bioinformatics, physiology, cell biology, clinical immunology, diabetology and transplantation research.

Although type 2 diabetes accounts for most of the diabetes epidemic, type 1 diabetes (T1D) is in Sweden one of the most common chronic disorders in children, with more than 800 new patients per year. In addition, an equal number of adult subjects are annually diagnosed with T1D. For unknown reasons the incidence of T1D has doubled during the past twenty years. The aim of our research is to clarify the etiology of T1D and to pave the way for development of new strategies for prevention and cure of TID. The work is organized in five projects with the following objectives:

1. Unravel the etiology of T1D.
2. Halter or prevent T1D in newly diagnosed patients by transplantation of autologous mesenchymal stem cells.
4. Transplantation of isolated islets to cure patients with the most severe T1D, experimental and clinical studies.
5. Induction of immunological tolerance: Regulator T cells for treatment of transplantation induced immune reactions.

Vascular interactions and human innate immunity

Disturbances in vascular function contribute to the development of several diseases and as a further consequence to human mortality. Diseases such as diabetes, heart failure, sepsis and ischemia reperfusion injury share many of the same risk factors and consequential endovascular complications. To answer specific questions about diseases involving vascular inflammation and innate immunity we utilize innovative in vitro models with human cellular components. They are unique in that they obtain relevant results regarding scientific questions in vascular disease models, creating a causal relationship between the conducted analyses and the final result.

Furthermore, there is a need of experimental models to gain knowledge of biopharmaceutical delivery into the blood stream, knowledge that will lead to benefit for the treated patients.

Most biopharmaceuticals are directed against proteins and cells of human origin. Utilization of our human whole blood models provides a possibility to investigate the inflammation and thrombus formation elicited by biopharmaceuticals that occur between the protein drug and cells, both in the fluid phase and at the cell surface.

The overall aim of our research is to further develop available in vitro models creating proof of concept and establish therapeutic strategies that will correctly mimic the early events of human innate immunity and vascular interactions.

Immuno-oncology group

Our work is focused on the development and evaluation of novel biologics and combinations thereof, where activation of tumour-specific T cells is key. These studies involve novel antibody-based therapies that specifically targets immune cells, and combinations thereof, to elucidate how these therapies can be used to target localized and metastatic cancer. In addition, we develop innovative therapeutic cancer vaccines in the form of peptide conjugates, as a means to prime T cells against tumor antigens.

Our research also tackles off-target effects related to these therapies, such as interactions with Fc receptors and how findings in murine models are translatable into human model systems. In human whole blood we study both adverse events in the form of first-infusion reactions related to interactions with immune cells and cascade systems, as well as recall responses using our novel peptide-conjugates, incorporating known T cell epitopes and the mode-of-action behind our peptide-conjugate delivery system.

In addition, we have focused our research on tumour-localized immunotherapies and we study this in an experimental bladder cancer model. Our aim is to locally enhance immune activation in the tumour micro-environment and tumour-draining lymph node, while sparing unnecessary systemic activation, thereby avoiding induction of auto-immune symptoms.

Immunostimulatory gene therapy for cancer

Our research focuses on cancer immunotherapy. This encompasses invention of novel strategies, mechanism-of-action and proof-of-concept studies, product development and performing clinical trials. We work in close contact with small biotech companies such as the Swedish based Lokon Pharma for product development. The aim of cancer immunotherapy is to modulate the immune system to make it target and kill cancer cells by the same mechanisms as when eliminating virally infected cells. There are many approaches being tested in clinical trials around the world with promising results and immunotherapy is becoming a cornerstone in cancer treatment. However, most new drugs are not yet available in Sweden and there are only few clinical trials with too few slots available to meet the demand.

Our research group develops immunostimulatory gene therapeutic strategies such as the next generation CAR T cells (ex vivo gene engineered cell therapy) and oncolytic viral vectors (in situ immune activating gene therapy). We have just completed the first academic trial using 3rd generation CAR T cells to treat B cell malignancy, and a follow-up trial with an optimized treatment schedule will soon be started. We have also finished an immunostimulatory gene therapy trial using adenovirus encoding CD40L (AdCD40L) for malignant melanoma. The AdCD40L has been redesigned to enhance lymphocyte expansion (LOAd703) and a trial in pancreatic cancer is ongoing in partnership with Lokon Pharma AB.
**Research**

The blood cascade system within the innate immunity system is critical for host defence and tissue repair, but is also a driving force in thromboinflammatory damage in disease and therapies.

**The Intravascular Immune System**

The blood cascade system recognises altered and foreign biosurfaces, which includes the cell membranes and biomaterials. The recognition surfaces trigger thromboinflammatory reactions when they come in direct contact with blood, plasma or other body fluids. This mechanism leads to adverse reactions in a number of common diseases/conditions/medical treatments.

In translational projects we are:

1. Performing basic mechanistic studies of thromboinflammation, e.g. newly identified activation mechanisms of the lectin pathway and non-protectolytical C3 activation on platelets and other phospholipid membranes.

2. Creating biocompatible biosurfaces (biomaterials or cell membranes) employing nano-profiling, PEGylation techniques, and phospholipid coatings conjugated with regulators of innate immunity for protection against thrombotic and complement attack. The studies are performed in vitro in whole blood models or in large animal models of allogeneic kidney transplantation. Investigating thromboinflammatory reactions in patients with cardiac infarction, multiple sclerosis and during hemodialysis. We use novel immunosays assessing complement, coagulation, and contact system parameters. These projects open up possibilities to identify new therapeutic interventions in transplantation of cells and whole organs, thrombotic diseases and treatments with biomaterials/scaffolds.

3. Investigating thromboinflammatory reactions in patients with cardiac infarction, multiple sclerosis and during hemodialysis. We use novel immunosays assessing complement, coagulation, and contact system parameters. These projects open up possibilities to identify new therapeutic interventions in transplantation of cells and whole organs, thrombotic diseases and treatments with biomaterials/scaffolds.

**Functional Studies of Immune Complexes in Rheumatic Diseases**

We develop new techniques to measure function of immune complexes (IC) and content of autoantibodies and autoantigens in IC in rheumatic diseases like rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Three examples:

1. We have defined a new RA-phenotype associated with TLR4-mediated production of chemokines driven by IC containing autoantibodies against collagen type II early after RA diagnosis. These patients have acute onset RA but good prognosis, and represent the opposite to patients with anti-citrullinated peptide antibodies (ACPA) both concerning clinical phenotype, association to HLA alleles and to smoking. Ongoing studies focus on cellular investigations of anti-CII IC function, associated risk SNPs, and clinical epidemiological studies to define the clinical role of anti-CII in care of RA patients.

2. We develop new techniques to quantify autoantibodies in circulating IC. These are evaluated in clinical studies, e.g. of belimumab (anti-BAFF)-treated SLE patients and in RA patients treated with intra-articular steroids. Preliminary evaluation show that anti-DNA content in IC, but not anti-DNA content in serum, is associated with clinical response to belimumab in SLE, and that number of specific anti-citrullinated peptide antibodies (ACPA) found in IC in RA synovial fluids, but not general ACPA levels, associate with length of remission in RA.

3. Comparative clinical and immunological studies between RA and SLE in Sudan. Our data supports that growing associations to HLA alleles and to smoking in SLE patients and in RA patients treated with intra-articular steroids. Preliminary evaluation show that anti-DNA content in IC, but not anti-DNA content in serum, is associated with clinical response to belimumab in SLE, and that number of specific anti-citrullinated peptide antibodies (ACPA) found in IC in RA synovial fluids, but not general ACPA levels, associate with length of remission in RA.

**Stromal Cell Mediated Immune Regulation in the Lymph Node**

**We Are a New Group** at IGP that with funding from Lennart Philipson and the Swedish Research Council is starting up our work in the spring of 2017. The group will work at the cross-road of tumour immunology and vascular biology. Our focus is on understanding the impact the highly specialized lymph node vasculature has on the structure and function of the lymph node in the regulation of adaptive immune responses, particularly the immune response in cancer disease.

Recent data from our own research and others’ shown that the lymphatic endothelium in the lymph nodes have unique functions and expression of immune-modulatory genes that cannot be found in the lymphatic vessels of other organs. Our data supports that growing peripheral tumours and metastatic tumour cells can affect the molecular patterning of the lymph node stroma, including the vascularis, thereby affecting immune regulation in cancer. We use advanced experimental models for genetic evaluation of specific endothelial gene functions and in vivo imaging of metastasis alongside studies of stromal changes in human tumour draining lymph nodes. Our emphasis is on the translational relevance of our research.

Our lab is specialized in advanced flow cytometry and cell sorting for stromal cell analysis, allowing us to sort rare subsets of endothelial cells for RNAseq with high precision. This is complemented by imaging to understand interactions between vessels, immune cells and tumour cells.

**We Want to Broaden the Focus on Stromal Cells in Cancer to Also Include Early Metastatic Sites, i.e. the Tumour Draining Lymph Node.**

Maria Ulvmar
Experimental and clinical oncology

The research programme includes both experimental projects, performed in the laboratory, and projects with a clear clinical focus.

In experimental projects, the researchers use modern molecular and cellular methods to study patient derived tumour cells and relevant models for the tumour in vitro and in vivo. The aim is to identify essential pathways that may cause cancer or that will affect disease progression. Another objective is to find novel biomarkers that can be used for improved diagnostics and prognostication, or that may function as targets for new treatment strategies.

The clinical research programme includes thorough evaluation of the effect of different treatment strategies, to find ways to determine which therapy is most efficient for the individual patients. New treatment modalities, including immunotherapy, are also studied. With the aim to improve immediate patient care, the researchers also study the effects of interventions to diminish treatment toxicity and improve health related quality of life.

Our overall goals are to gain insight into the complex molecular mechanisms underlying tumour evolution, and to identify novel prognostic and/or predictive markers and treatment targets. We also investigate the consequences of the disease and treatment for the patients’ wellbeing.

The programme has successfully implemented clinically relevant tumor model systems for functional studies in vitro and in vivo, high-throughput capabilities for compound library screens, large-scale genomic and epigenomic profiling, and combined this with bioinformatic and clinical expertise.

Our aims are also to diminish treatment toxicity and improve health related quality of life. Another aim is to find ways to improve treatment results and improve patients’ quality of life.

REGULATORS OF BLOOD VESSEL FORMATION

Mats Hellström’s research focuses on finding signalling components that are specific for the cells that line the inner walls of blood vessels. He has identified paladin as a possible candidate and he is studying in detail the role of paladin in blood vessel formation.

ACUTE LEUKEMIA

Linda Holmfeldt’s research on acute leukemia aims to increase the understanding of why many patients do not respond to treatment or suffer from a relapse of the disease. They also want to identify changes in the tumour cells that can be used to develop more efficient treatment alternatives.

MULTIPLE MYELOMA

The goal of Helena Jernberg Wiklund’s projects is to identify targets essential for tumour cell survival and explore in models of multiple myeloma if their function can be blocked in parallel survival pathways.

CARING SCIENCES IN ONCOLOGY CARE

The group headed by Birgitta Johansson studies how cancer patients feel during and after therapy, and how they have experienced the therapy and care. Another aim is to find ways to improve treatment results and improve patients’ quality of life.

CANCER IN THE AIRWAYS OR KIDNEYS

Magnus Lindskog’s research aims to contribute to improved and individualised therapies for cancer that is diagnosed in a late stage.

IMPROVED CANCER THERAPY

Peter Nygren and his team focus on improving the efficacy of cancer treatment by providing information allowing for optimal drug selection for the individual patient. They also want to identify new compounds with enhanced efficacy against tumour types for which effective therapies are lacking.

CHRONIC LYMPHOCYTIC LEUKEMIA

Richard Rosenquist Brandell’s efforts aim to increase the understanding of mechanisms behind development of chronic lymphocytic leukemia, to improve and optimize the diagnostic and prognostic information and to reveal new strategies for therapy.

CANCER CAUSING MUTATIONS

Tobias Sjöblom uses genetic approaches in human cancer cells to study mutations that cause common cancer. The findings may aid in development of methods for early tumour detection, improved diagnosis, and targeted cancer chemotherapy.
ResearCh

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MATS HELSTRÖM


LINDA HOLMFEIDT

The goal with our studies is to pave the way for novel treatment alternatives, improved and less invasive diagnostics, and improved risk stratification for patients suffering from acute leukemia.

ResearCh

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GUNILLA ENBLAD

The research projects focus on three types of lymphomas: Diffuse large B-cell lymphoma (DLBCL), Hodgkin lymphoma (HL) and mantle cell lymphoma (MCL).

In large population-based materials we perform comprehensive characterization of the patients and tumour samples with special focus on the inflammatory microenvironment and immune escape mechanisms in relation to clinical outcome. Serum and plasma biomarkers are studied before, during and after treatment in order to find early prediction of response and toxicity. Furthermore, we perform next generation sequencing on clinically relevant subgroups as e.g. patients with an autoimmune disease and lymphoma. We also aim to further elucidate age and gender differences in survival of the lymphomas.

We also perform clinical studies on lymphomas by participating in national and international networks and have studies for primary treatment and salvage therapy for HL and MCL and salvage therapy for DLBCL as well as proton beam radiotherapy of HL.

We have, as the first centre in Europe performed a study of genetically modified T cells, CAR T cells targeting CD19 for patients with lymphomas and leukemias. Fifteen patients could be safely treated with six patients achieving a complete remission. The next study will be started spring 2017.

In recent years the importance of new drug development for HL and MCL and salvage therapy for DLBCL is increasing and understanding of how the formation of new blood vessels is regulated may lead to the development of new therapies.

Due to toxicity, the survival rate is lower than changes in tumour size indicate. The analyses are done on paraffin-embedded formalin-fixed material, frozen tissues and serum and plasma taken at baseline and during follow-up. We use immunohistochemistry, plasma proteomics and mutation analyses, and we perform functional studies on MR images.

All patients diagnosed with colorectal cancer since 2010 from Uppsala and Dalarna (rectal cancer only) have been identified. All clinical and diagnostic investigations are characterized and the analyses are ongoing.

Our research focuses on finding signalling components that are specific for endothelial cells, the cells that line the inner walls of blood vessels. We have identified several possible candidates and one of these, called paladin, we are analyzing in more detail. We have shown that paladin is an endothelial enriched novel lipid phosphatase regulating signaling downstream of multiple growth factor pathways, including vascular endothelial growth factor (VEGF), and that lack of paladin leads to altered blood vessel growth and function.

Paladin is the first endothelial selective lipid phosphatase that is described. We hope that our results will contribute to an increased understanding of the fundamental signaling processes governing angiogenesis in general, and in the long run contribute to development of better drugs modulating angiogenesis in patients.

Colorectal cancer – clinical and translational studies

Our research addresses the questions: Can the risk of recurrence and the need for adjuvant therapy be predicted in primary colon cancer? Can high-risk patients be identified already before surgery using imaging or blood analyses? What drugs can eradicate potential remaining tumour cells? Can the probability of response to radiotherapy or chemoradiotherapy be predicted in primary rectal cancer? What is the risk of systemic disease? Can the response in metastatic disease to particular drugs be predicted? Can response or progression to a given treatment be detected earlier than changes in tumour size indicate?

The analyses are done on paraffin-embedded formalin-fixed material, frozen tissues and serum and plasma taken at the onset of relapse and treatment resistance.

In an ongoing functional evaluation of mutations we identified in a genomic analysis of pediatric ALL, we investigate the impact of mutations that affect the function of so called epigenetic regulators. These are factors that control the activity of our genes by changing the chromosome structure. Our studies are expected to render information about effects these mutated epigenetic regulators have on specific gene activities.

Knowledge gathered from our studies will likely make way for improved treatment strategies of these high risk cancer types.

Molecular characterization of acute leukemia

Our research focuses on acute leukemia – a cancer of the bone marrow that can be of either myeloid (AML) or lymphoid (ALL) origin. Despite the best available treatment, after initial recovery, most patients experience a relapse that most often is lethal. Due to toxicity, the survival rate cannot be improved by intensified treatment with the drugs available today, and new therapeutic options are direly needed.

To get a better understanding of the underlying causes of progression of AML, we perform a molecular characterization of primary leukemic cells. We utilize a combination of high resolution analysis methods to get as complete a picture as possible of the alterations present in the genome, transcriptome, epigenome and proteome of the cells. These analyses, in turn, serve as the basis of a functional evaluation to investigate the association between identified alterations and the onset of relapse and treatment resistance.

Tumour biology and clinical studies of lymphomas

Our goal is to increase the knowledge about the biology behind the diseases, how patients can be treated in the best way and development of a new immunotherapy, genetically modified T cells (CAR T cells).

Data from the analyses are then integrated in U-CAN, our biobank, to facilitate analyses of unselected populations and international networks and have studies for primary treatment and salvage therapy for HL and MCL and salvage therapy for DLBCL as well as proton beam radiotherapy of HL.

The analyses are done on paraffin-embedded formalin-fixed material, frozen tissues and serum and plasma taken at...
**Dissecting the epigenomic network in multiple myeloma**

Our current focus is to decipher the underlying mechanisms leading to aberrant epigenetic silencing and to functionally validate the role of repressed genes in multiple myeloma in vitro and in vivo.

AIMING TO EVALUATE possible links between exogenous survival factors, genetic alterations and the epigenome of multiple myeloma (MM), we initially undertook an integrative genomics approach on dissecting the differences in gene expression between non-malignant and malignant plasma cells. As a result we generated proof-of-principle that the IGF-I receptor is an attractive target for intervention in MM, and that this survival circuit acts via epigenetic gene silencing.

We have now generated the first global epigenomic map in MM and normal plasma cells, showing that MM-unique Polycomb targets are significantly enriched in advanced stages of the disease and in patients with poor survival. Pharmacological intervention by selective inhibitors of clinical relevance induced reactivation of silenced genes, among which we have identified novel miRNAs targeting MM oncogenes. Functional studies of targets of Polycomb, and consequences of gene reactivation in vitro and in vivo are currently the focus of our investigations.

We are now embarking on the intrinsic network of interactions between epigenetic modifiers that mitigate the response to inhibitors of Polycomb and maintain persisting gene silencing in MM. We are also examining the complex interaction between epigenetics and metabolism in MM by generating metabolomic profiles on the response induced by drug treatment, as well as investigating basal differences between different entities of MM.

**Caring sciences in oncology care**

**OUR RESEARCH FOCUSES** on cancer patients’ wellbeing during and after treatment and we are aiming to find ways to reduce treatment toxicity, psychosocial distress and improve quality of life (QoL).

One randomised controlled trial (RCT), included in the Uppsala University Psychosocial Care Programme, evaluates the effects of internet based stepped care for patients with self-reported anxiety and depression, on anxiety, depression and QoL, compared to standard care. Also, the cost-effectiveness of the intervention will be evaluated. This study includes over 500 patients of whom 249 were included in the RCT due to anxiety and depression symptoms. Main results will be available in the beginning of 2018.

Another RCT (n=148), which will be reported within this year, is investigating if an internet based education can improve satisfaction with care and the image of repositioning is to try to identify, in tumour cells from patients to be active in cancer in the airways or kidneys.

**Prognostic and predictive factors in cancer in the airways or kidneys**

**IN OUR RESEARCH WE STUDY PATIENTS** with cancer in the airways, i.e. lungs or head and neck region, and kidney cancer. Our work is contributing to improved and individualised therapies for cancer that is diagnosed in a late stage. This includes finding methods to identify patients with limited metastasis (to lymph nodes and oligometastasis) that can benefit from combinatorial therapies.

The rapid clinical development of new drugs that modulate the body’s immune reaction against the cancer (check point inhibitors), or treatments that target blood vessel formation in the tumour (tyrosine kinase inhibitors), is promising but also imposes new challenges: How do we identify the patients that are most likely to benefit from the new drugs? For patients with metastatised, advanced cancer and short expected survival, symptom controlled therapy and palliative care might be a better choice. These patients also have to be identified, to receive individualised care at the right time point.

The group is involved in several subprojects focusing on identifying prognostic and therapy predictive factors:

- Predictive factors in immune modulating and anti-angiogenesis cancer therapy.
- Optimised treatment of oligometastasised kidney and lung cancer.
- Rational radiation therapy in locally advanced lung and head and neck cancer.
- Therapies for cancer patients at the end of life.

**Improved cancer therapy based on drug repositioning**

**NEW STRATEGIES FOR CANCER DRUG discovery are needed. One such strategy is drug repositioning, i.e. the finding of a new indication for an already existing drug. In this approach, on/off-patent drugs in use for other indications, drugs discontinued or withdrawn but with yet with unrecognized cancer activity can be rapidly advanced into clinical trials for this new indication since the required documentation to support clinical trials is already available.**

Examples of successful repositioning in medicine are aspirin as an antiplatelet agent, and, in cancer, thalidomide for treatment of myeloma. A simple and pragmatic, yet potentially very fruitful, type of repositioning is to try to identify, in clinically relevant cancer models, activity against new cancer diagnoses among old and new cancer drugs already in use for a few limited indications.

With this background, our overall aims are to identify and clinically explore drugs suitable for repositioning for cancer treatment with special focus on colorectal cancer. In brief, old and new drugs that can do useful tricks in this cancer diagnosis are to be identified and explored.

One drug already identified by us for this purpose is melbendazole, soon to be investigated in a clinical phase 2 trial at Uppsala University Hospital. Another is nitazoxanide with specific activity against quiescent starving tumour cells and a third is ivermectin, observed in a screen in tumour cells from patients to be active against colorectal cancer.

**Acta Oncol 2013.**
Molecular characterisation of chronic lymphocytic leukemia

**CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)** is the most common leukemia among adults worldwide and represents a highly heterogeneous disease entity regarding biological and clinical parameters. CLL remains an incurable disease and accurate stratification of patients is challenging, highlighting the need for novel biomarkers and treatment strategies.

Our research centers on comprehensive characterization of the CLL genome, transcriptome, and methylation in well-defined patient subgroups, thus gaining detailed insight into the spectrum of molecular events occurring in patients belonging to clinically aggressive subgroups. In detail, using well-established sequencing techniques in conjunction with novel technologies we aim to decipher the biological heterogeneity of the disease and improve prognostication in tandem with identifying novel molecular markers that may be exploited as therapeutic targets. International multicenter collaborations and membership in the European Research Initiative on CLL (ERIC) afford our group the possibility to investigate large number of patient samples from clinically and biologically relevant CLL subgroups. Our sequencing expertise, coupled with the Clinical Genomics Facility at SciLifeLab, enables us to work towards rapid incorporation of novel findings into clinical practice.

Finding and understanding cancer-causing mutations

**MUTATIONS THAT CAUSE** normal cells to lose control over cell division and maintenance can be inherited or acquired during a person’s lifetime and are important contributors to cancer development. With a focus on colorectal cancer, our research is centred around four main topics: a) identification of cancer-causing mutations, b) investigation of how specific mutations contribute to tumour development or metastasis, c) strategies to utilize the specific genetic properties of cancer cells for targeted treatment, and d) development of methods and procedures to aid in improving diagnosis. Ongoing research covers development of methods for faster and more accurate identification of cancer cell mutations in clinical sequencing, identification of mutated genes in colorectal cancer patient materials, knock-in and knock-out studies of candidate cancer genes in human cell lines, and development of a novel class of anti-cancer drugs. Several of these themes are exemplified in a recent publication by Mathot et al. Our research on methods for extraction of DNA and RNA from tissue specimens has also resulted in a spin-out company, EsScale Biospecimen Solutions, and has been brought to the market as a CE/IVD compliant diagnostic kit.

Translational cancer research is dependent on high-quality patient materials and Tobias Sjöblom is Director of the U-CAN project, where clinical samples and information are collected from cancer patients for the purpose of supporting high-quality research.

**Cancer studies with focus on translational immunotherapy**

**THE RESEARCH IS TRANSLATIONAL** with main focus to conduct immunotherapy studies in cancer patients. We collaborate closely with the research group of Angelica Loskog but also with Sara Mangsbo and a project is planned with Anna Dimberg.

CD40 is an important costimulatory molecule. We have recently finished a study with AdCD40L intratumoural injections in metastatic melanoma patients (n=24). AdCD40L was given alone or in combination with low dose cyclophosphamide +/- radiation therapy. We plan to develop the CD40L concept further and will this autumn launch a study assessing intratumoural injections with an oncolytic virus in pancreatic and colorectal cancer patients with advanced disease.

The introduction of PD1 inhibitors in malignant melanoma patients makes it likely that earlier detection of relapse with scans is of benefit. A national randomized phase 3 study (TRIM) with Uppsala as the primary site opened in April. The study compares overall survival, disease-free survival, economic cost-effectiveness, and quality of life in patients with two different schedules for follow-up after radical surgery for high-risk melanoma.

In another project, potential predictive markers for renal cell cancer (RCC) are assessed. Immunohistochemistry is applied on tumour tissue from a cohort of patients with advanced RCC (n=139) who have been treated with tyrosine kinase inhibitors.
Human Protein Atlas

The Swedish Human Protein Atlas project was set up to allow for a systematic exploration of the human proteome. The overall aim is to determine the spatial distribution of all human proteins on tissue, cellular and subcellular level using antibody-based proteomics.

ANTIBODIES AGAINST ALL HUMAN PROTEINS
The strategy to meet this aim is large-scale, high-throughput generation and validation of antibodies against all human protein-coding genes. The antibodies are used for immunohistochemistry for distribution of the protein expression in normal and cancer tissues, and for immunofluorescence on cell lines for determination of spatial distribution at a subcellular level. The analysis is combined with mRNA expression data derived from deep RNA sequencing (RNA-seq).

The Human Protein Atlas project was initiated in 2003 and is funded by the Knut and Alice Wallenberg foundation. It is run in as a collaboration between IGP, the KTH Royal Institute of Technology and SciLifeLab.

THE HUMAN PROTEIN ATLAS WEBSITE
All data generated by the Human Protein Atlas project is publically available on the website www.proteinatlas.org, updated on a yearly basis. The database is developed in a gene-centric manner, and contains millions of high-resolution images, released together with application-specific antibody validation. Each gene has a separate summary page, providing a detailed overview on RNA and protein expression levels across human tissues and cells. From the summary page, one is able to browse deeper into cell-type specific expression patterns, and navigate among the primary images as if one was looking through a microscope.

In addition to internally generated RNA-seq data, the webpage comprehensively summarizes expression data from other sources, including the GTEx consortium and the FANTOM5 consortium.

PATHOLOGY ATLAS
Cecilia Lindskog Bergström is site director at the HPA site in Uppsala, which is part of IGP.

“It’s fantastic to see the increasing number of researchers from all over the world visiting and using our webpage, and the atlas will continue to evolve in the next years”

Tissue-based gene expression profiling

THE DEVELOPMENT OF technologies for gene sequencing and availability of antibodies has created an unprecedented possibility for combining quantitative and spatial analyses of gene expression patterns in both healthy and diseased tissues. Well-defined tissues from the Pathology Biobank have been used for both mRNA sequencing (quantitative data) and immunohistochemistry (spatial data).

Validation of antibodies is crucial for antibody-dependent applications and consequently an important project is to validate antibodies towards unknown proteins. The analysis of specific transcripts and corresponding proteins is vital for antibody validation, but also generates new knowledge regarding tissue-specific proteins.

To analyze gene expression levels in cancer and correlation to patient survival, we have used the Cancer Genome Atlas database (TCGA) and data have been generated for 20,000 genes in more than 8,000 patients representing 17 major forms of cancer. The unbiased analysis revealed a large number of prognostic genes, both favorable (high expression = good prognosis) and unfavorable (high expression = poor prognosis) genes in the different types of cancer. A Pathology Atlas has been created to display the cancer data.

A third area of research aims to utilize and translate basic knowledge obtained through the above efforts into clinical utility within the cancer pathology field. Main cancer forms with well-defined patient cohorts include colorectal (U-CAN), lung, breast and gynecologic cancer.

Our research aims to create a knowledge resource of gene expression patterns in tissues and to utilize this resource for translational research; to develop clinical research and create the tools for diagnostic pathology required for precision medicine.
Medical genetics and genomics

Research in this programme aims to clarify functions of the human genome and to identify genetic mechanisms important for development and in diseases.

A common theme of the research groups in the programme is the identification of different types of genetic variation and how these variants influence human health and disease. Genetic variation is correlated to gene expression and phenotypic variation in humans as well as in different established model systems.

**FORENSIC DNA IDENTIFICATION**
The general objective of Marie Allen’s research is to develop highly sensitive and discriminating assays for forensic DNA analysis of challenging samples. New identification assays will allow smaller amounts and also degraded DNA to be analysed.

**GENOMIC MEDICINE**
Marie-Louise Bondeson’s research aims to increase the understanding of the genetic causes and molecular processes behind developmental disorders. Such knowledge is important for diagnosis, prognosis, treatment and risk for recurrence.

**DRUGGABLE DISEASE MECHANISMS**
Niklas Dahl’s group is identifying novel genetic variants causing Mendelian traits and to model these phenotypes in different biological systems. The long-term objectives are to discover pathways and targets suitable for therapeutic interventions in such disorders.

**ZEBRAFISH MODEL**
The aim of Marcel den Hoed’s research is to identify and characterise causal genes for cardiovascular and metabolic disorders. The work will increase the understanding of the underlying causes of human disease, and could result in completely new ways to prevent and treat such diseases.

**MOLECULAR ONCOLOGY**
Analysis of post-zygotic or somatic genetic variation is the overall theme of research in Jan Dumanski’s group. They work with translational disease-related projects and with basic questions addressing somatic variation in normal human cells.

**NEURODEVELOPMENTAL DISORDERS**
Lars Feuk uses high throughput sequencing combined with bioinformatic analyses to study genetic variation and expression. The research ranges from basic studies of genetic variation and transcription to specific analyses of neurodevelopmental disorders.

**LOSS OF CHROMOSOME Y**
Lars Forsberg’s group has discovered that men with mosaic loss of chromosome Y (LOY) in peripheral blood cells have a shorter survival and increased risk for cancer. Their work focuses on determining what happens in cells after they have lost the Y chromosome.

**GENOMICS, EPIDEMIOLOGY AND TRANSLATIONAL MEDICINE**
Research in the Gyllensten lab covers several fields, from human genomics and molecular epidemiology to more applied projects in gynaecological cancer and translational medicine.

**REPRODUCTIVE MEDICINE**
Helan Åkerud’s group studies molecular mechanisms that regulate the development of a fertilized egg into an embryo, implantation of the embryo in the uterus and development of the placenta. The main goal is to be able to help more involuntarily childless couples to have a baby.
Sensitive methods for improved forensic DNA identification

NGS for exploratory research and clinical implementation

Decoding of the human genome is a major challenge. Our research focuses on (i) identification of gene variants associated with abnormal development and disease (ii) clarifying novel disease mechanisms at different resolutions and (iii) identification of druggable and disease associated targets of the central nervous system (CNS). A major effort is on neurodevelopmental and neurodegenerative disorders that comprise a heterogeneous group for which progress has been slow. Limiting factors have been the access to biological material and model systems to faithfully recapitulate human pathophysiology. Induced pluripotent stem cell (iPSC) technology provides the potential to overcome this problem. To this end, we generate iPSC and neuronal derivatives from healthy individuals as well as from patients with various disorders of the CNS (e.g. Epilepsy, Down syndrome, Alzheimer disease).

The disorders are caused by specific gene variants that are also introduced in control iPSCs using CRISPR-Cas9 editing to generate isogenic control/disease cell lines. Established protocols are used to obtain various neuronal subpopulations validated by imaging, FACS and IHC. Functional analysis (patch clamp, growth, synaptic formation) and high throughput molecular and/or treatment of disease. Results from large-scale genome-wide association studies (GWAS) have identified hundreds of loci that are robustly associated with the risk of cardiovascular and metabolic diseases. However, the causal variants and genes remain unknown for most loci. Before we can use results from GWAS as biomarkers or novel drug targets, we need to identify causal genes, and ideally also the tissues, cell types and pathways through which these variants and genes exert their effects.

My group takes findings from GWAS or sequencing efforts as a starting point, and uses bioinformatics approaches to predict which variants and genes are causal. We subsequently use zebrafish model systems for further in vivo characterisation. Zebrafish develop quickly post-fertilisation, and are transparent during the earliest stages of development. Thanks to advances in fluorescence imaging using labelled transgenes, automated positioning of non-embedded zebrafish larvae, objective image quantification opportunities, and multiplex mutagenesis using CRISPR-Cas9, it has now become possible to perform high-throughput, largely image-based genetic screens using zebrafish model systems. My group has developed and validated such model systems and is currently characterising hundreds of genes that are predicted to play a role in cardiovascular and metabolic diseases. Our results will increase our understanding of the underlying causes of disease, and, in the long term, lead to new or improved ways to treat or prevent them.

Zebrafish model systems for human disease

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Molecular oncology and genetics of human aging

ANALYSIS OF POST-ZYGOTIC VARIATION (or acquired during lifetime or somatic genetic variation or genetic mosaicism) in human cells is the overall theme of research in the group. We work with translational disease-related projects and with basic questions addressing somatic variation in normal human cells. An emphasis is on structural genetic variation, which has emerged over the past 10 years as a dominating type of human inter-individual genetic differences and is also a dominating type in post-zygotic variation. Our specific projects are:

- **Mosaic Loss Of chromosome Y (LOY)** in blood cells is associated with smoking as well as shorter survival and higher risk of cancer risk for Alzheimer’s disease in aging males. We study the functional impact of LOY on human cells and develop LOY as a clinically useful biomarker.

- **Post-zygotic genetic variation: studies of normal human aging/longevity** from genetic standpoint and age-associated genetic aberrations.

- **Novel bio-markers for breast cancer:** disease prediction and progression. We study acquired genetic variation in normal breast cells from healthy women and from women affected with breast cancer in order to identify very early changes, which predispose to the development of breast cancer.

Loss of chromosome Y (LOY) in human health and disease

MEN LIVE SHORTER LIVES compared to women. LOY in blood cells could, as a male-specific genetic risk factor, help explain this sex difference. The blood of men affected with LOY consists of a mixture of cells with or without the Y chromosome and current methods can readily detect when >10% of the blood cells lack chromosome Y. LOY is the most common during life acquired human mutation and affects at least 20% of old men.

Our discoveries show that LOY in blood is associated with increased risk for pathology and death in aging men. For example, we have found that men with LOY in blood have an increased risk for all-cause mortality, non-hematological cancer and Alzheimer’s disease. We have also shown that LOY is induced by smoking.

It is still unknown how LOY in blood cells can be associated with disease in other organs. One hypothesis is that immune system functions could be compromised in affected cells. The functional aspects of LOY are central in the ongoing research. Identification of men with LOY could help serve earlier diagnosis of disease, which could lead to better treatment options and higher survival in aging men. We are now developing new methods for detection of LOY in blood samples with better sensitivity and specificity, compared to available methods. Focus is on applications for flow cytometry, which is available in most hospitals. The goal is to establish LOY as a new and predictive biomarker for risk of disease in middle-aged and aging men.

From genomics and epidemiology to translational medicine

THE GYLLENSTEN LAB conducts research in several fields, from human genomics and molecular epidemiology to more applied projects in gynaecological cancer and translational medicine. Among the recent project highlight in genomics are the establishment of a database of human genetic variability in Sweden, based on whole human genome sequences of 1,000 individuals (SwGen), the generation of local reference genomes for the Swedish population based on de novo assembly of long-read DNA sequencing technology. In molecular epidemiology our lab is using a systems biology approach to study human physiology and determine how genetic, epigenetic and lifestyle factors influence the proteome, glycome and lipidome. We have recently shown that protein biomarker levels are strongly affected by non-disease causing variation such as genetic polymorphisms and lifestyle factors (see side column). The translational medicine project aims at developing a protein biomarker test for early diagnosis of gynaecological cancer (cervical, endometrial and ovarian cancer) that can be used both to improve the diagnosis and in population screening.

Our lab is also pioneering the use of self-collection of vaginal fluid in cervical cancer screening, and are studying the use of repeated HPV typing to improve the organised cervical cancer screening.
The mystery of the hidden heritability of human traits

DURING THE LAST DECADE, thousands of genetic variants have been identified to influence the variation in human phenotypes or the risk for of developing diseases like obesity, asthma, myocardial infarction, hyperlipidaemia or hypertension. However, the genetic variants that have been identified only explain a small part of the heritability of human phenotypes, and a substantial part of the heritability, commonly referred to as the hidden heritability, is still unknown.

Our hypothesis is that the hidden heritability is attributed to a combination of: a) rare genetic variants that have not be assessed in previous studies, b) common variants with small effects that have not been detectable in the studies performed so far, and c) interactions between genes and environment, or between pairs of genes.

Our research is interdisciplinary and brings together the fields of genomics, epigenomics, proteomics and epidemiology with three specific aims. Firstly, to give a precise description of how genetic variation influences the amount and function of the proteins that are expressed by our genes and secondly, to identify downstream disease related effects caused by alterations in specific proteins. The third aim is to identify how genes interact with each other and with our lifestyle to influence risk of disease. We are working with population-based cohorts, using state of the art methods for whole-genome sequencing and the most recent technologies for measuring proteins at a large scale.

Gene regulation and human disease

METABOLIC DISEASES INCREASE in prevalence in Sweden and the rest of the world. Many environmental factors and hundreds of genes contribute to morbidity. We investigate the genetic components by identifying positions in the genome where the environment induces a response that differs between individuals and how that contributes to disease. We have screened for variation in gene regulatory signals in liver and other cells using our established pipeline and detected tens of thousands of genetic variants with variable response to the environment and hundreds that likely contribute to disease.

We use several strategies to link them to the gene they control. We prioritize gene variants of the highest medical importance and have made detailed studies of several to show which pathways, environmental factors and transcription factors that control their activity.

The results are integrated with a parallel project in which we analyse metabolites, RNA expression and protein levels in all key metabolic tissues in normal controls, people with prediabetes and type 2 diabetes. This links variable gene regulatory signals to metabolic consequences and identifies new options for therapeutic intervention for this rapidly growing ailment. Some mutations in cancer disturb gene regulation by changing the binding of transcription factors or structural proteins and this contributes to malignancy. We screen for such events using the same principles as for the inherited variants described above.

Reproductive Medicine

THE RESEARCH GROUP studies the reasons behind infertility, with the main goal to be able to help more involuntarily childless couples to have a baby.

Our research focuses on reproductive medicine, i.e. diagnosis and treatment of infertility. We are interested in molecular mechanisms that regulate the development of a fertilized egg into an embryo, implantation of the embryo in the uterus and development of the placenta. The clinical outcomes when these processes are not regulated properly are infertility, repeated miscarriages and complications during pregnancy, such as intrauterine growth retardation and preeclampsia.

Our research is translational and we have close collaborations with different clinics in Sweden and abroad working with women’s health. Within these networks, patients with diagnoses of interest are included and embryos, blood or tissue samples (mainly uterus and placenta), are collected in biobanks.

By performing basal research on this material we aim to get new insights about the different diagnoses studied. Increased understanding of important molecular mechanisms will hopefully provide us with the possibilities to develop new diagnostic tools and therapies within the field of assisted reproduction.

How an infecting virus kidnaps the synthetic machinery of its host

ADENOVIRUSES have been widely used to study the molecular events that take place in infected cells. Our studies have shown that an infection with adeno virus type 2 can be divided into four periods.

The first period occurs before the adeno viral gene expression has commenced. During this time, changes in cellular gene expression are triggered by the virus entry process, and its intracellular transport along microtubules.

During the second period, there is a large increase in the number of differentially expressed cellular genes primarily those that are involved in cell cycle regulation, cell proliferation and antiviral response.

During the third period the virus has gained control of the cellular metabolic machinery, resulting in an efficient replica-
Medical radiation sciences

Research in the programme aims to expand the knowledge base for the use of radiation in medicine and basic biology.

Ionizing radiation is widely used in medicine for diagnostics and therapy of different diseases. Radionuclide imaging facilitates detection of disease-associated molecular phenotypes of tissue, and selection of optimal therapy.

External beam radiation therapy is an efficient way to treat localized cancer by a concentrated dose to the tumour, while targeted delivery of cytotoxic radionuclides may be efficient for eradication of disseminated cancer. The use of radioactive tracers in vitro and in vivo can also elucidate many aspects of normal biology and pathogenic alterations in biochemistry.

MEDICAL RADIATION PHYSICS
Successful radiation therapy is a compromise trying to maximize the probability for tumour control while keeping risks for severe side effects acceptable low. Anders Ahnesjö’s group applies a multiscale approach to improve methods and find strategies to widen the therapeutic window between cure and side effects.

RADIATION BIOLOGY AND DNA REPAIR
Research in Bo Stenerlöw’s group focuses on cellular and molecular effects of ionizing radiation. They study cells’ defence signalling and DNA repair mechanisms, with the goal that their findings should lead to more efficient tumour therapy and fewer adverse effects.

TUMOUR TARGETING USING ENGINEERED SCAFFOLD PROTEINS
Radionuclide imaging is non-invasive and provides important information about proteins in tumours. The main goal of Vladimir Tolmachev’s research is to develop the methodology for using radionuclides in diagnostics and therapy of malignant tumours.

WE INVESTIGATE ROUTES TO IMPROVE radiotherapy for increased cure rates and/ or reduced side effects. In a multi-scale approach, we investigate clustering textures of ionization locations in a nanometer scale, and also different techniques for patient/tumor position management during radiation at mm scale.

Different types of radiations used for radiotherapy have different cell sterilization ability, and we investigate this variation by studying the spatial distribution of ionization sites in nanometer resolution through radiation transport simulations with Monte Carlo methods, for the ultimate goal of quantitative modelling to support treatment dose optimization.

At the macroscopic level we are, in collaboration with the national proton therapy facility Skandion, developing a Granty-based simulation framework to study the patient motion interplay effects with the scanned proton beams used to target tumor volumes. We also investigate use of real time patient surface imaging as an indicator for positional adjustments during treatment.

The use of functional images from MRI and PET as basis for “dose painting” is explored aiming for patient individualized prescription of spatially varying dose levels. Higher dose to the most viable parts of the tumor can potentially increase tumor control probability without increasing the risks for normal tissues complication, but requires changes in clinical delivery to ensure dose delivery safety.
Radionuclide targeting using engineered scaffold proteins

**THE AIM OF OUR RESEARCH** is to utilize radionuclide tumor targeting for diagnosis and therapy of cancer, with a special focus on head and neck cancer. This is done by improving targeted diagnostics through new promising radiotracers, and by improving radiation therapy using novel radiosensitizing drugs.

**THE REPAIR OF DNA DAMAGE** is fundamental for the survival of a cell and an increased knowledge about DNA repair mechanisms might have future clinical implications. The complex network of repair and regulatory proteins represents a rich set of potential targets to exploit in the development of more effective chemo- and radiotherapeutic strategies in cancer therapy.

**Radiation biology and DNA repair**

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The last decades, research on DNA repair has led to novel insights in cellular repair but several important aspects of radiation-induced DNA double-strand breaks (DSB) are still unresolved. Although the major protein complexes involved in DSB repair have been identified, it is still not fully understood how, when and where the major protein complexes come together and repair DSB.

We are currently investigating how repair proteins interact and how they may regulate other repair pathways and cellular processes. Further, it is evident that complex and clustered lesions, induced by high LET radiation (e.g., heavy ions) are much more difficult to restore, but there is no information about failure in specific steps in the repair process.

Our research is focused on DNA damage localization within chromatin and the mechanisms involved in DNA damage recognition at clustered damaged sites. In parallel with the basic research on DNA damage response, we study novel drugs and inhibitors that have the potential to make tumours more sensitive to radiation.

**WE DEVELOP A NEW TYPE OF CANCER-TARGETING AGENTS AND RADIATION SENSITIZING STRATEGIES FOR IMPROVED PERSONALIZED CANCER MANAGEMENT OF HEAD & NECK CANCER.**

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Molecular tools

The research programme invents, develops and applies radically new molecular approaches to detect and analyse DNA, RNA, proteins and cells.

Molecular tools for molecular medicine are in rapid development. Radically improved methods can offer entirely new biological insights, reveal disease processes at potentially curable stages, and serve to evaluate new drugs and monitor responses to therapy.

The techniques developed in the Molecular Tools programme are widely used and include padlock probes, proximity ligation, and other approaches for high-multiplex, high-performance analysis of DNA, RNA, or protein in solution or at cellular resolution in situ. The efforts are focused both on the development of new methods and on applying the established techniques in biomedical investigations.

The techniques are suitable to measure levels of individual molecules or interacting complexes of molecules, or to visualize these in cells and tissues. They are employed in basic molecular and cell biological research, and for a number of medical applications, for instance in genetics, tumour biology and in cardiovascular disease, taking advantage of samples from biobanks. Recent research directions in the programme include development of procedures for evaluating experimental and clinical drugs, for single cell analyses, and in a longer perspective for rapid molecular diagnostics at the point of care. The latter techniques may prove valuable in routine health care and in Third World countries.

Advanced molecular tools for proteome analyses and diagnostics

OUR RESEARCH FOCUSES ON development of advanced molecular tools and implementation of those technologies in biology and medicine. The aim is to detect and measure single- and complex molecules with high sensitivity, specificity and accuracy beyond the capacity of the current state-of-the-art technologies.

We apply our technologies to screen proteins for diagnostics or early diagnostics of different diseases. We also analyse proteins, their modifications and interactions, to better understand the emergence of these diseases. The technologies are used very broadly but our primary research is focused on neurodegenerative diseases such as Alzheimer’s disease, and on cancer diseases, for instance prostate cancer.

A flow cytometry-based and multicolour method (ExoPLA) was developed to detect specific exosomes on single molecule level. Finally, another flow cytometry-based PLA technology was developed for sensitive detection of fusion proteins, which allowed us to detect BCR-ABL1 on protein level in chronic myeloid leukemia.

ExoPLA is used for specific and sensitive detection of individual exosomes.

Molecular tools for the future of diagnostics

PROGRESS IN MOLECULAR MEDICINE provides a basis for new, efficient diagnostics to curtail disease and optimize therapy, which will profoundly alter healthcare.

Our lab focuses on inventing molecular tools for this future diagnostics. Building on a few simple premises, such as designing assays that depend on specific detection via fixed pairs of affinity reagents even in high multiplex, we have developed powerful tools for DNA and protein detection.

Our oligonucleotide-, padlock- and proximity-ligation assays are now in use in thousands of labs worldwide, and diverse applications of the probes have been commercialized by eight companies spun out from our lab so far, or through licenses to twelve leading international biotech companies. Several of our tools are also provided as services to Swedish scientists via four facilities of the SciLifeLab organization, offering early access to these new research techniques.

Some newer molecular techniques, currently in development in our lab, promise further enhanced detection or visualization of even very rare nucleic acid sequence variants or single protein molecules for e.g. single cell studies or high-throughput screening of tissue sections. Increasingly in focus in our lab is the development of high-performance molecular assays for the point of care, offering great convenience, speed, and sensitivity in multimodality, multiplex formats.
The programme focuses on CNS tumours, balancing the investigation of basic disease mechanisms with new approaches to drug development.

The programme includes rapidly expanding projects on glioblastoma and medulloblastoma that combine hypothesis-driven functional biology approaches with large-scale, data-driven approaches.

**MAST CELLS IN BRAIN TUMOURS**
Elena Chugunova’s research aims at gaining more insight into the involvement of mast cells in the development of the brain tumour glioma. By increasing the understanding of brain cancer biology she hopes that new treatment strategies can be developed.

**BRAIN TUMOUR DEVELOPMENT AND INVASION**
Karin Forsberg Nilsson’s research group incorporates experience of neural stem cells with glioma biology. They focus on the tumour microenvironment and examining the invasive niche they aim to find new candidate drugs that prevent invasion.

**SYSTEMS BIOLOGY**
The group headed by Sven Nelander develops new, systems biology based strategies to chart the molecular networks that cause cancer. Their main aim is to understand the importance of regulatory changes in cancer cells.

**CHILDHOOD BRAIN CANCER**
Fredrik Swartling and his group are exploring the role for transcription factors MYC and MYCN in childhood brain tumours. The objective is to identify cells of brain tumour origin and to understand signalling pathways involved in tumour initiation and tumour progression.

**A CELL OF ORIGIN-BASED STRATEGY**
Lene Uhrbom’s research is focused on understanding how the cell of origin in combination with various genetic alterations affects tumour development, progression and response to treatment. The goal is to uncover genes, pathways and targets to which directed therapies can be developed.

**HUMAN MALIGNANT GLIOMA**
Glioblastoma is the most common form of malignant brain tumours in adults. Bengt Westermark’s goal is to understand the molecular mechanisms of glioblastoma development. This knowledge may increase the possibilities of developing novel treatment modalities.

**THE HUMAN GLIOMA CELL CULTURE (HGCC) REPOSITORY**
A public IGP-based resource of 176 patient-derived cell cultures that enables cell-based modeling of glioblastoma. Each culture is annotated by de-identified clinical data and the majority has undergone genomic characterization on multiple platforms. All molecular subtypes are represented making HGCC a valuable tool for precision medicine including systematic drug screening, biomarker discovery and hypothesis-driven studies of disease mechanisms. HGCC is an open resource and our cells have been distributed to >60 research projects worldwide.

**OUR PROGRAMME IS WELL ESTABLISHED INTERNATIONALLY, AND HAS SEVERAL ACADEMIC AND INDUSTRIAL PARTNERS.**
Mast cells as immune regulators in glioma and brain metastases

**Regulation of brain tumour development and invasion**

**OUR RESEARCH AIMS TO IMPROVE**

Treatment of malignant brain tumours, specifically glioblastoma (GBM), which is molecularly heterogeneous and invariably fatal. We focus on the tumour microenvironment in disease progression. During tumour evolution, GBM progresses from an initial, hypoxic environment to an infiltrative disease sustained within an invasive niche. We examine this niche, in vivo and in vitro, to find new candidate drugs that prevent invasion. Due to a unique composition of the brain extra-cellular matrix, where proteoglycans are prevalent, our analysis of these molecules informs about disease mechanisms, and suggests therapeutic targets. The neurogenic and tumorigenic niches are similar and we incorporate our experience of neural stem cells with GBM biology, leveraging the close relationship between these two fields.

Furthermore, we explore novel regulators of GBM and medulloblastoma. Our candidate genes are identified either as highly regulated in neural stem cell differentiation, or alternatively, in a GWAS of dog glioma.

Subpopulations of cells with stem cell-like properties, called cancer stem cells (CSCs) are likely responsible for relapse. Within the Neuro-Oncology programme we have established a clinically annotated biobank of >1000 patient-derived GBM CSCs, retaining the characteristics of the original tumour and can now model a large part of the GBM heterogeneity in vitro and in mouse models.

**WE HAVE EXPANDED**

Our understanding of the role of inflammation in gliomas by demonstrating that mast cells (MCs) infiltrate mouse and human glioma, with a positive correlation for malignancy grade. Our preliminary data also demonstrated the abundant accumulation of MCs in human brain metastases, originating from different primary tumours.

The given research proposal aims to investigate the role of MCs in glioma-associated inflammation, and the role of MCs in brain metastases.

In this proposal the functional studies are performed by using in vivo models, including MC-deficient mice (My-CreR-DTA). All mechanisms of interactions between MCs and corresponding tumour cells, interactions with other immune cells and functional plasticity of MCs are explored by implementing human in vitro studies, and will also include analysis of patient material and TMA.

The present study will generate new knowledge about the interrelation between MCs and particular tumour cells, and also explore the interplay with other immune cells. We believe that the findings in this proposal will provide a new insight into the role of MCs in glioma and the connection between immunoregulation, tumor microenvironment and metastasis. This will contribute to improved treatments of cancer and eventually prolong patients’ lives.

**We study tumour relapse in our new preclinical cancer treatment (PCT) centre, a national facility for advanced image-guided irradiation that mimics the advanced radiation therapy done on cancer patients.**

**Systems biology of neural cancers**

**OUR PRIMARY RESEARCH GOALS**

Are directed towards understanding the complex regulation in cancer cells, utilizing existing and new therapeutic strategies. Combining mathematical and experimental methods, my lab focuses on cancers of the nervous system. This is a challenging but important area of investigation, where IGP has an excellent unit with complementary expertise.

In one line of work, my team is developing patient-derived cancer stem cell cultures as a system for precision medicine of the brain cancer glioblastoma. For instance, we are analysing such cells using several orthogonal genomic assays and drug screening to obtain new predictive models of drug response.

In a second line of work, we work on model-based data integration strategies for cancer stratification and target discovery. My lab has 12 members and receives funding from several organisations, most recently a 5-year grant from the Swedish Strategic Research Foundation (SSF, March 2017) and the Swedish Cancer Society’s Senior Investigator Award (April 2017).

Taken together, our work will result in an improved understanding of the vulnerabilities of brain cancers, concrete therapeutic improvements and more powerful tools for brain tumour biology and beyond.

**The aim of our research is to improve survival of medulloblastoma, the most common malignant pediatric brain tumour.** MYC proteins are mis-regulated in more than half of all types of human cancer. Medulloblastoma with elevated MYC levels correlates with very poor prognosis. About three out of four children with medulloblastoma survive but often experience long-term side effects from standard treatment including radiation and chemotherapy.

We have developed various MYC-driven transgenic tumour models and culture cells from patients as patient-derived xenografts (PDXs). We further study clinically relevant cancer drivers in normal or iPSC-derived brain stem cells in order to model medulloblastoma development. We also developed a forward genetics screen to identify novel drivers of brain tumours and use sequencing and methylation arrays together with advanced bioinformatics to study tumour cell mechanisms.

Recently, we showed that the stem cell factor SOX9 is promoting metastasis and we are now studying how rare SOX9-positive cells give rise to brain tumour relapse. We want to understand what drives tumour recurrence and how these cells develop therapy resistance. We screen for drugs that can target these rare cells and can be used together with standard radiotherapy. These studies are performed in our PCT-centre, a new preclinical facility that we started to study advanced image-guided radiation therapy in models.
A cell of origin-based strategy to decipher glioblastoma

**Glioblastoma** (GBM) is an aggressive, highly heterogeneous and currently incurable primary brain tumour. The median survival is 15 months from diagnosis despite maximal surgical resection, chemotherapy and radiotherapy.

Our goal is to uncover new mechanisms, pathways and targets that are important in GBM by investigating how the cell of origin for GBM shapes the phenotype of GBM cells and the outcome of therapy. We have had a longstanding interest in the cell of origin for GBM and the present investigation builds directly on previously published results from the group (see key publications), that form a unique experimental platform of validated mouse models, patient-derived GBM cells and tissues, and cell of origin-based knowledge and candidate genes.

The specific aims of our research is to investigate:
1) The mechanisms behind the cell of origin-dependent treatment response.
2) The role of the cell of origin-specific gene LGR5 in GBM.
3) The molecular basis for GBM initiation and progression from an oligodendrocyte precursor cell in vivo.
4) New cell of origin-defined mouse GBM models to be able to study more of human GBM diversity.

The cell of origin for GBM is unknown and has been an understudied area of research. We believe that such knowledge is required for a more complete understanding of the underpinnings of GBM.

Human malignant glioma – from oncogenic mechanisms to treatment

**Glioblastoma is characterized** by an extensive heterogeneity, both between and within individual tumours, which severely complicates the development of effective treatment.

We have established multiple clones from patient samples and found extensive molecular and phenotypic variability, with a wide range of responses to radiation and drugs. This variability was linked to a proneural-mesenchymal shift in the transcriptome. Drug resistance was associated with an altered DNA methylation profile at promoter regions of mesenchymal master regulators and enhancers. Currently we are searching methods to reprogram the epigenome of resistant cells, to make them vulnerable to treatment.

In addition to focusing on the aberrations in glioblastoma cell signalling, we try to harness remnants of normal growth regulatory pathways to treat glioblastoma. In a study of the response to the growth inhibitory effect of bone morphogenetic protein 4 (BMP4), we found a wide range of responsiveness. BMP4 response was positively correlated with a proneural mRNA expression profile, and high expression of the stem cell factor SOX2. SOX2 was consistently down regulated in BMP4-treated cells. Forced expression of SOX2 attenuated the BMP4 response, implying a causal relationship between SOX2 down regulation and responsiveness. The BMP4-SOX2 axis is an interesting target for therapy, which we are currently investigating.
Vascular biology

The programme studies the development and disease implication of the blood and lymphatic vasculature.

The formation of new blood vessels – angiogenesis - is an important and strictly controlled process that under normal circumstances takes place during embryonic development, in wound healing, and in the female menstrual cycle. However, several diseases, including cancer, are accompanied by exaggerated angiogenesis that leads to a disorganized and dysfunctional vasculature that may propagate the disease. The programme Vascular Biology studies how angiogenesis is regulated, both during embryo development, in adults and in diseases, using human tissue samples, mouse and zebrafish models. We are particularly interested in how growth factors and other regulating proteins stimulate or inhibit angiogenesis during development, and how vessel permeability to molecules and cells is regulated in the CNS and in peripheral organs. We also study the mechanisms underlying the formation of functional lymphatic vessels and the development of fibrosis.

DEVELOPMENTAL GENETICS
Christer Betsholtz’ group studies cellular and molecular mechanisms of angiogenesis, vascular permeability and other vascular functions in embryonic development, adult homeostasis and disease. A particular focus is placed on the microvascular pericyte.

VASCULAR BIOLOGY
A main focus in Lena Claesson-Welsh’ group is on the important growth factor VEGF and its signalling regulating blood and lymphatic vessel formation and function. A particular interest is in vessel permeability and its role in cancer and retinopathies.

VASCULAR PERMEABILITY AND VESSEL MALFORMATIONS
The disease Cerebral Cavernous Malformations (CCM) is a genetic, familial or sporadic, disease characterized by vascular malformations in the central nervous system. Elisabetta Dejana’s research efforts are directed towards developing strategies to treat the disease by reducing size and fragility of the malformations.

CELLULAR ADAPTIVE BEHAVIOUR
Katie Bentley’s interdisciplinary research group exploits the predictive power of computer simulations to uncover new mechanisms in angiogenesis. They integrate in silico, in vitro and in vivo approaches to develop a dynamic, single to collective cell understanding of how blood vessels are able to grow well-adapted networks.

THE VASCULATURE AS A TARGET FOR CANCER THERAPY
The focus of Anna Dimberg’s research is to understand how the vasculature affects cancer progression through regulation of the tumour microenvironment. The group also studies how vascular targeting can be used to improve treatment response, with a special emphasis on promoting immune cell recruitment during cancer immunotherapy.

REGULATION OF LYMPHATIC VASCULATURE
Lymphatic vasculature is an integral part of the circulatory system with essential functions in tissue fluid homeostasis and immune surveillance. Taija Mäkinen and her group aim to understand the mechanisms that regulate lymphatic vascular growth in development and disease.

“We exploit advanced imaging and image analysis, (single cell) RNA sequencing, computer modeling, state-of-the-art genetic in vivo models for studying vascular development and homeostasis, genetic diseases, cancer and retinopathies in a concerted effort to reach deep understanding of vascular function in health and disease.”
Cross-disciplinary study of cellular adaptive behaviour

**THE CELLULAR ADAPTIVE BEHAVIOUR (CAB) Lab is interdisciplinary, integrating in silico, in vitro and in vivo approaches to develop a dynamic, single to collective cell understanding of how blood vessels are able to grow well-adapted networks in healthy tissue yet form maladapted networks in diseases such as retinopathy and cancer.**

We primarily exploit the predictive power of computer simulations to uncover new mechanisms in angiogenesis. Our simulations draw on concepts and approaches from the Adaptive Systems/Evolutionary Robotics fields, with a focus on hybrid agent-based models alongside other spatiotemporal modelling approaches. These help us to untangle the complex cell signalling, shape and movement dynamics as cells coordinate and compete during vascular morphogenesis.

Our integrated modelling approach previously revealed that Notch negative feedback interplays with positive feedback pathways to generate different collective endothelial cell movement during blood vessel growth under normal and disease conditions. We recently validated model predictions in vivo uncovering the first elements of a differential adhesion based mechanism during blood vessel growth.

We are now investigating whether abnormal cell movement, junctional adhesion and temporal dynamics of ‘cell decisions’ may cause vascular malformations and how these may be targeted by new therapeutics.

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**Developmental genetics**

**OUR RESEARCH TEAM INVESTIGATES**

the composition and function of blood vessels and some of its associated structures and cell types. In particular, we study molecular and cellular mechanisms of angiogenesis and vascular permeability during embryonic development, as well as in adult homeostasis and disease.

Vessels throughout the body consist of the same principal cell types - endothelial cells and mural cells, but these are specialized in organ-specific ways, and there are even sub-specializations within the organs. We have a special interest in the pericytes, the capillary-associated mural cell, whose functions are still very poorly understood. We also focus on the vascular network in the central nervous system, particularly the brain and the retina, where we study vascular development and the development and function of the blood-brain and blood-retinal barriers. A recent addition to our methodologies is single-cell RNA sequencing, by which we characterize and compare vascular cells within and between organs, developmental stages, vascular mutants, and diseases.

Beyond vascular biology, we also study platelet-derived growth factors (PDGFs) and their role during organogenesis and disease. Among the target cells for PDGFs are vascular cells, fibroblasts, and neuronal cells, which makes PDGF a crucial and versatile growth factor in development. We study the role of PDGF signalling during alveolarization in the developing lung and during pathological processes in the brain.

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**Vascular biology**

**VESSELS SERVE TO KEEP**

the homeostasis of the healthy vasculature. On the other hand, many diseases are accompanied by a poorly functioning vasculature that aggravates the disease process.

The family of vascular endothelial growth factors (VEGFs) and their receptors, VEGFRs, α, β and γ, are main regulators of vascular function in health and disease. We are particularly interested in how these factors/receptor induce vascular permeability and how excess vessel leakage in disease impairs the condition of the affected tissue.

We have identified the signalling pathway activated by VEGFA/VEGFR2 that engages the cytoplasmic tyrosine kinase c-Src, leading to dismantling of endothelial adherens junctions. Mice carrying a mutation of a single tyrosine residue in VEGFR2, Y949, cannot activate c-Src and vessels are therefore sealed to leakage of large molecules. We see reduced edema and suppressed metastatic spread in cancer-challenged mice, better survival after myocardial infarction, and reduced pathological development in retinopathy.

We are now studying vascular leakage in different mouse models to pinpoint the contribution of the different VEGF receptors. We ask how blood vessel leakage and the resulting edema affect lymphatic vessel function. We are moreover screening small molecule compounds to develop a drug to specifically suppress VEGFR2-induced Src signalling while sparing other VEGF-regulated endothelial biology.

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**Regulation of vascular permeability and vessel malformations**

**THE CONTROL OF VASCULAR permeability is a major clinical problem in different diseases such as ischemic stroke, peripheral edema, inflammation and tumours.** Endothelial cells, that constitute the internal vascular layer in contact with blood, play a key role in controlling the passage of solutes and inflammatory cells from the blood to the underlying tissues. Endothelial cells grow in monolayers and are connected one to another by junctional proteins. The dynamic opening and closure of these structures allow the controlled passage of fluids and cells in the surrounding tissues. However in several pathological situations junctions are dismantled and permeability is increased. Our group described the molecular and functional organization of endothelial cell-to-cell junctions and the mechanisms that regulate their assembly and disassembly at intercellular contacts. We studied the highly specialized vasculature of the brain that protects the central nervous system from blood derived noxious agents and, at the same time, promotes the passage of nutrients by a complex system of transporters.

We focused our work on a genetic disease called Cerebral Cavernous Malformations characterized by large vascular malformations localized in the brain microcirculation. In these malformations, endothelial junctions are altered and the vessels are fragile and bleed frequently. Our efforts are directed to develop specific pharmacologic inhibitors to reduce size and fragility of the malformations.
**The role of Angiopoietin-1/Tie2 signalling in kidney fibrosis**

**OUR OVERALL AIM** is to study the role of Angiopoietin-1 and its tyrosine kinase receptor, Tie2, in kidney fibrosis, to define mechanisms and to identify new therapeutic targets. Fibrosis is a pathological wound repair process that fails to cease, even when the initial insult has been removed. Fibrosis, with resultant loss of organ function, is the endpoint of many diseases. Despite this, no effective anti-fibrotic therapies exist.

Angiopoietin proteins are proteins that bind the tyrosine kinase receptor Tie2, expressed on the endothelium of blood vessels. Angiopoietin-1 binding to Tie2 results in stabilization and quiescence of the vessel. In kidney, presence of renal tubulointerstitial fibrosis is predictive of progressive decline in kidney function.

Fibrosis is characterized by an increase in myofibroblasts which deposits extracellular matrix. Although the key cell driving fibrosis its origin remains controversial. Identification of factors that regulate fibrotic responses is important to find new targets for the treatment of kidney diseases.

Preliminary data suggest that loss of Angiopoietin-1 or Tie2 increases fibrosis in experimental models of kidney fibrosis. Ongoing studies are design to elucidate the mechanisms, which could include impaired blood vessel function and increased endothelial-to-mesenchymal transition.

Other interests in the lab include the role of Angiopoietin-1 in tumour growth and metastasis as well as the role of Angiopoietin-1 in other kidney diseases.

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**Lymphangiogenesis - cellular and molecular dynamics**

**ORGAN FORMATION REQUIRES** coordination of molecular, cellular and physical processes in a spatiotemporal manner. Zebrafish is a unique model organism that allows studying how these processes happen in real time in an embryo. Using elegant genetic models, we can dissect the molecular factors that drive organogenesis.

My group studies lymphatic organ formation in zebrafish, as a main model system. Lymphatic vessels are predominantly derived from defined venous vascular network, posing an intriguing question of how cells know to form one vasculature from another.

The overarching goal of my lab is to broaden our understanding of how lymphatic vessels form and establish function, and apply this knowledge to development of new therapeutics. To achieve this my lab will focus on two major areas:

1. Defining heterogeneity in lymphatic progenitor populations at the molecular and cell behavioural levels.
2. Dissecting factors regulating cell cycle rates and cell growth to control tissue morphogenesis and fate decision in the developing vasculature.

We are a young lab that is currently supported by Swedish Research Council Starting grant.

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**Regulation of lymphatic vasculature in development and disease**

**THE KEY AIM OF OUR RESEARCH** is to understand how endothelial cells lining blood and lymphatic vessels communicate with each other and the tissue environment to co-ordinate vascular morphogenesis. Most of our research has focused on the lymphatic vasculature that was traditionally considered a passive drainage system responsible for removal of fluid, molecules and cells from tissues.

However, emerging evidence in the last few years shows active roles of lymphatic vessels in inflammation, immunity, lipid metabolism and metastasis, and consequent involvement in common diseases such as obesity, autoimmune diseases, atherosclerosis and cancer. This exciting development suggests a high degree of functional specialisation of endothelial cells of specific vascular beds.

Our second major aim is therefore to understand organ-specific regulation of lymphatic vessel formation and function. We utilise and develop advanced mouse genetic tools to spatially and temporally control expression of genes in specific cell types of interest.

By identifying and functionally characterising genes causative of lymphatic diseases we additionally aim to uncover mechanisms of vascular development that are directly relevant to human pathology.