UPPSALA
UNIVERSITET

ANNUAL REPORT 2011

Department of Radiology, Oncology and Radiation Science

Håkan Ahlström, Professor, Prefekt/Fastställd av 2012-06-04, Dnr: 2012/6.

List of Contents

Introduction

In the year shift 2010-2011 the department changed its name from ORKI to Department of Radiology, Oncology and Radiation Science (ROS) since the Section of Clinical Immunology moved to the Department of Genetics an Pathology (IGP).

The research part and educational part of section of Nuclear Medicine and Imanet, the activities of positron emission tomography (PET) previously owned by General Electric, were included in ROS during 2010. This inclusion is anticipated to facilitate integration of both functional and morphological information from PET and MRI in the fields of oncology, neurology and cardiovascular diseases. New employments are needed for this, e. g. a clinical professor in PET is at present recruited.

U-CAN, Uppsala-Umeå Comprehensive Cancer Center, an infrastructure for high-quality basic, translational and clinical research financially supported by the Swedish Research Council has a great potential of allowing high-quality research based on high quality clinical information and biobanked material. The appointment of a professor in radiation physics will strengthen the already strong research in radiation physics centred to radiation therapy and the coming clinical research proton beam therapy facility, the Scandion clinic. Two new professors in oncology, replacing the retiring professors in 2013, decided by the faculty in December 2010, will allow the department to continue strong in research with further development in a lively active research field.

Integration between the hospital unit of Nuclear Medicine (clinical studies) and the Section of Biomedical Radiation Science (preclinical developments) is ongoing and will be pushed further, regarding education, seminars and research. These activities represent one true translational research within the department.

Our relatively small department is doing well in comparison and the future is bright, which is the result of the work done by excellent teachers, researchers, medical and nursing professionals, administrators and laboratory workers.

Uppsala May 1, 2012

Håkan Ahlström, M.D., Ph.D.
Professor in Radiology
Head of the Department

Organization

The Department of Radiology, Oncology and Radiation Science, is divided into three different sections.

1. Section of Oncology
   1.1 Unit of Radiation Physics
2. Section of Radiology
   2.1 . Section of Nuclear Medicine and PET
3. Section of Biomedical Radiation Sciences
4. Section of Metal Biology Research

Head of the Department
Håkan Ahlström, M.D., Ph.D., Professor in Radiology

Assistant Head, Section of Oncology
Ingela Turesson, M.D., Ph.D., Professor in Oncology

Assistant Head, Section of Radiology
Anders Magnusson, M.D., Ph.D., Professor in Radiology

Assistant Head and Deputy Head of Department: Section of Biomedical Radiation Science
Bo Stenerlöw, Ph.D., Professor in Biomedical Radiation Sciences.

Teaching Staff

Adjunct Professors:	**Section of Oncology**
	Anders Ahnesjö
	Carl Blomqvist
	Gunilla Enblad
	Section of Radiology
	Rickard Nyman
	Pär Gerwins
Professors:	**Section of Biomedical Radiation Sciences**
	Jörgen Carlsson
	Bo Stenerlöw
Professors/Chief Physicians:	**Section of Oncology**
	Bengt Glimelius
	Peter Nygren
	Ingela Turesson

Professors/Chief Physicians:	**Section of Radiology** Håkan Ahlström Elna-Marie Larsson Anders Magnusson Raili Raininko
Junior University Lecturers:	**Section of Radiology** Natasha Eckborg Mitra Mehravaran Ulla Nikkola Ohlson
Associate Professors/ Senior Lecturers:	**Section of Oncology** Birgitta Johansson **Section of Radiology** Lars Johansson **Section of Metal Biology Research** Ulf Lindh **Section of Biomedical Radiation Science** Lars Gedda Anna Orlova Vladimir Tolmachev
Director of Undergraduate Studies:	**Section of Oncology** **Section of Radiology** Maria Lönnemark, M.D., Ph.D. Ass. Professor Ulla Nikkola, Master of Medical Science **Section of Biomedical Radiation Science** Bo Stenerlöw, Ph.D. Professor
Research Staff	
Scientists:	**Section of Oncology** Mattias Berglund Nongnit Laytragoon-Lewin Erika Nordberg Fredrik Qvarnström Martin Simonsson Ulf Thunberg

Section of Radiology
Angelika Danielsson
Joel Kullberg
Irina Velikyan

Section of Biomedical Radiation Sciences
Sara Ahlgren
Marika Nestor

Ph.D. Students:

Section of Oncology
Gloria Bäckström
Nina Cavalli-Björkman
Lena Cederblad
Maryam Delforoush
Peter Eriksson
Per Fessé
Helena Granstam Björneklett
Gustaf Hedström
Sara Häggblad Sahlberg
Andreas Johansson
Antoula Koliadi
David Kudrén
Stefan Lorin
Claudia Lundgren
Marjut Niinivirta
Cecilia Nilsson
Greger Nilsson
Anna Pettersson
Calin Radu
Mattias Sandström
Martin Simonsson
Carl Sjöberg
Linda Sooman
Annika Thalén-Lindström
David Tilly
Maria Fernanda Villegas Navarro
Anne von Heideman
Kenneth Wikström
Xuping Wu
Lennart Åström

Section of Radiology
Johan Berglund
Nuno Canto Moreira Figueira de Alme
Pär Dahlman
Angeliki Dimopoulou

Per Eckerbom
Mats Ola Eriksson
Olof Eriksson
Raquel Espregueira Cruz Freire Themudo
Johannes Finnsson
David Fällmar
Malin Helenius
Lars Jangland
Johan Krause
Hans Erik Källman
Christina Lundberg
Elin Lundström
Arvid Morell
Firas Mosavi
Richard Nordenskjöld
Ruta Nylander
Jakob Swanberg
Johanna Swärd
Tomas Söderman
Catrin von Below

Section of Nuclear Medicin and PET
Kerstin Heurling
Johan Lilja
Dan Sandberg

Section of Biomedical Radiation Sciences
Mohamed Altai
Hanna Björkelund
Lina Ekerljung
Amelie Fondell
Ann-Sofie Gustafsson
Lovisa Göstring
Jennie Malmberg
Diana Spiegelberg
Thuy Tran
Zohreh Varasteh

Administrative Staff

Administrative assistant:

Section of Oncology
Inger Hjertström Öst
Marina Forslund

Course Administrator:

Section of Radiology
Annika Häger

Financial Coordinator:	**Section of Radiology** Christl Richter-Frohm
Financial and Personnel Administrator:	**Section of Oncology** Sigrid Simonsson Westerström
	Section of Biomedical Radiation Science Maria Östh Eklind
Research Coordinator:	**Section of Radiology** Elin Lundström

Technical Staff:

Research Engineers:	**Section of Oncology** Ola Norrlid
	Section of Biomedical Radiation Sciences Christina Atterby
Research Nurses:	**Section of Radiology** Gunilla Arvidsson Monika Gelotte Anders Lundberg
Research Assistant:	**Section of Oncology** Eva Westergren
	Section of Radiology Johanna Mårtensson
Technicians:	**Section of Metal Biology Research** Erika Rönnbäck

Financing 2011

Income	SEK	Expenses	SEK
Government Funding Undergraduate Studies	7,014,627	Employees	33,454,106
Government Funding Research and Graduate Studies	10,337,472	Operational costs	25,495,317
Government Funding through the County Council of Uppsala (ALF-Grant)	7,693,655		
Government and Private Grants	23,722,996		
Commissioned Researach	7,215,652		
Commissioned Educataion	552,142		
Interest	628,901	Interest	250,977
Total:	***57,165,444***	***Total:***	***59,200,400***

Scientific Reports

Section of Radiology

Research Group 1:.MRI and PET of the whole body

Principal Investigator: Håkan Ahlström

Uppsala University has a particularly strong international position in the fields of MRI and PET imaging. This was recently emphasized in the international evaluation of all research at Uppsala University, a project called “Quality and renewal-2011”, where the research field PET/MRI in oncology and cardiovascular disease received the highest possible rating, i.e. top quality or world leading.

At the end of 2011, Uppsala received funding from the Swedish Research Council (main applicant Håkan Ahlström) to install the first fully integrated PET/MR equipment (3T magnetic resonance tomography combined with positron emission tomography) in Sweden. The governance of the PET/MR equipment will be assigned to Sweden Bio-Imaging, a network aimed at facilitating collaboration between researchers in Sweden working in bioimaging and related fields. U-CAN and EpiHealth, the infrastructures that have been established by the Swedish Research Council, will be given access 40% of the time and the remaining 60% will be open access time prioritized by Sweden Bio-Imaging. The governance model is described in the figure below.

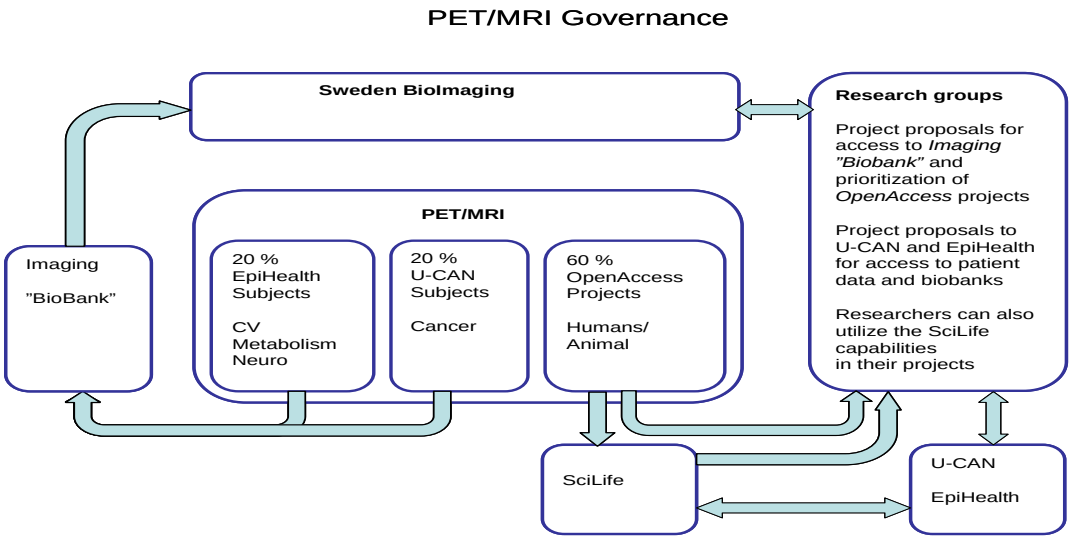

Fig. 1.

The aim is not only to facilitate access time for research projects but also to facilitate the build-up of a unique imaging “biobank”, including 4,000 subjects recruited from the U-CAN and EpiHealth cohorts during 5 years, to be made available to researchers within Sweden and prioritized by Sweden BioImaging. Individual researchers can also apply for access to patient and subject data from the U-CAN and EpiHealth records as well as biobank information.

The main aims for the research group are:

The overarching goal is to increase the understanding of human physiology and pathology by combining acquired information from positron emission tomography (PET) and magnetic resonance imaging (MRI) and deploy this knowledge to guide diagnosis, prognosis and interventions in the fields of oncology and cardiovascular diseases with the latter also including obesity and diabetes. There are two different main aims:

- To develop and validate integrated PET/MRI methods for studies of the obesity-diabetes-atherosclerosis disease process and its consequences by using the currently funded PET-MR equipment.
- To improve detection, staging, characterisation, prognostic estimation and therapy evaluation of tumours by using the currently funded fully integrated whole-body PET/MR equipment.

Project 1: Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) for studies of the obesity-diabetes-atherosclerosis disease process and its consequences

1.1 PET/MRI IN OBESITY

Objective: The objective of this study is to investigate the energy homeostasis in obese and lean subjects and determine to what extent the obese phenotype originates from disturbed energy homeostasis because of either decreased activated brown adipose tissue or other energy saving mechanisms.

We plan to examine 20 human subjects with PET/MRI and stimulate the brown adipose tissue by keeping the subjects cold with different paradigms prior to imaging. The position of the brown adipose tissue will be determined by ^{18}F-FDG PET and the amount will be quantified by MRI using different sequences. The optimal subject preparation and imaging paradigms will be determined.

We thereafter plan to use the established BAT method and combine it with body composition imaging and measurements of energy efficiency measured by 31P-MRS at baseline and immediately following exercise in 100 subjects (50 lean and 50 obese subjects, age and gender matched) subjects in the EpiHealth cohort (described in section 4.6) to establish a foundation for understanding the energy homeostasis in lean vs. obese subjects.

1.2 PET/MRI IN DIABETES

Objective: There are two main objectives with PET/MRI in diabetes.

1. Validate the betacell imaging method in humans and use that to investigate the relationship between pancreatic lipid levels and beta-cell mass in T2D subjects.

2. Investigate the role of dysfunctional metabolism in various tissues and its role in the development of T2D.

We plan to validate the pre-clinical findings in a clinical study in subjects with Type 1 diabetes (10 controls and 10 T1D) using [^{11}C]5-HTP. We then plan to combine this information with assessment of pancreatic lipid levels with MRI in 40 subjects to determine the relationship between pancreas lipid levels and beta cell mass.

In addition we plan to develop an integrated automated method that determines the exact amount of various tissues as well as the metabolism in these tissues by investigating the 18F-FDG uptake in them. This method will be applied in the EpiHealth cohort in 400 subjects with various forms of metabolic disturbance (lean, obese, pre-diabetics, diabetics) to map the levels and tissue origin of the metabolic disturbances. The technical part of this project is described in more detail in section 4.5 of this proposal.

1.3 PET/MRI IN ATHEROSCLEROSIS

Objective: The objective with this study is to determine the prognostic value of plaque characteritc imaging including both plaque morphology and plaque inflammation on future MACE.

As described in the survey of the field, MRI can be used to investigate the composition of the atherosclerotic plaques and 18F-FDG PET can be used to investigate the inflammatory status of the same, hence yielding an integrated investigation of both composition and function. It is however not clear how to best integrate this information to better understand the prognostic value of this test. We therefore plan to investigate the prognostic value of combined PET/MRI of aortic and carotid arteries with the aim of understanding the importance of plaque inflammation vs. plaque morphology in a cohort (n=400) selected from the EpiHealth study. They will be investigated at baseline with 18F-FDG -PET and high resolution structural MRI and the FDG-uptake in the vessel wall will be determined. In addition multisequence analysis of MRI will be performed to quantify plaque volume, fibrous cap thickness and volume of lipid rich necrotic core. The patients will then be followed for 3 years with respect to outcome in terms of MACE (Cardiac Death, Myocardial Infarction and Stroke) to determine the predictive value of combined PET/MRI in plaque imaging.

1.4 PET/MRI IN MAJOR ADVERSE CARDIOVASCULAR EVENTS

Objective: The objective of this study is to determine the prognostic value of myocardial characteristic imaging combining coronary flow reserve and LV Function and infarct scar volume on future MACE.

As described previously PET of coronary flow reserve has been shown to have strong prognostic value in patients. In combination with MRI of infarct size (late enhancement scanning after contrast injection) and ventricular function we hypothesize that integrated ^{15}O-PET/MRI will have an important prognostic value for future major adverse cardiovascular events (MACE, i.e. cardiac death, myocardial infarction and stroke).

Previous studies were done in scattered patient groups and no studies have investigated this opportunity for secondary prevention. We therefore aim to test this in a population of stable CAD patients with the aim of determining the prognostic value of this test. We plan to include 300 patients with known myocardial infarctions and follow them for 3 years with respect to MACE.

1.5 WHOLE BODY PET/MRI ATLAS FOR STUDIES OF OBESITY, DIABETES AND ATHEROSCLEROSIS

Whole-body MRI and PET scans contain huge amounts of spatially detailed information. However, in research studies these datasets are typically heavily reduced to a few measurements (e.g. visual scores or diameters/areas/volume measures or intensities measures in regions of interest). Both cross sectional and longitudinal studies likely benefit from a more detailed analysis, however. We will attempt to use the potential of the available data. To realize this we need to develop methods that utilize both the functional and anatomical information available in MRI and PET scans.

Project 2: Whole-body PET/MR for detection, staging, characterization, prognostic estimation, and early therapy evaluation of tumors

2.1. VALIDATION OF DIFFERENT WHOLE-BODY PET AND MR METHODS IN ONCOLOGY USING DATA FROM THE PET/MR EQUIPMENT AND THE U-CAN PROJECT AS REFERENCES.

Consecutive investigations with the PET/MR equipment in patients with different cancer diagnoses, i.e. malignant lymphoma, neuroendocrine tumours, and prostate cancer will be performed at diagnosis, during and after treatment according to the program of the U-CAN project.

2.2. DEVELOPMENT OF A NEW CONCEPT FOR COMPUTER AIDED DIAGNOSIS AND EARLY THERAPY EVALUATION IN ONCOLOGY USING WHOLE-BODY DATA FROM THE PET/MR EQUIPMENT.

Members of the group during 2011

Håkan Ahlström, Professor, MD, PhD
Lars Johansson, PhD, University Lecturer
Tomas Bjerner, MD, PhD, Associate Professor
Charlotte Ebeling Barbier, MD, PhD
Tomas Hansen, MD, PhD
Antonina Bergman, MD, PhD
Joel Kullberg, PhD
Robin Strand, PhD
Filip Malmberg, PhD
Jan Weis, PhD, physicist

Firas Mosavi, MD, PhD student
Johanna Swärd, MD, PhD student
Arvid Morell Physicist, PhD student
Franciskus Ortiz-Nieto, physicist, PhD student
Rachel Themudo, M.D., PhD student
Per Hammar, M.D., PhD student
Lina Sjöberg, M.D., PhD student
Christina Lundberg, MD, PhD student
Elin Lundström, physicist, PhD Student
Anders Lundberg, Technician
Gunilla Arvidsson, Technician

Publications 2009-2011

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Dissertations 2011

Olof Eriksson: Imaging Islets of Langerhans by Positron Emission Tomography: Quantification of Beta-Cell Mass in the Native Pancreas and the Islet Graft. Dissertation February 3, 2011

Johan Berglund: Separation of Water and Fat Signal in Magnetic Resonance Imaging Advances in Methods Based on Chemical Shift. Dissertation October 21, 2011

Funding 2009 – 2011

The Swedish Cancer Foundationa, three year grant	1,165,000 SEK
The Swedish Researach Council, three year grant	1,200,000 SEK
The County Council, Uppsala, ALF-grant, 2011	5,100,000 SEK
The Vinnova Foundation	6,120,400 SEK
The Juvenile Diabetes Foundation	1,000,000 SEK
The AstraZeneca Company	9,998,240 SEK
Commissioned Research, other funding	2,063,190 SEK

Research Group 2: Neuroradiology

Principal Investigators: Elna-Marie Larsson, Professor and Raili Raininko, Professor

Project 1: Brain tumors

Responsible investigators: Prof. Raili Raininko and Prof. Elna-Marie Larsson. In collaboration with Depts of Oncology, Neurology, Neurosurgery and Neuropathology and Umeå University

Evaluation of brain tumors with different MR and PET methods: primary and differential diagnostic and evaluation of the therapy effects.

Project 2: Normal aging, dementia and neurodegenerative disorders

A. MRI evaluation of cerebral perfusion and cerebrovascular lesions in an elderly population – correlation with cardiovascular disease

Responsible investigator: Elna-Marie Larsson, in collaboration with the Department of Medical Sciences.

Brains have been examined in a population of 75-year-old persons. The prevalence of parenchymal and perfusion changes are compared with cardiovascular risk factors, cardiac MRI, US of the carotid arteries and cognitive changes.

B. Dementia

Responsible investigator: Elna-Marie Larsson, in collaboration with Department of Geriatrics

Different MRI methods at 3T are compared with FDG-PET to find the optimal combination of methods for dementia diagnosis and characterization

C. Normal pressure hydrocephalus (NPH)

Responsible investigator: Elna-Marie Larsson, in collaboration with Department of Neurology

MRI studies on patients with clinical suspicion of NPH

D. Genetic diseases affecting central nervous system (CNS)

Responsible investigator: Raili Raininko, in collaboration with Depts of Neurology, Child Neurology and Clinical Genetics.

Studies on the brain, spinal cord and muscles with magnetic resonance imaging (MRI) for morphology and with MR spectroscopy (MRS) for brain metabolism to evaluate pathogenesis and to develop early diagnostics. Patients and their healthy relatives (persons at risk) are examined. In 2011, we have mostly concentrated in adult-onset autosomal leukodystrophy (ADLD) with autonomic symptoms (follow-up study started 1994) and in Marionesco-Sjögren syndrome

Project 3: Hippocampus

Responsible investigator: Raili Raininko

A. Morphological development of the hippocampus
has been studied with ultrasound **(US)** in premature infants and with MRI in fetuses.

B. The effect of severe pain and growth hormone on the hippocampus

In collaboration with Professor Torsten Gordh, Depepartment of Surgical Sciences.

A MRI and MRS study

Project 4: Cerebrovascular disease, traumatic brain injury

A. MRI study of the brains treated by hypothermia after cardiac arrest

Responsible investigator: Raili Raininko, in collaboration with Depepartments of Anesthesiology and Intensive Care and Neurology

Patients treated by hypothermia after cardiac arrest, are evaluated with MR methods. The results will be related to neurological recovery.

B. Cerebral MR angiography (MRA)

Responsible investigator: Johan Wikström

Evaluation of MRA as a follow-up method after embolization of intracranial aneurysms

C. MR-study of traumatic brain injury, especially diffuse axonal injury. Comparison of different MR techniques and their clinical relevance.

Responsible investigator: Raili Raininko, in collaboration with Departments of Rehabilitation Medicine, Surgical Sciences and Neurosurgery

Patients with mild and severe brain injuries are examined with MR methods in the acute phase and after 3 months. The aim is to find the methods which are the most sensitive to demonstrate brain injury and have the highest prognostic value.

Project 5: Multiple sclerosis (MS)

Relationship of the immunological reactions and MR changes in multiple sclerosis (MS)

Responsible investigator: Raili Raininko, in collaboration with Depts of Clinical Immunology and Neurology

Patients having different types of MS in different phases of the disease are studied with immunological tests and MRI. The aim is to achieve better knowledge on tissue reactions and pathological processes in the brain and spinal cord.

Project 6: Functional (fMRI)

Responsible investigators: Elna-Marie Larsson, and Johan Wikström, in collaboration with Departments of Woman´s and Children´s Health, Psychology and Neuroscience/Functional Pharmacology

Evaluation of female sexual hormones on amygdala activation

Evaluation of amygdala activation after unilateral hippocampus resection

fMRI study after sleep deprivation.

Project 7: Fetal MRI

MRI studies on the fetuses and the placenta

Responsible investigator: Johan Wikström, in collaboration with Department of Woman´s and Children´s Health.

Evaluation of the value of fetal MRI during the second trimester.

Post mortem MRI of aborted fetuses.

Biometric studies on fetal brain in prenatal MRI.

Studies on the placenta in normal pregnancy, preeclampsia and intrauterine growth restriction using ^{31}P-MRS, BOLD MRI with T2* measurements and diffusion-weighted MRI.

Members of the neuroradiology research group during 2011

Raili Raininko, Professor of Neuroradiology
Elna-Marie Larsson, Professor of Neuroradiology
Johan Wikström, M.D., Ph.D., Docent
Shahin Abdsaleh, MD, PhD
Dragan Bajic, MD, PhD
Nuno Canto Moreira, MD, PhD student
David Fällmar, MD, PhD student
Ruta Nylander, MD, PhD student
Johannes Finsson, MD, PhD student
Johanna Mårtensson, MR physicist
Romina Romanos Zapata, MD
Micaela von Ehren, MD
Linnea Cerwén, MD
Vilma Velickaite, MD

Publications 2009-2011

1. Wikström J, Bjørnerud A, McGill S, Johansson L. Venous saturation slab causes overestimation of stenosis length in 2D time-of-flight magnetic resonance angiography. *Acta Radiol. 50:55-60, 2009*
2. Hansen T, Ahlström H, Söderberg S, Elmgren A, Wikström J, Lind L, Johansson L. Visceral adipose tissue, inflammation, adiponectin and atherosclerosis assessed by whole-body magnetic resonance angiography in an elderly population. *Atherosclerosis. 205:163-7, 2009*
3. Wikström, J, Hansen T, Ahlström H, Johansson L, Lind L. Lower extremity artery stenosis distribution in an unselected elderly population and itsrelation to a reduced ankle brachial index (ABI). *J Vasc Surg.50 :330-4, 2009*
4. Sundblom, J., Melberg, A., Kalimo, H., Smits, A., Raininko, R.: MR characteristics and neuropathology of the spinal cord in adult-onset autosomal dominant leukodystrophy with autonomic symptoms. *Am. J. Neuroradiol. 30:328-335, 2009*

5. Melberg, A., Moslemi, A.R., Palm, O., Raininko, R., Stålberg, E., Oldfors, A.: A patient with two mitochondrial DNA mutations causing PEO and LHON. *Eur. J. Hum. Genet. 52:47-48,2009*

6. Mannerkoski, M., Heiskala, H., Raininko, R., Åberg, L., Sarna, S., Wirtavuori, K., Autti, T.: Brain magnetic resonance imaging of siblings from families with two or more children with learning disabilities and need for full-time special education. *Acta Radiol. 50:437-445, 2009*

7. Örlén, H, Melberg, A, Raininko, R., Kumlien, E., Entesarian, M., Söderberg, P.,Påhlman, M., Darin, N., Kyllerman, M., Holmberg, E., Engler, H., Eriksson, U., Dahl, N.: SPG11 mutations cause Kjellin syndrome, a hereditary spastic paraplegia with thin corpus callosum and central retinal degeneration*. Am J Med Genet B Neuropsychiatr. Genet. 150B:984-992, 2009*

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12. Raininko, R., Mattsson, P.: Metabolite concentrations in supraventricular white matter from teenage to early old age: A short echo time ^{1}H MRS study. *Acta Radiol.* 51:309-315, 2010

13. Bannbers E, Kask K, Wikström J, Sundström Poromaa I. Lower levels of prepulse inhibition in fertile women in comparison with postmenopausal women. *Psycho-neuroendocrinology* 35:422-429, 2010, IF 3.788

14. Weis J, Ring P, Olofsson T, Ortiz F, Wikström J. Short echo time MR spectroscopy of brain tumors: grading of cerebral gliomas by correlation analysis of normalized spectral amplitudes. *JMRI J Magn reson Imaging 31:39-45, 2010*

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24. Heradstveit B, Larsson EM, Skeidsvoll H, Hammersborg S-M, Wentzel-Larsen T, Guttormsen AB, Heltne JK. Repeated Magnetic Resonance Imaging and Cerebral Performance after Cardiac Arrest – A pilot study. Resuscitation 2011;82:549-55

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31. Schuster, J., Sundblom, J., Thuresson, A-C., Hassin-Baer, S., Klopstock, T., Dichgans, M., Cohen, O.S., Raininko, R., Melberg, A., Dahl. N.: Genomic duplications mediate overexpression of lamin B1 in adult-onset autosomal dominant leukodystrophy (ADLD) with autonomic symptoms. Neurogenetics 12:65-72, 2011
32. Bajic, D., Canto Moreira, N., Wikström, J., Raininko, R.: Development of the hippocampal region demonstrated on fetal MRI. A preliminary report. NRJ Digital-Neuroradiol. J 1:555-557, 2011
33. Canto Moreira, N., Teixeira, J., Raininko, R., Wikström, J.: The ear in fetal MRI: What can we really see? Neuroradiology 53: 1001-1008, 2011
34. Melberg, A., Sundblom, J., Raininko, R: White matter disorders with autosomal dominant hereditary. Acta Neurol. Scand. 124:71-72, 2011
35. Raininko, R., Melberg, A.: Radiological aspects of genetic disorders with adult-onset CNS symptoms. NRJ Digital – The Neuroradiology Journal 1:24-37, 2011

Reviews 2009-2011:

1. Raininko, R., Melberg, A.: Radiological aspects of genetic disorders with adult-onset CNS symptoms. DNJ Digital - Neuroradiol. J (in press)

Book Chapters 2009-2011

1. Järnum H, Knutsson L, Larsson EM.: Brain tumours: evaluation of perfusion using 3D-FSE-pseudocontinuous arterial spin labelling. Chapter in Tumors of the central nervous system, volume 3, Brain tumors (part 1). Springer 2011.

Funding 2009-2011:

Faculty of Medicine	SEK 1.500.000
Akademiska sjukhuset, ALF-grant	SEK 1.500.000
External funding, commissioned research	SEK 100.000

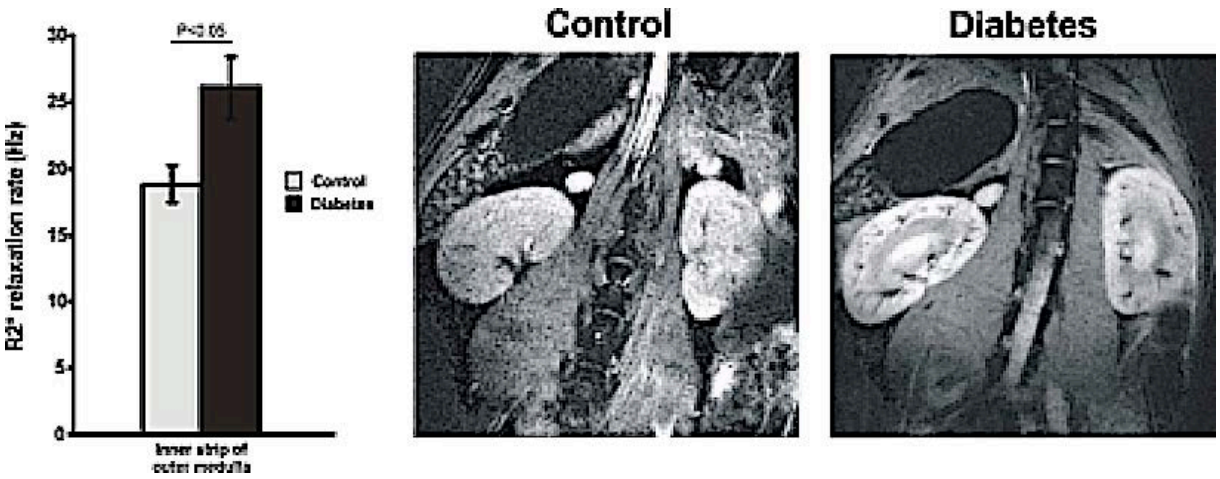
Research Group 3: Non-invasive imaging of renal function during diabetes and hypertension

Principal Investigator: Per Liss

Diabetes and hypertension are the leading causes of kidney failure. The mechanisms underlying the development of the nephropathy are still largely unknown despite intense research and there is currently no effective treatment available to prevent or reverse the kidney dysfunction. Furthermore, a diagnostic tool for identifying the hypertensive and diabetic patients at increased risk for developing kidney dysfunction is lacking.

In experimental studies we have reported that diabetic rat and mouse kidneys have severely altered oxygen metabolism and oxygenation (2-8) and the proposed research program will extend these studies to include hypertensive and diabetic patients contrasted to healthy volunteers.

The purpose of this research program is to investigate the ability of using non-invasive imaging MR-techniques to early identify the subgroup of patients among diabetic and hypertensive patients that later will develop nephropathy. The parameters that will be imaged are involved in renal oxygen metabolism which we in experimental settings have found to be important in the development of diabetic nephropathy.



BOLD-MRI of rat kidneys using a Philips 1.5T medical MR scanner. Left: Diabetics display increased R2 indicating increased deoxyhemoglobin levels, i.e. reduced oxygenation. Right: T2*-weighted image of control and diabetic kidney. Published in [2]*

Members of the group during 2011

Per Liss, Associate Professor, M.D, PhD, Senior Physician
Tomas Bjerner, Associate Professor, M.D, PhD, Senior Physician
Per Eckerbom, MD, Ph.D. Student, Senior Physician

Fredrik Palm, Professor, PhD
Peter Hansell, Professor, PhD
Angelica Fasching, Research Engineer

Collaborators

Michael Häggman, Associate Professor, M.D, PhD, Senior Physician
Gunnar Tufvesson, Professor, M.D, PhD, Senior Physician
Erik Larsson, Professor, M.D, PhD, Senior Physician
Alireza Biglarnia, Associate Professor, M.D, PhD, Senior Physician
Per-Ola Carlsson, Professor, M.D, PhD, Senior Physician
Anders Persson, Associate Professor, M.D, PhD, Senior Physician

Funding 2009 - 2011

Akademiska Sjukhuset, ALF-grant, 3 years 2011-2013:	SEK 700.000
Swedish Diabetes Association:	SEK 105.000
Akademiska Sjukhuset, ALF-grant, 2011:	SEK 150.000

Project 1: Non-invasive measurement of renal blood flow, intrarenal oxygenation and diffusion in diabetic patients with newly diagnosed microalbuminuria.

Project 2: Can non-invasive measurements of changes in renal blood flow, intrarenal oxygenation and diffusion in patients with type 1 diabetes be used to predict later development of nephropathy?

Project 3: Non-invasive measurements of changes in renal blood flow, intrarenal oxygenation and diffusion in patients undergoing pancreas transplantation.

Project 4: Correlation of fibrosis in the kidney to non-invasive measurements of renal blood flow, intrarenal oxygenation and diffusion in patients with renal cancer and diabetes.

Publications 2009 - 2011

1. Iodinated contrast media decrease renomedullary blood flow. A possible cause of contrast media-induced nephropathy. Liss P, Hansell P, Carlsson PO, Fasching A, Palm F. Adv Exp Med Biol. 645:213-8. 2009.

2. Reduced oxygenation in diabetic rat kidneys measured by T2* weighted magnetic resonance micro-imaging. Edlund J, Hansell P, Fasching A, Liss P, Weis J, Glickson JD, Palm F. Adv Exp Med Biol. 645:199-204. 2009.
3. Nitric oxide and kidney oxygenation. Palm F, Teerlink T, Hansell P Curr Opin Nephrol Hypertens. 2009 Jan;18(1):68-73.
4. Diabetes, oxidative stress, nitric oxide and mitochondrial function. Friederich M, Hansell P, Palm F Curr Diabetes Rev. 2009 May;5(2):120-44.
5. Blood pressure, blood flow, and oxygenation in the clipped kidney of chronic 2-kidney, 1-clip rats: effects of tempol and Angiotensin blockade. Palm F, Onozato M, Welch WJ, Wilcox CS. Hypertension. 2010 Feb;55(2):298-304.
6. Nitric oxide originating from NOS1 controls oxygen utilization and electrolyte transport efficiency in the diabetic kidney. Palm F, Fasching A, Hansell P, Källskog O. Am J Physiol Renal Physiol. 2010 Feb;298(2):F416-20.
7. Tubular reabsorption and diabetes-induced glomerular hyperfiltration. Persson P, Hansell P, Palm F. Acta Physiol (Oxf). 2010 Sep;200(1):3-10.
8. The roles of NADPH-oxidase and nNOS for the increased oxidative stress and the oxygen consumption in the diabetic kidney. Edlund J, Fasching A, Liss P, Hansell P, Palm F. Diabetes Metab Res Rev. 2010 Jul;26(5):349-562.
9. Renal oxidative stress, oxygenation, and hypertension. Palm F, Nordquist L. Am J Physiol Regul Integr Comp Physiol. 2011 Nov;301(5):R1229-41.

Research Group 4: Uroradiology

Members of the group:

Anders Magnusson, Professor
Henrik Björkman, M.D., Ph.D.
Pär Dahlman, M.D.
Allina Dimopoulou, M.D., Research Student
Gaute Hagen, M.D., Ph.D.
Malin Helenius, M.D., Research Student
Maria Lönnemark, M.D., Ph.D., Docent, Study Director for Medical Education
Eva Lundqvist, Medical Student
Monica Segelsjö, radiographer

Research Projects:

- Dose Reduction at CT-examinations of the Urinary Tract.
- Optimized radiological examination of macroscopic haematuria.
- CT-guided intervention
- CT-guided ablation of kidney tumours
- The use of reconstructive 3D-images at preoperative planning.
- Functional information in CT images

- Radiologic follow-up of patients after pancreatic transplantation.
- Nursing in connection with CT-examinations

Dissertations 2011

Pär Dahlman: CT Urography - efforts to reduce the radiation dose. Dissertation on April 1, 2011.

Publications 2009-2011

1. Knutson T, Fridblom P, Ahlström H, Magnusson A, Tannergren C, Lennernäs H.:Increased Understanding of Intestinal Drug Permeability Determined by the LOC-I-GUT Approach Using Multislice Computed Tomography Mol Pharm. 2009 Jan 14. [Epub ahead of print]
2. Dahlman P, Jangland L, Segelsjö M, Magnusson A.: Optimization of Computed Tomography Urography Protocol, 1997 to 2008: Effects on Radiation Dose. Acta Radiol. 2009 May;50(4):446-54.
3. Hagen G, Wadström J, Magnusson M, Magnusson A.: Outcome after Percutaneous Transluminal Angioplasty of Arterial Stenosis in Renal Transplant Patients. Acta Radiol. 2009 Apr;50(3):270-5.
4. Whitaker IS, Rozen WM, Smit JM, Dimopoulou A, Ashton MW, Acosta R.: Perito-neo-cutaneous perforators in deep inferior epigastric perforator flaps: a cadaveric dissection and computed tomographic angiography study. Microsurgery. 2009;29(2):124-7.
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6. Biglarnia AR, Nilsson B, Nilsson T, von Zur-Mühlen B, Wagner M, Berne C, Wanders A, Magnusson A, Tufveson G.: Prompt reversal of a severe complement activation by eculizumab in a patient undergoing intentional ABO-incompatible pancreas and kidney transplantation. Transpl Int. 2011 Aug;24(8):e61-6.
7. Dimopoulou A, Raland H, Wikström B, Magnusson A.: MDCT angiography with 3D image reconstructions in the evaluation of failing arteriovenous fistulas and grafts in hemodialysis patients. Acta Radiol. 2011 Nov 1;52(9):935-42.
8. Lundqvist E, Tufveson G, Duraj F, Wadström J, Biglarnia AR.: Ureteroperitone-ostomy - a rare complication after kidney transplantation. Transpl Int. 2011 Sep;24(9):e75-6.

Scientific presentations:

The members of the group have participated in several congresses within the field of Uroradiology and presented their research both nationally and internationally.

Section of Nuclear medicine & PET

The Nuclear medicine & PET research group was formally established in early 2011, after Uppsala PET Centre was taken over by Uppsala University Hospital from GE Healthcare. The group is closely related to the Molecular Imaging Section, Medical Imaging Centre, at Uppsala University Hospital, with access to a cyclotron for production of positron-emitting isotopes, GMP laboratories for tracer production, two PET/CT, two dedicated PET, two SPECT/CT and a SPECT scanner. Furthermore, there is a close collaboration with the Pre-clinical PET platform, part of the Department of Medicinal Chemistry, and with Uppsala Imanet as part of a research agreement with GE Healthcare. The group's research has a focus on the development and qualification of radiopharmaceuticals for clinical molecular imaging and therapeutic nuclear medicine, including diagnostic uses, use in drug development and clinical research, and applications in external radiation therapy and targeted radiotherapy. Chemistry and pre-clinical PET research activities are not reported in this overview, as they are formally part of the Department of Medicinal Chemistry.

Research group

Principal investigator: Assoc. Prof. Jens Sörensen, MD, PhD

Members of the group during 2011

Assoc. Prof. Jens Sörensen, MD, PhD
Assoc. Prof. Mark Lubberink, PhD
Assoc. Prof. Irina Velikyan, PhD
Assoc. Prof. Gunnar Antoni, PhD
Lieuwe Appel, PhD
Cecilia Wassberg, MD, PhD
Anders Wall, PhD
Lars Göran Andersson, MD, PhD
Mattias Sandström, PhD
Cathrin von Below, MD, PhD student
Firas Mosavi, MD, PhD student
Ulrike Garske, MD, PhD student
Torsten Danfors, MD, PhD student
Johan Lilja, PhD student
Kerstin Heurling, PhD student
My Jonasson, PhD student
Tanja Kero, MD, PhD student
Dan Sandberg, MD, PhD student
Gustaf Tegler, MD, PhD student (Vascular Surgery)
Camilla Andersson, PhD student
Mikko Aarnio, MD, PhD student
David Fällmar, MD, PhD student (Neuro-radiology)
Ida Häggström, PhD student (Umeå University)
Hans Harms, PhD student (VUmc Amsterdam)

Sandeep Golla, project worker
Sandeep Padala, project worker

Publications of group members 2009-2011

1. Razifar P, Engler H, Ringheim A, Estrada S, Wall A, Långström B. An automated method for delineating a reference region using masked volume-wise principal-component analysis in 11C-PIB PET. Journal of Nuclear Medicine Technology. 2009; 37(1):38-44.
2. Appel L, Geffen Y, Heurling K, Eriksson C, Antoni G, Kapur S. BL-1020, a novel antipsychotic candidate with GABA-enhancing effects : D2 receptor occupancy study in humans. European Neuropsychopharmacology. 2009; 19(12):841-850.
3. Lindhe Ö, Sun A, Ulin J, Rahman O, Långström B, Sörensen J. [(18)F]Fluoroacetate is not a functional analogue of [(11)C]acetate in normal physiology. European Journal of Nuclear Medicine and Molecular Imaging. 2009; 36(9):1453-1459.
4. Ullmark G, Sundgren K, Milbrink J, Nilsson O, Sörensen J. Osteonecrosis following resurfacing arthroplasty : A clinical positron emission tomography study of 14 cases. Acta Orthopaedica. 2009; 80(6):670-674.
5. Ullmark G, Sörensen J, Nilsson O. Bone healing of severe acetabular defects after revision arthroplasty. Acta Orthopaedica. 2009; 80(2):179-183.
6. Furmark T, Henningsson S, Appel L, Åhs F, Linnman C, Pissiota A, et al. Genotype over-diagnosis in amygdala responsiveness : affective processing in social anxiety disorder. Journal of Psychiatry & Neuroscience. 2009; 34(1):30-40.
7. Åhs F, Pissiota A, Michelgård Å, Frans Ö, Furmark T, Appel L, et al. Disentangling the web of fear: amygdala reactivity and functional connectivity in spider and snake phobia. Psychiatry Research. 2009; 172(2):103-108.
8. Linnman C, Appel L, Söderlund A, Frans Ö, Engler H, Furmark T, et al. Chronic whiplash symptoms are related to altered regional cerebral blood flow in the resting state. European Journal of Pain. 2009; 13(1):65-70.
9. Häggström I, Johansson L, Larsson A, Östlund N, Sörensen J, Karlsson M. Semi-automatic tumour segmentation by selective navigation in a three-parameter volume, obtained by voxel-wise kinetic modelling of C-11-acetate. Radiation Protection Dosimetry. 2010; 139(1-3):214-218.
10. Degerman Gunnarsson M, Lindau M, Wall A, Blennow K, Darreh-Shori T, Basu S, et al. Pittsburgh compound-B and Alzheimer's disease biomarkers in CSF, plasma and urine : An exploratory study. Dementia and Geriatric Cognitive Disorders. 2010; 29(3):204-212.
11. Linnman C, Appel L, Furmark T, Söderlund A, Gordh T, Långström B, et al. Ventromedial prefrontal neurokinin 1 receptor availability is reduced in chronic pain. Pain. 2010; 149(1):64-70.

12. Sikk K, Taba P, Haldre S, Bergquist J, Nyholm D, Askmark H, Danfors T, Sörensen J, Thurfjell L, Raininko R, Eriksson R, Flink R, Färnstrand C, Aquilonius SM. Clinical, neuroimaging and neurophysiological features in addicts with manganese-ephedrone exposure. Acta Neurol Scand. 2010 Apr; 121(4):237-43. Epub 2009 Dec 17.

13. Sörensen J, Valind S, Andersson L G. Simultaneous quantification of myocardial perfusion, oxidative metabolism, cardiac efficiency and pump function at rest and during supine bicycle exercise using 1-¹¹C-acetate PET : a pilot study. Clinical Physiology and Functional Imaging. 2010; 30(4):279-284.

14. Forsberg A, Almkvist O, Engler H, Wall A, Långström B, Nordberg A. High PIB retention in Alzheimer's disease is an early event with complex relationship with CSF biomarkers and functional parameters. Current Alzheimer research. 2010; 7(1):56-66.

15. Hansen T, Wanhainen A, Sörensen J, Johansson L. Lymph nodes as a potential pitfall in carotid plaque imaging with FDG-PET/CT. Atherosclerosis [Internet]. 2010 Dec 21

16. Heijne M, Raijmakers PG, Harms HJ, Lubberink M, Halbmeijer R, Appelman YE, m.fl. Coronary steal: revealing the diagnosis with quantitative cardiac PET/CT. J Nucl Cardiol. 2010 Dec; 17(6):1118-1121.

17. Van der Veldt AAM, Hendrikse NH, Harms HJ, Comans EFI, Postmus PE, Smit EF, m.fl. Quantitative parametric perfusion images using 15O-labeled water and a clinical PET/CT scanner: test-retest variability in lung cancer. J. Nucl. Med. 2010 Nov; 51(11):1684-1690.

18. Rijzewijk LJ, van der Meer RW, Lubberink M, Lamb HJ, Romijn JA, de Roos A, m.fl. Liver fat content in type 2 diabetes: relationship with hepatic perfusion and substrate metabolism. Diabetes. 2010 Nov; 59 (11):2747-2754.

19. van der Veldt AAM, Hendrikse NH, Smit EF, Mooijer MPJ, Rijnders AY, Gerritsen WR, m.fl. Biodistribution and radiation dosimetry of 11C-labelled docetaxel in cancer patients. Eur. J. Nucl. Med. Mol. Imaging. 2010 Okt; 37(10):1950-1958.

20. Vermeltfoort IA, Raijmakers PG, Lubberink M, Germans T, Van Rossum AC, Lammertsma AA, Knaapen P. Feasibility of subendocardial and subepicardial myocardial perfusion measurements in healthy normal with (15)O-labeled water and positron emission tomography. J Nucl Cardiol 52:745-749, 2011 (IF 2.8)

21. Eriksson, O., Carlsson, F., Blom, E., Långström, B., Korsgren, O., Velikyan, I., Preclinical evaluation of a 68Ga-labelled biotin analogue for the application in islet transplantation, Nuclear Medicine and Biology, accepted, 2011.

22. Velikyan, I., Positron Emitting [68Ga]Ga-Based Imaging Agents: Chemistry and Diversity, Medicinal Chemistry, 7, 338-372, 2011.

23. Sandström, K., Haylock, A-K., Velikyan, I., Speigelberg, D., Kareem, H., Tolmachev, V., Lundqvist, H., Nestor, M., Improved tumor-to-organ ratios of a novel hEGF radionuclide conjugate with pre-administered anti-EGFR Affibody molecules, Cancer Biotherapy & Radiopharmaceuticals, 26(5), 593-601, 2011.

24. Blom, E., Velikyan, I., Monazzam, A., Razifar, P., Nair, M., Vanderheyden, J-L., Krivoshein, AV., Backer, M., Backer, J., Långström, B., Synthesis and characterization of [68Ga]GaNOTA-PEG-scVEGF and [68Ga]GaDOTA-PEG-scVEGF PET tracers, JLCR, 54, 11, 685-692, 2011.

25. Borges, JB, Velikyan, I., Långström, B., Sörensen, J., Ulin, J., Maripuu, E., Sandström, M., Widström, Ch., Hedenstierna, G. Ventilation distribution studies comparing Technegas and Gallgas using 68GaCl3 as the label, J Nuc Med, 52, 206-209, 2011.

26. Velikyan, I., Sundin, A., Eriksson, B., Lundqvist, H., Sörensen, J., Bergström, M. and Långström B., Imaging biomarkers for diagnosis and quantification with positron emission tomography: assistance to therapy Nucl Med Biol, 37(6): 724, 2011,

27. Åhs F, Palmquist AM, Pissiota A, Appel L, Frans O, Liberzon I, Furmark T, Fredrikson M. Arousal modulation of memory and amygdala-parahippocampal connectivity: A PET-psychophysiology study in specific phobia. Psychophysiology. 2011 Nov; 48(11):1463-9.

28. Linnman C, Appel L, Fredrikson M, Gordh T, Söderlund A, Långström B, Engler H. Elevated [11C]-D-deprenyl uptake in Chronic Whiplash Associated Disorder suggests persistent musculoskeletal inflammation. PLoS ONE 2011 Apr; 6(4): 1-6.

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Dissertations 2011

1. Mattias Sandström. Dosimetry of radionuclide therapy with ^{177}Lu-octreotate. November 15, 2011

Funding

Centrala ALF-medel per year: (50 % salary for Principal Investigator)	600,000 SEK
Akademiska sjukhusets utvecklingsfond (ML), 2011	100,000 SEK
Lions cancerfond, 2009.	100,000 SEK
Skofonden 2008 – 2010	100,000 SEK
Parkinsonfonden, 2011	100,000 SEK
Särskild ALF satsning (ML, LA), 2011	200,000 SEK
Swedish Research Council, 2011 (JS, co-applicant), PET-MRI	43,000,000 SEK
GE Healthcare, per year, in collaboration with Uppsala University Hospital	14,000,000 SEK

Project 1: Cardiovascular PET

Jens Sörensen, Mark Lubberink, Tanja Kero, Lars Göran Andersson, Gustaf Tegler

1. Introduction of [^{15}O]water as a clinical quantitative myocardial blood flow and viability tracer
2. In vivo visualization of amyloid deposits in the heart with [^{11}C]PIB and PET
3. [^{11}C]acetate in patients with valvular insufficiency
4. [^{18}F]-FDG, [^{11}C]PK11195 and [^{11}C]D-Deprenyl in abdominal aortic aneurysms

Project 2: Neurology

Jens Sörensen, Torsten Danfors, Mark Lubberink, My Jonasson, Johan Lilja, Kerstin Heurling, Lieuwe Appel, Anders Wall, David Fällmar

1. Diagnostic imaging of parkinsonism with a single [^{11}C]PE2I PET scan as a replacement for DATSCAN-SPECT and [^{18}F]FDG-PET
2. Assessment of GABA-A receptor density and general cerebral function with a single dynamic [^{18}F]flumazenil scan compared to [^{18}F]FDG + [^{11}C]flumazenil
3. Social phobia brain function and genetics ([^{11}C]PE2I, [^{11}C]DASB) in collaboration with Prof. Tomas Furmark, Uppsala University
4. Post-traumatic stress disorder, in collaboration with prof. Mats Fredriksson, Uppsala University
5. Transplation of NGF-producing cells in Alzheimer's disease patients: a study with [^{11}C]nicotine and [^{18}F]FDG, in collaboration with Prof. Maria Eriksdotter-Jönhagen, Karolinska Institute
6. Inflammation in Alzheimer's disease: [^{11}C]PIB, [^{11}C]D-Deprenyl and [^{18}F]FDG, in collaboration with Prof. Agneta Norberg, Karolinska Institute
7. Acquisition of a normal database for glucose metabolic rate brain images with [^{18}F]FDG and PET/CT, in collaboration with GE Healthcare / Uppsala Imanet
8. Comparison of [^{18}F]FDG and arterial spin labelling MRI in dementia patients, in collaboration with Prof. Elna-Marie Larsson, Uppsala University
9. Pain imaging with [^{11}C]DDE, in collaboration with Prof. Torsten Gordh, Uppsala University

Project 3: Oncology

Ulrike Garske, Irina Velikyan, Cecilia Wassberg, Mattias Sandström, Cathrin von Below, Firas Mosavi, Mark Lubberink, Jens Sörensen

1. Targeted radiotherapy of neuroendocrine tumours with ^{177}Lu-DOTA-octreotate
2. Perfusion measurements of liver metastases in colorectal cancer after treatment with imatinib and anakinra using [^{15}O]water and PET/CT

3. Lymph node staging in prostate cancer using [^{11}C]acetate-PET
4. [^{11}C]methionine in low-malignant gliomas
5. ^{111}In-labelled affibody ABY-025 for detection of HER-2-positive breast cancer
6. Somatostatin receptor expression in neuroendocrine tumours as measured with [^{68}Ga]DOTATOC and [^{68}Ga]DOTATATE
7. [^{18}F]Fluoride and [^{11}C]acetate in prostate cancer bone metastases
8. [^{18}F]FDG-PET in lymphoma

Project 4: Other clinical projects

1. [^{11}C]hydroxy-tryptophane (HTP) for measurement of pancreatic beta cell function in Type-1 and 2 diabetes, in collaboration with Prof. Olle Korsgren, Uppsala University, and the Pre-clinical PET platform
2. Evaluation of bone metabolism in orthopedic and maxillofacial implants with [^{18}F]fluoride PET, in collaboration with Profs. Olle Nilsson, Hans Mallmin, Jan Hirsch and Assoc .Profs. Gösta Ullmark, Andreas Thor and the preclinical PET platform.
3. Measurement of absolute cerebral blood flow during cardiopulmonary bypass and selective cerebral perfusion using [^{15}O]water and PET, in collaboration with Assoc. Prof. Fredrik Lennmyr and the Pre-clinical PET platform.
4. Patient expectations and experiences of PET-CT – optimization of logistics and patient experience.

Project 5: Physics and methodology

Mark Lubberink, Mattias Sandström, My Jonasson, Johan Lilja, Kerstin Heurling, Jens Sörensen, Hans Harms, Ida Häggström

1. Dosimetry of targeted radiotherapy with ^{177}Lu-DOTA-octreotate
2. Development of noise reduction techniques allowing for low-dose [^{18}F]FDG imaging
3. Development of a simplified scan protocol and automated parametric imaging methods for [^{11}C]PE2I PET
4. Reproducibility of liver metastases perfusion measurements with [^{15}O]water
5. Low-dose CT artefact reduction in hip transplants
6. Quantitative accuracy of parametric myocardial and tumour blood flow images based on HYPR-LR-filtered dynamic [^{15}O]water PET
7. Development of tracer kinetic models for various PET tracers.

Section of Oncology

Research Group 1: The Lymphoma group

Principal Investigator: Gunilla Enblad

Members of the Group:

Gunilla Enblad, MD, PhD, Ass. Professor
Hans Hagberg, MD, PhD, Ass. Professor
Daniel Molin MD, Ass. Professor
Anna Laurell, MD, PhD
Magdalena Adde, MD, PhD
Ingrid Glimelius, MD, PhD
Ulf Thunberg, BSci, PhD
Mattias Berglund, BSci., PhD
Gustaf Hedström, MD, PhD Student
Maryam Delfourosh, BSci., PhD Student
Ingemar Lagerlöf, PhD Student (Linköping)
Karin Ullberg, PhD Student (Karlstad)

Collaboration with

Clinical genetics
Richard Rosenquist Brandell, MD, PhD, Professor
Patrik Georgii Hemming, MD, PhD
Reumatology
Eva Baecklund, MD, Ass. Prof.
Carin Backlin, BSci, PhD
Infectious Diseases
Karlis Pauksens, MD, Ass. Prof.
Amelie Kinch, MD, PhD Student
Pediatrics
Gustaf Ljungman, MD, Ass. Prof.
Annika Englund, MD, PhD Student
Radiology
Håkan Ahlström, MD, Professor
Gunnar Åström, MD, PhD
Pathology
Christer Sundström, MD, Prof.
Rose-Marie Amini, MD, Ass. Prof.

National collaboration through the Swedish lymphoma group and the Swedish Hodgkin group. International collaboration through the Nordic groups and through international clinical trials

Publications 2009-2011

1. Thymidylate synthase polymorphism relevant for survival in patients with diffuse large B-cell lymphoma? Berglund M, Roos G, Thunberg U. Leuk Lymphoma. 2009 Oct; 50(10):1723-5.
2. A follicular dendritic cell line promotes somatic hypermutations in Ramos cells in vitro. Canedo P, Thorsélius M, Thunberg U, Sällström J, Sundström C, Rosén A, Söderberg O. Scand J Immunol. 2009 Jan; 69(1):70-1.
3. High-dose therapy and autologous stem cell transplantation versus conventional therapy for patients with advanced Hodgkin's lymphoma responding to front-line therapy: long-term results. Carella AM, Bellei M, Brice P, Gisselbrecht C, Visani G, Colombat P, Fabbiano F, Donelli A, Luminari S, Feugier P, Browett P, Hagberg H, Federico M. Haematologica. 2009 Jan; 94(1):146-8. Epub 2008 Nov 10

4. Cancer of the parotid gland; 56-years of follow-up. A single centre experience on recurrence and survival. L Cederblad, S Johansson, G Enblad and E Blomquist. Acta Oncol. 2009 Jan 13:1-8. [Epub ahead of print].

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6. Long-term risk of cardiovascular disease in Hodgkin lymphoma survivors--retrospective cohort analyses and a concept for prospective intervention. A Andersson, G Enblad, A Gustavsson, U Näslund, B Malmer. Int J Cancer. 2009 Apr 15; 124(8):1914-7.

7. Rheumatoid arthritis, treatment with corticosteroids, and risk of malignant lymphomas. K Hellgren, J Askling, A Iliadou, A Ekbom, N Feltelius, C Backlin, G Enblad, R Rosenquist, C Sundstrom, L Klareskog, E Backlund. Ann Rheum Dis. 2009 May 12. [Epub ahead of print]

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10. Genome-wide microarray-based comparative genomic hybridization analysis of lymphoplasmacytic lymphomas reveals heterogeneous aberrations. Buckley PG, Walsh SH, Laurell A, Sundström C, Roos G, Langford CF, Dumanski JP, Rosenquist R. Leuk Lymphoma. 2009 Sep; 50(9):1528-34.

11. Pre-emptive treatment with rituximab of molecular relapse after autologous stem cell transplantation in mantle cell lymphoma. Andersen NS, Pedersen LB, Laurell A, Elonen E, Kolstad A, Boesen AM, Pedersen LM, Lauritzsen GF, Ekanger R, Nilsson-Ehle H, Nordström M, Fredén S, Jerkeman M, Eriksson M, Väärt J, Malmer B, Geisler CH. J Clin Oncol. 2009 Sep 10; 27(26):4365-70. Epub 2009 Aug 3.

12. Phase III study to evaluate temsirolimus compared with investigator's choice therapy for the treatment of relapsed or refractory mantle cell lymphoma. Hess G, Herbrecht R, Romaguera J, Verhoef G, Crump M, Gisselbrecht C, Laurell A, Offner F, Strahs A, Berkenblit A, Hanushevsky O, Clancy J, Hewes B, Moore L, Coiffier B. J Clin Oncol. 2009 Aug 10; 27(23):3822-9. Epub 2009 Jul 6.

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15. Genetic variation in tumor necrosis factor and risk of diffuse large B-cell lymphoma and follicular lymphoma: differences between subgroups in Swedish patients. Thunberg U, Enblad G, Turesson I, Berglund M. Leuk Lymphoma. 2010 Aug; 51(8):1563-6.

16. TP53 Mutations are infrequent in Newly-Diagnosed Chronic Lymphocytic Leukemia N Zainuddin, F Murray, M Kanduri, R Gunnarsson, K Ekström Smedby, G Enblad, J Jurlander, G Juliusson, R Rosenquist. Leuk Res. 2010 Sep 24. [Epub ahead of print]

17. Quantitative Evaluation of $p16^{INK4a}$ Promoter Methylation using Pyrosequencing in de novo Diffuse Large B-cell Lymphoma. N Zainuddin, M Kanduri, M Berglund, M Lindell, R-M Amini, G Roos, C Sundström, G Enblad, R Rosenquist. Leuk Res. 2010 Oct 28. [Epub ahead of print]

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35. Tissue microarray and digital image analysis: a methodological study with special reference to the microenvironment in Hodgkin lymphoma. Glimelius I, Qvarnström F, Simonsson M, Ekwall A, Smedby KE, Molin D, Amini RM.Histopathology. 2012 Mar 6. doi: 10.1111/j.1365-2559.2012.04185.x. [Epub ahead of print]

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37. Gender differences in fertility-related information received by young adult cancer survivors: Results of a large survival cohort in Sweden. G Armuand, K Rodriguez-Wallberg, L Wettergren, J Ahlgren, G Enblad, M Höglund, C Lampic. Accepted in JCO.

Dissertations 2009 - 2011

Magdalena Adde: Aggressive B-cell lymphomas. Studies of treatment, FDG-PET evaluation and prognostic factors. Uppsala 2009-05-09. (Main tutor: Gunilla Enblad)

Ingrid Glimelius: Hodgkin lymphoma – an interplay between tumour cell and microenvironment. Uppsala 2009-05-16. (Main tutor: Gunilla Enblad)

Norafiza Zainuddin: Molecular genetic analysis in B-cell lymphomas. A focus on the p53 pathway and p16 ^{INK4A}. Uppsala 2010-03-31. (Main tutor: Gunilla Enblad)

Anne Andersson: Long-term side effects after treatment of Hodgkin's lymphoma. Umeå 2011-05-20. (Gunilla Enblad co-tutor)

Project description

The projects of the lymphoma group are translational spanning from preclinical laboratory projects to clinical trials and studies of imaging. The main areas of research are briefly described.

Project 1: Lymphoma microenvironment

Studies of the microenvironment in Hodgkin lymphoma and the relation to the neoplastic cells, the Hodgkin and Reed-Sternberg (HRS) cells has been a focus of the group for over 20 years. The studies have led to five dissertations (Gunilla Enblad, Daniel Molin, Marie Fischer, Ricardo Carvalho and Ingrid Glimelius). The main findings have been that eosinophils and mast cells surrounding the HRS cells can contribute to the clinical course by stimulating the HRS cells via the CD 30 receptor. Furthermore, we have recently been able to show that the composition of the microenvironment is dependent on the HRS cells as well as the genetic variation and personal traits of the patient (manuscript submitted). Studies of the role of macrophages and T-cell subsets are ongoing. The studies have been extended to diffuse large B-cell lymphomas and recently to the relation to certain micro-RNA (mir), in particular mir 155 (manuscript in preparation).

Project 2: Molecular genetics of diffuse large B-cell lymphomas (DLBCL)

We have studied subgroups of DLBCL and the role of p53 mutations and methylation of p16, leading to two dissertations (Mattias Berglund and Norafiza Zainuddin). Furthermore, a number of single nucleotide polymorphisms have been studied and related to clinical presentation. At present, the expressions of a number of different mir are under investigation in different parts of lymphomas with different proportion of neoplastic cells. Furthermore, we aim to study tumour material from young adult patients with DLBCL. Our hypothesis is that young adults have a different disease with a lower expression of bcl-2 and translocations involving IRF4. We have also studied the effects and mechanisms of a new drug, PPP, in DLBCL in vitro (manuscript in preparation). We are currently studying curcumin in DLBCL and HL in vitro and have found synergistic effects with some chemotherapeutic drugs commonly used. Mechanisms for resistance are studied with focus on major vault protein (manuscript in preparation)

Project 3: Etiology of lymphomas

Etiologic factors of lymphomas are studied by comparing three groups of lymphoma patients; those who develop lymphomas without known risk factors, patients who develop lymphomas and who have an underlying autoimmune disease and post-transplant lymphomas. Large retrospective materials have been collected together with clinical information. The tumor materials are characterized with regard to lymphoma subtype and presence of Epstein Barr virus (EBV). Clinical factors are analyzed in order to detect risk factors for development of lymphomas. We are also studying tumour material from a large epidemiological study, SCALE. We have also started a national prospective study, collecting frozen tumour material, blood and plasma samples from all new patients with an autoimmune disease (Auto-lymfom).

Project 4: Clinical studies of Hodgkin lymphoma (HL)

We have since 1985 managed the national care program for HL and the registry of all Swedish patients. Since 2000, the patients are registered in the national lymphoma registry. This registry has led to a number of publications and dissertations (Gunilla Enblad, Rose-Marie Amini, and Daniel Molin, Ingrid Glimelius). We are currently studying how the treatment results have developed for elderly patients with HL and how a new chemotherapy regimen (BEACOPP14) has been used in HL. The results of a prospective phase II Nordic trials of early and intermediate stages of HL conducted 1999-2005 are being evaluated (manuscript in preparation). New imaging techniques i.e FDG-PET and whole body MRI are studied prospectively and in relation to micro-environment (can a hostile microenvironment be detected by imaging?). Pulmonary toxicity of the chemotherapeutic drug Bleomycin is studied prospectively. We are also participating in an international multi-center study evaluating FDG-PET as early response marker for advanced HL (RATHL) and are the Swedish coordinating center. We have also taken active part in a large retro and prospective study of late toxicity after treatment of HL, the SHIP-trial. The results of the study have led to four publications so far and to a planned dissertation May 2011 (Anne Andersson, Umeå, Gunilla Enblad, co-tutor). Lastly, we have taken the initiative to National video conferences on HL, every second week, where all new cases are discussed. From 2011 and onwards all patients who are to receive radiotherapy will also have a proton plan done. The aim is to study potential advantages of proton beam radiotherapy and to make a treatment protocol for the Skandion clinic.

Project 5: Clinical studies of other lymphomas

We have studied outcome of new therapy and new techniques leading to one dissertation (Magdalena Adde). We are participating in a number of national, Nordic and international studies on mantle cell lymphomas, DLBCL, follicular lymphomas, T-cell lymphomas and CNS-lymphomas. In some of the studies we have leading roles as initiating researchers.

In summary, the group are conducting studies of virtually all aspects of lymphomas and actively participate in the prospective U can study.

Funding 2009 – 2011

The Swedish Cancer Foundation	424,350 SEK
Private Foundations	1,182,000 SEK
Other foundations	843,040 SEK
The county Council, Uppsala, ALF	1,172,000 SEK

Research Group 2: The aetiology of malignant lymphomas – the SCALE study.

Principal Investiator: Bengt Glimelius

Project description

The aetiology of malignant lymphomas, with totally about 2 000 new cases a year in Sweden or about 30 different types of malignant tumours from the lymphoid system, is poorly known. There has been a marked increase during several decades, although it has levelled off during the past decade. In order to better understand the reasons behind malignant lymphomas and the increase, a population-based case control study was performed in Sweden and Denmark between 1999 and 2002. Totally 3 740 cases and 3 187 controls were interviewed. The participation rate for cases varied between 80 – 90% according to subgroup (mean 83%) and for controls 73 %. The majority of those interviewed contributed serum, plasma and blood cells for specific analyses. This study, which is so far the greatest study of its kind with intention to explore reasons for malignant lymphomas have already given valuable information about the relevance of different exposures. The studies continue along several lines in collaboration with other groups in an international network (InterLymph).

Infections have a well-established role in the development of specific lymphoma subtypes for example EBV in Hodgkin Lymphoma (HL), HHV8 in Kaposi's sarcoma, HIV in some subtypes and HTLV1 in T-cell lymphomas. The possibilities to explore associations with these and other viruses are excellent in the SCALE material. We have in ongoing studies showed a correlation between HCV and risk of NHL, in particular of B-cell origin. The associations between EBV and HL have been further confirmed and risk estimates at various times after the mononucleosis infection have been defined. We have also seen an association between borrelia infection or history of tic bites and particularly mantle cell lymphomas. This original finding by us is now further explored. We have collected tissue blocks from all mantle cell lymphomas in the SCALE study and also from other lymphomas with borreliosis/positive borrelia serology in order to analyse for borrelia DNA in the tumour tissues (with Birgitta Sander, Huddinge).

Some of the previous associations between a certain exposure and a particular lymphoma subtype is further studied in depths with analyses of variations in DNA repair genes and immune function genes. We have also performed full scale genome wide association studies (GWAS) on specific subtypes. The studies for diffuse large B-cell lymphomas (DLBCL) are done in collaboration with a group in Lund, the studies on chronic lymphocytic leukaemia (CLL) in collaboration with Uppsala (Richard Rosenquist) and the Nordic CLL study group and the GWAS explorations and analyses of different SNPs in collaboration with among others (David Hunter, Harvard, Christine Scibola, UCSF Berkley and Liu Jianjun, Singapore).

HL is a particular type of lymphoma with very few tumour cells and abundant of apparently normal inflammatory cells around. We have explored the constitution of the microenvironment and patient traits, like polymorphisms in the ECP genes and selected exposures from the questionnaires.

Finally, we explore associations between questionnaire information of lifestyle, socio-economic status, family history and co-morbidities and survival in specific subgroups. We concentrate on the major subgroups, DLBCL, follicular lymphomas and HL. Clinical information including stage at presentation and treatment is collected in collaboration with the Lymphoma study groups in the two countries. For more uncommon subtypes, data are pooled with similar studies within InterLymph. This information is put in relation to analysis of tumour markers in serum and plasma, like immunoglobulin class levels, YKL-40 and cytokines like IL-6.

The above mentioned presently ongoing subprojects are only examples.

Members of the group in Uppsala during 2011:

Bengt Glimelius, M.D., Professor, Senior Physician
Christer Sundström, M.D., Professor, Senior Physician
Gunilla Enblad, M.D., Adjuct Professor, Senior Physician
Richard Rosenquist, professor, Senior Physician
Daniel Molin, Associate Professor, Senior Physician
Ingrid Glimelius, Ph.D., Junior Physician

Publications 2009-2011

1. Biggar RJ, Christiansen M, Rostgaard K, Ekström Smedby K, Adami H-O, Glimelius B, Hjalgrim H, Melbye M. Immunoglobulin subclass levels in patients with non-Hodgkin lymphoma. Int J Cancer 124; 2616-20 (2009).
2. Henrik Hjalgrim, Klaus Rostgaard, Paul CD Johnson, Annette Lake, Lesley Shield, Ann-Margaret Little, Karin Ekstrom-Smedby, Hans Olov Adami, Bengt Glimelius, Stephen Hamilton Dutoit, Eleanor Kane, G Malcolm Taylor, Alex McConnachie, Lars P Ryder, Christer Sundstrom, Paal Skytt Andersen, Ellen T Chang, Freda E Alexander, Mads Melbye, Ruth F Jarrett. HLA-A alleles and infectious mononucleosis suggest critical role for cytotoxic T-cell response in EBV-related Hodgkin lymphoma. PNAS 107:6400-5 (2010).
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Funding 2009 - 2011

Swedish Cancer Society	6,015,000 SEK
Vinnova	500,000 SEK
Other funding	614,860 SEK
The County Council, Uppsala, ALF-funding	1,252,000 SEK

Research Group 3: Caring sciences in oncology

Principal Investigator: Birgitta Johansson

Project 1: Screening and assessment of psychological distress among cancer patients

More than one in four patients with cancer experience psychological distress during their illness and should be offered psychological and/or medical treatment. Oncologists and nurses lack appropriate methods to correctly identify cancer patients' psychological concerns. Especially patients with high levels of depression remain undetected. Use of screening instruments is one way to improve identification of patients with psychological problems, but there is a need to develop appropriate screening routines in oncology practice. The project aims to develop and evaluate screening and assessment methods feasible for use in clinical routine. We have included about 650 cancer patients in two subsequent research projects during 2005-2010. Until now two manuscripts have been submitted for publication. The results revealed that screening

with the Hospital Anxiety and Depression Scale (HADS) is feasible for screening in routine care. A large proportion (>80%) of the patients agreed to participate in screening for anxiety- and depression symptoms. Patients with such symptoms reported an impaired health related quality of life. The symptoms decreased over time but were still frequent six months after the initial screening. Screening identifies patients with persistent symptoms and increases referral to clinical assessment and utilization of psychosocial support compared to standard care. The newly translated Swedish version of the commonly used Distress Thermometer (DT) has been evaluated using HADS as gold standard. The DT demonstrates a good overall accuracy compared to HADS total score ≥15 when choosing the cut-off score of ≥4 for screening in oncology settings with heterogeneous cancer patients. The DTs capacity to monitor changes over the six months period was also good.

Project 2: Internet based screening and stepped care for cancer patients with anxiety and depression symptoms – A randomized controlled trial

The conclusion from earlier randomized controlled trial is that future projects should include screening and target interventions for those at risk for significant and prolonged psychological distress. Development of internet based screening and psychosocial support would provide possibilities to offer cancer patients adequate interventions regardless of the distance to the clinical center. The aim of this project is to evaluate the effects of internet based interventions on anxiety, depression and health related quality of life in cancer patients with anxiety and depression symptoms, compared to standard care, and to evaluate the health-economic effects of the intervention. A further aim is to evaluate internet based screening of anxiety and depression in cancer patients. Patients with newly diagnosed breast, prostate or colorectal cancer and patients with recurrent breast or colorectal cancer will be included. Patients with anxiety or depression symptoms will be randomized to an internet based stepped care intervention or to standard care. Stratification will be made for stage of disease. The internet based stepped care intervention has been developed during 2011. Step 1 comprises web-based patient education including psycho-education and easy interventions strategies employed within Cognitive Behavioral Therapy (CBT). The goal is to increase patients' knowledge about the cancer and its treatments and to provide them with strategies to cope with psychological, physical and social concerns. Step 2 comprise conventional internet based CBT for common psychological concerns. The CBT is structured and manualized and include conventional treatment methods with homework and weekly contacts with the psychologist. The inclusion will start before summer 2012.

Project 3: Effects of a dietary intervention on acute gastrointestinal side effects and health-related quality of life: a randomized controlled trial in prostate cancer patients undergoing radiotherapy

Radiation induced gastrointestinal side effects including proctitis occurs in approximately 25% of patients undergoing curative radiotherapy for prostate cancer. Dietary interventions designed to reduce gastrointestinal side effects of pelvic radiotherapy

are scarce. Results from previous studies indicate that some forms of fibre- and lactose restricted diets may contribute to decrease acute gastrointestinal toxicity. However, these restricted diets were not part of any primary intervention or evaluated in a controlled manner. The aim of this study was to evaluate the effects of dietary advices on gastrointestinal side effects compared to standard care. The primary hypothesis was that the intervention may be effective in decreasing acute gastrointestinal side effects. Secondarily, it was hypothesized that by decreasing gastrointestinal side effects, the dietary intervention may possibly also indirectly affect other aspects of HRQOL. We have included 130 prostate cancer patients undergoing radiotherapy and randomised them to a dietary intervention or to standard care. The follow-up time was 24 months. Until now two manuscripts have been submitted for publication. The results suggest that the dietary intervention had no effect on gastrointestinal side effects or other aspects of HRQOL. During radiotherapy, the percentage of patients with bowel symptoms and bloated abdomen was lower in the intervention group compared to standard care, but the between-group differences were not statistically significant. We have also developed and evaluated the Gastrointestinal Side Effects Questionnaire (GISEQ). The GISEQ is capable of yielding consistent measures and adequately reflect the concept of gastrointestinal bother. The questionnaires are easy to use and can be quickly evaluated, making them useful as a nursing assessment tool in the clinical management of radiation-induced side effects.

A subsequent randomised controlled trial including prostate cancer with a more advanced stage of disease was initiated 2009. The patients receive radiotherapy including a larger part of the large intestine. Until now about 80 patients have been included at three hospitals in the the Uppsala-Örebro Region.

Members of the group in during 2011:

Birgitta Johansson, PhD/Senior Lecturer
Christina Persson, Med.dr./Dietician
Anna Pettersson, M. Sc./Ph.D. Student
Annika Thalén-Lindström, M. Sc/Ph.D. Student
Marina Forslund, Research Assistant
Eva Westergren, Research Assistant

Collaboration

Bengt Glimelius, Professor, Department of Oncology, Uppsala University
Ingela Turesson, Professor, Department of Oncology, Uppsala University
Peter Nygren, Professor, Department of Oncology, Uppsala University
Karin Nordin, Professor, Public health and caring sciences, Uppsala University
Claudia Lampic, Associate Professor, Department of Care Sciences, Karolinska Institutet
Regional Oncologic Center, Uppsala University Hospital
The Swedish Research Network in Cancer Care
Uppsala University Psychosocial Care Programme, U-CARE

Funding 2009 -2011

Uppsala University Hospital, ALF:	301,500 SEK
Uppsala University Medical faculty:	203,000 SEK
Uppsala-Örebro Regional Research Council:	500,000 SEK

Publications

1. Berglund, Å., Byström, P., Johansson, B., Nygren, P., Frödin, J-E., Pedersen, D., Letocha, H. and Glimelius, B. An explorative randomised phase II study on sequential chemotherapy in advanced upper gastrointestinal cancer. Medical Oncology, 2010, 27, 65-72.
2. Byström, P., Berglund, Å., Nygren P., Wernroth, L., Johansson, B., Larsson, A., Einarsson, R., Glimelius, B. An explorative study on the clinical utility of baseline and serial serum tumour marker measurements in advanced upper gastrointestinal cancer. Oncology Reports, 2010, 24, 1645-1652
3. Johansson, B., Fogelberg-Dahm, M., Wadensten, B. Evidence-based practice – the importance of education and leadership. Journal of Nursing Management, 2010, 18, 70-77
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Research Group 4: Cancer Pharmacology

Principal Investiator: Peter Nygren

This research group is devoted to preclinical identification of potentially new cancer drugs, mechanistic characterization of such drugs, development of predictive tests for drug activity and provision of preclinical data packages to support IND applications for early phase clinical trials. Several cancer types are of interest but there is specific focus on colorectal and pancreatic cancer.

By high-throughput screen (HTS) of a 1 200 compound library against tumour cells from patients with colorectal cancer, looking for better effect against these cells compared with cell lines and normal cells, the acridine derivative acriflavin was identified as a colorectal cancer specific drug, i e showing better activity against such tumour cells compared with those from ovarian cancer or chronic lymphocytic leukemia, a pat-

tern not observed for drugs established for clinical use in colorectal cancer. Mechanistic characterization based on gene expression profiling and analysis in the connectivity map indicated that acriflavin is a topoisomerase I and II inhibitor. Acriflavin or its analogs are concluded to be promising leads for drug development against colorectal cancer.

During 2011 compound libraries (diversity set Lopac, tyrosine kinase inhibitor set and Pharmacon-1600 with molecules already tested in the clinic) were screened for cytotoxic activity against colon cancer cell line models harbouring specific mutations in signal transduction pathways of relevance for colorectal cancer, ie Kras, Braf, Pi3K, Akt, Wnt and MLH. It was possible to identify molecules being selectively active against cells with mutations in these pathways which is promising since such mutation status is mostly associated with poor prognosis and/or poor response to established drugs. These hit molecules will now be further investigated in more advanced cancer models, ie tumour spheroids (see below) and in xenografts in vivo in rodents. This project is part of a collaboration with cancer research groups at the Rudbeck laboratory and funded by a grant from the Swedish Foundation for Strategic Research.

A new 3-D colon cancer tumour model was established in which cells from tumour cell lines are cultured on a new type of culture plates (Sciwax), allowing the cells to reproducibly form tumour spheroids. When characterizing these spheroids, the cells were found to express genes and cell surface proteins related to, eg hypoxia and stem cells indicating that the model adequately reflect the conditions in solid tumours. The hypoxic status of central cells was confirmed using a gfp reporter cell lines. Compared with monolayer cultures, the spheroids gradually turned more resistant by time. Thus, by selection spheroids of various age for experiments, models representing a range of drug resistance are obtained and could be used for further characterization of promising drugs from monalayer HTS. A new, simple and less laborious method to quantify cytotoxic effects in the spheroids was developed and is based on direct measurement of fluorescence from gfp marked cells in a culture incubator equipped with phase contrast imaging acquisition eqiupment (Incucyte).

Publications 2009 – 2011

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6. Laryea D, Gullbo J, Gustavsson M, Isaksson A, Larsson R, Nygren P. Characterisation in vitro of the cytotoxic properties of the benzimidazole fungicides benomyl and carbendazim in human tumour cell lines and primary cultures of patient tumour cells. Anti-Cancer Drugs 21: 33-42, 2010.

7. Von Heideman A, Berglund Å, Larsson R, Nygren P. Safety and efficacy of NAD depleting cancer drugs – results of a phase I clinical trial of CHS 828 and overview of published data. Cancer Chemother Pharmacol 65: 1165-72, 2010.

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10. Byström P, Berglund Å, Nygren P, Wernroth L Johansson B, Larsson A, Einarsson R, Glimelius B. An explorative study on the clinical utility of baseline and serial tumour marker measurements in advanced upper gastrointestinal cancer. Oncol Rep 24: 1645-52, 2010.

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Funding 2009 - 2011

The Swedish Foundation for Strategic Research: 1,200,000 SEK
The Uppsala/Örebro Regional Research Fund: 400,000 SEK

Dissertation 2011

Anne von Heideman, MD: Exploring Cancer Drugs in Vitro and in Vivo

DNA damage response (DDR) of epithelial, mesenchymal and melanocyte cell lineages in clinical setting of radiotherapy.

Principal Investigator: Ingela Turesson

Specific aims

1. To investigate DNA-damage response (DDR) for various cell-types in normal tissues.
2. In particular, we aim to quantify DDR to radiotherapy, in the dose range 0.05 to 4 Gy.
3. Our purpose is to establish dose-response relationships for various DDR markers and different cell types in the skin as a clinical model.

Background

DNA-damage response of normal tissue: Cells exposed to genotoxic insults, such as ionising radiation, activate a signalling cascade to repair the damaged DNA. In particular, DNA double strand breaks (DNA DSBs) are critical events. Proper genome maintenance, ensured by the cellular DNA-damage response (DDR) machinery is a prerequisite for normal development and prevention of premature aging and diverse devastating diseases including cancer. This issue is also of paramount relevance for most of the reversible and irreversible side effects caused by radiotherapy used for the majority of cancer diseases.

The importance of cellular DNA damage response (DDR) is stressed by numerous clinical and in vitro observations. Many results demonstrate that inherited or introduced functional defects in DDR pathways can result in an increased risk of tumour development. Furthermore, an exaggerated DDR can be observed during the early stages of tumour development, suggesting that these mechanisms can function as an important anti-cancer barrier.

New techniques and recently identified molecular markers have provided increasingly more detailed information about the cellular responses to DNA damage. It is now possible to detect and quantify specific effects even following induction of very low amounts of damage. Surrogate markers for DNA DSBs, such as γH2AX and 53BP1, provide detailed information about how these serious DNA lesions are handled in individual cells. Molecular markers for cellular proliferation and cell cycle checkpoints further extend the possibility to study the DDR course of events in cells, within their tissue, at clinically relevant damage levels.

Cell kill occurs through apoptosis, mitotic failure or autophagy, mainly implicated by activation of the ATM/p53 pathway in non-malignant tissues. An alternative outcome of this DDR pathway is complete DNA damage repair and a reversible arrest or otherwise permanent arrest. Choosing death or life is cellular and tissue dependent, but also related to the amount of DNA damage inflicted.

Senescence is a particular important response that can persist and might cause long term consequences of cytotoxic cancer treatments. ATM places a major role for senescence. Genotoxic stress that induces persistent DNA damage triggers a senescence-associated secretory phenotype (SASP) and suppresses p53 in normal cells. SASP changes the tissue microenvironment by secretion of various factors. Examples of such factors are cytokines and chemokines and their receptors, i.e interleukins 6 and 8 and CXCR2. These are activated by NFKβ and C/EBPβ.The cell surface IL-1a is an essential cell-autonomous regulator of the IL-6/Il-8 network through both NFKβ and C/EBPβ. Furthermore, persistent DNA-DSBs activate NFKβ and C/EBPβ, in addition to long-lasting activation of ATM.

Project description

Clinical assay: The accessibility of the skin makes it suitable for clinical research. In addition to visual inspection, multiple biopsies can be collected at different doses and time points from the same patient. Thereby all the well defined cell-lineages can be explored before, during and after genotoxic treatments, i. e. radiotherapy. Such a dose and spatiotemporally tissue sampling provides insights about interactions between cells from various cell lineages, i.e the communication between keratinocytes and melanocytes, and epithelial and mesenchymal cells, respectively. In comparison with deeper situated tissues of the body, another advantage is that the actual dose delivered of ionizing radiation (IR) to the skin at a particular location can be accurately determined. This prerequisite in combination with its structural properties of acutely and late responding cell populations make skin an excellent clinical model for studying radiation induced DNA damage response (DDR) in normal tissues.

Between 1993 and 2007 we have collected 2000 skin biopsies from 115 prostate and 45 breast cancer patients undergoing curative radiotherapy. The samples are 3mm in diameter, taken under local anaesthesia, immediately fixed in 5% formaldehyde and embedded in paraffin.

We are establishing dose-response relationships for various molecular markers involved in the DDR pathways. We use immunhistochemistry, immunofluorescence and imaging techniques, as well as qRT-PCR and in-situ hybridisation. We are able to explore a wide dose range of IR, 0.05 up to 4 Gy per fraction, repeated daily over 5 to 7 weeks. Unexposed control biopsies have been taken prior to the start of treatment.

DNA damage response (DDR) in epithelial cells*:* In cancer treatment, there is currently a focus upon which cell types that demonstrate hypersensitivity (HRS) at very low doses of genotoxic damage, i.e DNA-DSBs. We have established that low-dose hypersensitivity exists below dose fractions less than 0.3 Gy for various endpoints in the DNA damage response [16, 34, 36]: 1) Induction of DNA double-strand breaks determined with γH2AX and 53BP1. 2) Growth arrest in the basal cell layer determined by p21 and mitosis. 3) Apoptosis, although very infrequent, determined with γH2AX. 4) Loss of keratinocytes in the basal layer determined by manual counting of cell density. The low-dose hypersensitivity that was followed by induced radioresistance persists for all measured effects on epidermal keratinocytes over a radiotherapy course of 7 weeks, given with daily dose fractions in the range of 0.05 to 1.1 Gy.

DNA damage response (DDR) in mesenchymal cells. The dermis contains predominantly fibroblast and endothelial cells but also infiltrating immune cells like macrophages and leukocytes. Multipotent mesenchymal stem cells (MSCs) are present in the dermis of human adult skin, and are able to undergo multi-lineage differentiation. These cells express the stem cells markers Oct 4, Nanog and SOX2. Little is known about the functional role of these pluripotency markers in adult stem cells. The phenotype is $CD31^-$ and $CD45^+$, unlike to the CD 31^+ endothelial and CD 45^+ fibrocytes, respectively.

Comparison of 53BP1-foci between epithelial keratinocytes and endothelial cells: Immunfluorescence staining with 53BP1, DAPI and CD31 for identification of endothelial cells was evaluated by digital image analysis on the same tissue sections for an accurate comparison of the induction and recovery kinetics of DNA-DSBs between various cell types.

We have established that endothelial cells demonstrated 30 to 50% lower numbers of 53BP1 foci compared to keratinocytes in the same section. A very clear hypersensitivity (HRS) at low doses was for the first time also established for endothelial cells. There was a significantly faster elimination of 53BP1 foci in the endothelial cells compared to that for keratinocytes. This finding suggest that there are significant differences in induction and recovery kinetics for DSBs between acutely responding epithelium and late responding endothelial, in response to fractionated radiotherapy.

Quantification of microRNA: Micro RNA is also an entity involved in DDR to various genotoxic insults. MicroRNAs (miRNAs) are short non-protein-coding RNAs that negatively regulate gene expression, and accounts for 1 to 3% of genes in mammalian genome. Estimates suggest that ~30% of all protein-encoding RNAs are subject to regulation by multiple miRNAs. MiRNAs have been implicated in the regulation of proliferation, differentiation, and apoptosis. To understand the cell-specific functions of miRNAs in DDR, it is important to define their expression pattern. Several methods have been developed for that purpose. We have used quantitative real-time PCR, separately on microdissected epidermis and dermis from the same biopsies. Recently members of the miR-34 family (miR-34 a, b, c) have been reported to be direct targets of the tumor suppressor transcription factor p53. It has been proved that the miR-34 members regulate the molecular pathways leading to apoptosis and reversible or permanent cell cycle arrest.

We have established the relative expression levels of miR-34a in epidermis and dermis over a period of about 11 weeks and observed a significant increase of miR-34a both in epidermis and dermis over the 5 week's treatment period. The relative increases in (miR-34a) expression compared to unexposed samples were very similar for epidermis and dermis. After completion of treatment the miR-34a declined significantly in the epidermis, but the expression level in dermis remained almost constant.

DNA damage response (DDR) in cutaneous melanocytes. Pigmentation of the skin results from synthesis of melanin by the melanocytes. Hyperpigmentation of the skin is observed not only as tanning after sun exposure, but also occurs in many other clinical situations, i.e. as postinflammatory pigmentation and as a consequence of adrenal insufficiency.

In radiotherapy, hyperpigmentation as well as depigmentation are observed frequently and are often long-lasting in the skin-exposed area. To our knowledge, the mechanisms behind these two IR-induced phenomena have not yet been explored. A reasonable hypothesis is that at least some mechanisms are shared between the various kinds of stress, including genotoxic insults, inducing alterations in pigmentation of the skin. The mechanisms regulating UVR-induced pigmentation have been investigated most extensively, and novel regulating pathways have been clarified recently. In particular, the interaction between keratinocytes and melanocytes in the regulation of pigmentation through UVR-mediated autocrine and paracrine stimulation and/or repression of specific pathways involving cytokines and their receptors has been highlighted. This type of DNA-damage response caused by genotoxic stress, like UVR, may be helpful in getting insights into the mechanisms that regulate the IR response of melanocytes *in situ* and the subsequent pathological pigmentation induced by radiotherapy.

Quantification of molecular markers: Melanocytes can be easily distinguished through their morphological characteristics in the eosin-PAS staining. ΔNp63 is a cell cycle regulator known to be expressed in keratinocytes, but ΔNp63 is undetectable in normal melanocytes. Therefore, all the ΔNp63-negative cells are associated with the melanocyte lineage. The microphthalmia transcription factor (MITF) is a melanocytic nuclear protein critical for all stages of the melanocyte lineage. MITF is responsible for regulation of the major enzymes in the melanin synthesis. MITF is also critical for melanocyte survival by regulating the endogenous expression of the anti-apoptotic protein Bcl-2. The expression of the Bcl-2 is very much lower and undetectable in the keratinocytes compared to the melanocytes in the epidermis.

We have established that during radiotherapy the number of ΔNp63-negative cells stayed constant, suggesting that the number of melanocytes is preserved throughout fractionated radiotherapy over 6.5 weeks for dose fractions below 1.1 Gy. However, we demonstrate an increase in the number of MITF and Bcl-2 stained cells in response to sub-therapeutic doses of radiation. Repeated dose fractions above 0.05 Gy trigger the melanocytes to express higher levels of the proteins MITF and Bcl-2. An undifferentiated subset of MITF-negative melanocytes showed a low-dose hypersensitivity reduction, in correspondence to the increase found in MITF stained cells. Altogether, our findings are compatible with an induction of radioresistance in melanocytes, and suggest that a subpopulation of MITF negative undifferentiated cells does exist in unirradiated interfollicular epidermis. Upon low doses of IR this subset upregulates MITF and Bcl-2. This study support that the DNA damage response of melanocytes to ionizing and ultraviolet radiation shares common main pathways.

Members of the research group in Uppsala:

Ingela Turesson, Professor, Consultant
Fredrik Qvarnström, Ph.D., Scientist
Martin Simonsson, Ph.D., Scientist
Ulf Thunberg, Ph.D, Scientist
Maj-Lis Book, BMA

Members of the research group in Gothenburg:

Jan Nyman, Ass. Professor, Consultant
Ingegerd Hermansson, Research Assistant
Karl-Axel Johansson, Ph.D., Physicist

Publications

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Funding

Swedish Cancer Society	600 000 SEK
ALF	325 000 SEK
SSM	250 000 SEK

Section of Biomedical Radiation Science

Research Group I: Protein-protein interactions

Principal Investigator: Karl Andersson

This group develops novel methods for the detection of how proteins interact with living cells. The group also applies the methods on tumor biology to better understand the biological consequences of protein interactions. All research is conducted in close collaboration with the spin-out company which commercializes the innovations and findings of the group.

Members of the group during 2011

Karl Andersson, Associate Professor, Group Leader
Hanna Björkelund, Ph.D. Student

Publications 2009-2011

1. Barta P, Malmberg J, Melicharova L, Strandgård J, Orlova A, Tolmachev V, Laznicek M, Andersson K. Protein interactions with HER-family receptors can have different characteristics depending on the hosting cell line. Int J Oncol. 2011 Dec 19. doi: 10.3892/ijo.2011.1307.
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Funding

Ridgeview Instruments AB

Project 1: Deciphering the EGF-EGFR interaction mechanism

Members of the group:

Karl Andersson
Hanna Björkelund
Lars Gedda

By use of advanced real-time interaction analysis, novel findings about the EGF-EGFR signaling system are presented. We have previously identified the strong dependency of choice of cell-line and have illustrated the impact of tyrosine kinase inhibitors on the EGF-EGFR interaction.

Research Group II: Oncological Nuclide Therapy: Receptor Expression and Clinical Studies

Principal Investigator: Jörgen Carlsson

Protein tyrosine kinase, PTK, receptor (e.g. EGFR and HER2) targeted tumor therapy, without radioactivity, have so far shown to be cytostatic and not cell-killing. Furthermore, resistance to such therapy has been reported. Thus, there is a need for improved therapy and that can hopefully be achieved by the use of radiolabeled targeting agents.

We focus here, to a large extent, on the appearance of EGFR and HER2 targeted therapy resistance in colorectal and breast cancer. The receptor expression can, in these cases, be used for targeted therapy delivering toxic beta- or alpha emitting radionuclides instead of using the non-radioactive antibodies trastuzumab (binding HER2 in breast cancer) and cetuximab (binding EGFR in colorectal cancer). Various types of antibodies, antibody fragments, affibody molecules and peptides are suitable for delivery of the radionuclides. The radionuclides cause extensive cell kill and the killing mechanism is, when the radiation dose is high, not dependent on disturbances in cell signaling. Analysis of tumor cell sensitivity when exposed to the radioactive targeting

agents is made. Molecular analysis of DNA damage and DNA repair is planned to be included.

Patient samples from primary tumors and various metastases from colorectal and breast cancer are analyzed regarding the expression of receptors. Data on expression during ongoing therapy is lacking but is urgently needed.

An imaging agent (ABY-025 labeled with 111In or 68Ga) for analysis of HER2 in primary breast cancers and corresponding metastases is presently used in a clinical study using PET/CT, SPECT/CT and IHC. Seven patients have been analysed since the study recently started. The results indicate that in most cases when the primary tumor has been HER2 positive at the time of operation of the primary tumor, then also the later appearing metastases are also HER2 positive. However, there are exceptions. The study will go on including as many patients as possible until the end of 2014.

Members of the group and collaboration partners (alphabetic order)

Adams Gregory, Fox Chase Cancer Center, Philadelphia, USA
Carlsson Jörgen, Prof., Biomedical Radiation Sciences, Uppsala University
Feldwish Joachim, PhD, Affibody AB, Stockholm
Frejd Fredrik, Assoc. Prof., Affibody AB, Stockholm and Uppsala University
Glimelius Bengt, Prof., Oncology, Uppsala University
Lennartsson Johan, Assoc. Prof., Ludwig Institute for Cancer Research, Uppsala
Lindman Henrik, MD, Oncology, Uppsala University Hospital
Micke Patrick, Assoc. Prof., Pathology, Uppsala University Hospital
Orlova Anna, Assoc. Prof., Biomedical Radiation Sciences, Uppsala University
Sandberg Dan, MD, Nuclear Medicine, Uppsala University Hospital
Stenerlöw Bo, Prof., Biomedical Radiation Sciences, Uppsala University
Ståhl Stefan, Prof., Biotechnology, Royal Institute of Technology, Stockholm
Sörensen Jens, Assoc. Prof. Nuclear Medicine, Uppsala University Hospital
Tolmachev Vladimir, Assoc. Prof., Biomedical Radiation Sciences, Uppsala University
Velikyan Irina, Assoc. Prof. Biomedical Radiation Sciences, Uppsala University
Wei Qichun, PhD, Oncology, guest scientist, Hangzhou, China
Wennborg Anders, MD, Affibody AB, Stockholm

Publications 2009-2011

1. Fondell A, Edwards K, Ickenstein LM, Sjöberg S, Carlsson J & Gedda L: Nuclisome: A novel concept for radionuclide therapy using targeting liposomes. Eur J Nucl Med Mol Imaging. 37, 114-123, 2010.
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Funding

Swedish Cancer Society, Annual grant during 2012-2014: 1.000.000 SEK/year

Research Group III: Tumour-targeted therapies

Principal Investigator: Lars Gedda

It is widely recognized that current cancer therapy strategies require significant improvements and new treatment concepts are urgently needed to shift cancer from an often fatal to a more manageable disease. The major obstacle for traditional cancer therapies is their relative low specificity towards tumour cells. One way to circumvent this problem is the use of tissue-targeted radiotherapy by means of radionuclides. This approach is still largely experimental and its success depends on the ability of radioactive isotopes or radionuclide conjugates to preferentially target tumour cells. Agents with better tumour specificity can be produced, as complement or replacement of earlier used methods, by taking advantage of the pheno- and genotypic changes characterising the transformation from normal to malignant cells. The transformation depends on a number of altered genes of which only some give rise to changes suitable as so called targets. These targets should preferentially be located on the surface of the cell membrane to be recognized by a targeting substance. A common phenotypic alteration in tumour cells is increased expression of membrane receptors. This could be a result of gene amplification or over-expression of the protein from the normal gene. Epidermal growth factor receptor (EGFR) and HER2 are such over-expressed receptors found in several cancers, for example colorectal and breast. In these cases EGFR and HER2 are suitable targets.

Members of the group during 2011

Sara Ahlgren, Post-Doc
Amelie Fondell, Post-Doc
Lars Gedda, Associate Professor
Lina Ekerljung, Ph.D. Student
Lovisa Göstring, Ph.D. Student

Publications 2009-2011

1. Piskounova S, Hulsart-Billström G, Gedda L, Bergman K, Engstrand T, Larsson S, Hillborn J and Bowden T. The effect of pre-incubation of chemically crosslinked injectable hyaluronan-based hydrogels loaded with rhBMP-2 on ectopic bone formation. Submitted, 2011.
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Dissertations 2011

Lovisa Göstring
Amelie Fondell
Lina Ekerljung

Funding

Swedish Cancer Society, Annual Grant	500.000 SEK
SOEB, Stiftelsen Olle Enqvist Byggmästare	600.000 SEK

Project 1: Two-Step Targeting for Effective Nuclide Therapy

Members of the group:

Sara Ahlgren, Ph.D. Student.
Amelie Fondell, Ph.D. Student
Lars Gedda, Ph.D., Associate Professor

Calculations have shown that treatment of cancer with radionuclide therapy would be much more efficient if the nuclide can be localized within the cell nucleus of the tumour cell rather than to the cell membrane or the cytoplasm, as in most cases today. This is especially important for Auger-electron emitting nuclides where the majority of energy is deposited very close to the site of decay. The aim of the project is to increase the possibility to treat spread tumour cells and metastases with radionuclide therapy. The intention is to deliver radionuclides, primarily Auger-electron emitters, to these tumour cells using targeted liposomes where targeting is directed against known target structures on tumour cells in a first step. The radionuclides should be released intracellularly and have the property to target chromosomal DNA in a second step. The concept is of general interest for tumours that shade single cells and give rise to metastases.

In our approach to radionuclide therapy, we want to combine the benefits of tumour cell targeting and the Auger-effect by attaching the Auger-electron emitting nuclide to DNA-intercalators in order to guide the radionuclide to the site of action, the cell nucleus. Daunorubicin and doxorubicin are two cytotoxic drugs that are successfully used for treatment of Kaposi's sarcoma, when incorporated into liposomes. These anthracyclines have shown to have the special requirements that is needed to avoid leakage from liposomes during transportation and yet can reach the cell nucleus after internalization. These properties were sought for during development of suitable DNA-inercalators for this project and within collaborators group derivatives of antharcy-clines able to retain DNA-binding after radiolabelling were finally successfully synthe-sized. The properties of the derivatives were adapted to minimize leakage from lipo-somes and non-specific binding to other structures than DNA.

The ^{125}I-labelled DNA intercalator was specifically delivered using targeted liposomes to circulating tumour cells in blood *ex vivo* and show tumour accumulation in HER2 expressing tumour cells *in vivo*. Efficacy studies showed remarkable effects of ^{125}I-labelled DNA intercalator when specifically delivered with targeting liposomes against HER2. Tumour bearing mice had significantly increased survival after treatment with HER2-targeting liposomes loaded with the ^{125}I-labelled DNA intercalator and for the group receiving highest dose half of the mice were tumour free after termination of study, still without any indication of normal tissue toxicity.

Project 2: Biological and Preclinical Studies of Receptor-Specific Targeting Agents for Tumour Treatment

Members of the group:

Lina Ekerljung, Ph.D. Student
Lovisa Göstring, Ph.D. Student
Lars Gedda, Ph.D., Associate Professor

The aim of this project is to develop methods for receptor-specific targeting for tumour treatment. The targeting agents could either affect signal transduction *per se*, preventing tumour growth, or their growth inhibition could be enhanced by delivery of alpha or beta-emitting radionuclides. Targeting agents with specificity towards the EGFR-family is in focus. Tumour associated over expression of these receptors, espe-cially EGFR and HER2, is part of the oncogenesis and high expression usually signifies high malignancy.

Different EGFR, HER2 and HER3-specific targeting agents are studied regarding their affect on proliferation, migration and apoptosis. Further, changed autophosphoryla-tion of the receptors as well as induced changes in the signal transduction (Erk1/2, Akt and PLC-gamma related signal pathways) are studied. Also possibilities for biological effect modification after administration of natural ligands and/or tyrosine kinase inhibitors are considered. An ideal situation is to have a tumour-targeting agent that in

addition to delivering radionuclides also modulates the intracellular signalling to increase radiosensitivity.

In vitro effects of novel HER2-binding affibody molecules on HER2 expressing cultured human tumour cells have been investigated. Dimer affibody molecules generally have much larger effects than the monomers. This is especially interesting when the dimmer and monomer bind the same epitope. While the dimer strongly phosphorylates HER2, the monomer has almost no effect on the receptor on either of the studied cell lines. One can speculate if the dimer molecules are able to simultaneously bind two receptors, and maybe even initialize receptor dimerization – and thereby result in autophosphorylation. Further, new kinds of bifunctional affibody molecules are studied, binding two different targets. This can be accomplished by linking an affibody that targets one receptor, HER2, with another one that targets a different receptor, EGFR. Such bifunctional molecule can be advantageous in sense of increased sensitivity and specificity as well as preventing or inducing dimerization.

Research Group IV: Head and Neck Tumour Targeting

Principal Investigator: Marika Nestor

Cancer cells differ from normal cells, for example by different protein expressions on the cell surface. In targeted radionuclide therapy, we take advantage of these differences, by using e.g. antibodies, antibody derivatives, or peptides to target these structures, and by arming these “missiles” with radionuclides. By delivering the radioactivity directly to the tumor cells, small metastases and disseminated tumor cells can be found and killed. By using radionuclides as warheads, multidrug resistance can be avoided, and the need to target every single tumor cell is reduced. There is great potential for targeted radionuclide therapy in the treatment of head and neck cancer. In this disease there is a vast need for a systemic treatment that is effective in locating or treating metastases at distant sites and minimal residual disease at the local and regional levels. Furthermore, head and neck cancer is intrinsically radiosensitive, and is therefore especially suitable for radiotherapy.

In the Head and Neck Tumor Targeting Group, we are studying several steps in the targeting process. Different protein structures, targeting molecules and radionuclides are assessed, and the different properties of the constructed radioconjugates are evaluated. By creating and evaluating novel tumor seeking radioconjugates, we hope to provide more sensitive and specific methods for identifying and treating head and neck cancer, and hopefully help improve long-term survival rates for this patient group in the future.

Members of the group during 2011:

Nestor Marika, Ph.D., Group Leader
Sandström Karl, M.D., Ph.D. student (dissertation Sept 2011)
Kareem Heewa, M.D., Licentiate student (dissertationMay 2011)
Spiegelberg Diana, Ph.D. Student
Haylock Anna-Karin, M.D., Ph.D. Student

Publications 2009-2011

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Dissertations 2011

Karl Sandström: Radioimmunodiagnosis of Head and Neck Squamous Cell Carcinoma (2011-09-16)

Funding:

SSMF (Svenska Sällskapet för Medicinsk Forskning)	528,000 SEK
Uppsala University, Department of Radiology, Oncology and Radiation Science	150,000 SEK
Inga-Britt och Arne Lundbergs Forskningsstiftelse	600.000 SEK
Swedish Cancer Society, Two Year Grant	450,000 SEK
Uppsala University, Med. Faculty, Two Year Grant	240,000 SEK

Project 1: Characterization of suitable target antigens

Diana Spiegelberg
Marika Nestor

We assess the amount of antigen expression in patient tumour tissue and cultured tumour cells using e.g. flow cytometry and radioimmunoassays. Current target antigens of interest in or research group are cell surface bound proteins such as CD44 and its isoforms, EGFR and HER2. CD44 is a multistructural and multifunctional cell surface molecule involved in cell proliferation, cell differentiation, cell migration, angiogenesis, as well as in signaling for cell survival. It has just recently come in focus in the field of tumour targeting, since it is one of the most common markers used for isolation of cancer stem-like cells. This makes it a highly interesting candidate for selective cancer targeting. CD44v6, an isoform of the membrane-associated glycoprotein CD44, is expressed in many types of human cancer, including head & neck squamous cell carcinoma. The difference in CD44v6-expression between healthy and malignant cells makes the CD44v6 antigen an attractive target for radionuclide tumour targeting.

Project 2: Development and characterization of suitable targeting molecules

Karl Sandström
Anna-Karin Haylock
Diana Spiegelberg
Heewa Kareem
Marika Nestor

Suitable targeting molecules towards the most promising antigens for targeted diagnostics and therapy of head- and neck cancer are developed and characterized for potential in radionuclide tumour targeting in this project. Novel targeting molecules and radioconjugates, using antibodies, antibody fragments, Affibody molecules or natural ligands, are selected, radiolabelled, and characterized in cultured tumour cells. In combination with targeting vectors, different radionuclides are assessed for suitable targeting applications, e.g. ^{111}In and ^{124}I for imaging and ^{177}Lu, ^{131}I, and ^{211}At for therapy. The best conjugates are then evaluated for diagnostic or therapeutic purposes in tumour bearing mice.

Research Group V: Radionuclide Molecular Imaging

Principal Investigator: Anna Orlova

Members of the group during 2011

Anna Orlova, Associate professor, group leader
Jennie Malmberg, PhD Student.
Zohreh Varasteh, PhD Student

Publications 2009-2011

1. Malmberg J, Sundström M, Wester K, Tolmachev V, Orlova A. Comparative biodistribution of imaging agents for in vivo molecular profiling of disseminated prostate cancer in mice bearing prostate cancer xenografts: focus on 111In- and 125I-labeled anti-HER2 humanized monoclonal trastuzumab and ABY-025 affibody. *Nucl Med Biol*, 2011; 38:1093-1102.
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Funding 2009 – 2011

Swedish Cancer Society (Cancerfonden)	450,000 SEK
Swedish Research Council (Vetenskaprådet)	900,000 SEK

Project 1: Novel radionuclide imaging methods for molecular profiling of prostate cancer – a way for personalized therapy

Anna Orlova
Jennie Malmberg
Zohreh Varasteh

Molecular imaging techniques might improve treatment of prostate cancer by better staging, personalising patient management and/or evaluation of early response to therapy.

Correct staging of prostate cancer is crucial for patient management. Conventional anatomical imaging modalities (CT and MRI) tend to understage prostate cancer due to poor sensitivity to soft tissue metastases. The false-negative results contribute to a significant number of patients with extraprostatic disease undergoing non-curative surgery. The use of ^{18}F-FDG for imaging of malignant tumours by positron emission tomography (PET or PET/CT) provides excellent sensitivity in many cancers. However, the utility of this method for prostate cancer is limited because glucose utilisation is low and FDG uptake is insufficient in up to 81% of primary prostate cancers. Other metabolic PET tracers have shown some promising results in the clinic but have low selectivity.

An alternative approach to visualisation of prostate cancer is radionuclide targeting of the prostate tumour markers, e.g. **PSMA** or **GPRP**. Expression of prostate tumour markers is low in normal prostate tissue, but is increased in prostate cancer and correlates with prostate cancer progression. Targeting of PSMA is utilised for imaging of prostate cancer using ^{111}In-labelled ProstaScint (capromab pendetide), which is approved for clinical use by FDA. Still, imaging of PSMA can be improved by both optimizing radionuclide for labelling and by optimizing a tracer format (e.g. the use of small targeting proteins instead of bulky IgG).

Alternative treatments for of androgen-independent prostate cancer could be targeting against **tyrosine kinase receptor**s family that are often overexpressed in advanced prostate cancers. This approach requires confirmation of the presence of receptors in cancer lesions and therapy monitoring for early response. This could be done by radionuclide diagnostic imaging.

The use of antibodies for diagnostics and therapy has a serious limitation. Antibodies are relatively bulky (170 kDa), which complicates their extravasation and penetration into malignant tissue. Blood clearance is also slow, which causes high background during imaging and high unspecific whole-body irradiation during therapy. Smaller antibody fragments provide better tumour-to-normal tissues radioactivity ratio than intact antibodies and size reduction is a proved approach to improvement of targeting properties of radionuclide probes for tumour imaging and treatment. The size of the immunoglobulin based tracers can only be reduced to 25 kDa for scFv or 15 kDa for domain antibodies. Affibody molecules are only half the size of the domain antibodies. ***Affibody molecules*** are three helical domain proteins of approximately 58 amino acids having a structure deriving from one domain of staphylococcal protein A. Our group participated in selection, evaluation and pre-clinical characterisation of Affibody molecules binding to different molecular targets relevant to prostate cancer, e.g. HER2,

EGFR, IGF1R. Preclinical data suggest that the affibody ligand provides at least one order of magnitude better imaging contrast (tumour-to-organ ratios) in murine xenograft model, than the best antibody fragments. The comparison of imaging properties of anti-HER2 ligands as full length antibody trastuzumab and Affibody molecule ABY-025 demonstrated that high contrast image with Affibody molecule can be obtained in much shorter time after injection of radiolabeled ligand probe. Furthermore, clinical data show that ^{111}In- and ^{68}Ga-labelled anti-HER2 Affibody molecule may be used for imaging of HER2-expressing metastases cancer patients.

Project 2: Development of *in vitro* predictive assay for renal and hepatic uptake of conjugates for radionuclide molecular targeting.

Anna Orlova
Jennie Malmberg
Zohreh Varasteh

Radionuclide-based diagnostic and therapy are rapidly developing areas of medicine, particularly in oncology. A promising direction in nuclear medicine is the development of radionuclide molecular targeting (RMT) agents detecting the presence of molecular biomarkers on primary or metastatic lesions. Information of molecular biomarkers can be utilized later for selection of patients for biomarker-specific therapy, e.g. immunotherapy. The use of RMT agents, which are labelled with cytotoxic nuclides (e.g. beta- or alpha-emitters) would permit direct radionuclide therapy of tumours. Potent imaging and/or therapeutic agent in nuclear medicine must have high and stable specific uptake in lesion (primary tumours or metastasis) and quick clearance from healthy organs. Imaging RMT agents with such features would provide better imaging contrast and, consequently, better imaging sensitivity. Therapeutic RMT agents would decrease radiation burden to patients and provide broader therapeutic window.

Biodistribution properties of an RMT agent depends on many factors, e.g. nature of targeting protein, its specificity to the target, its charge and lipophilicity and a labelling method, and cannot be predicted *a priori*. Therefore developing of RMT includes biodistribution studies in laboratory animals. Prediction of a high liver and kidney uptake of an RMT agent would enable exclude this agent from consideration at early stage. **The goal of this project is the development of *in vitro* assays for prediction of liver and kidney uptake of potential RMT agents.** Achieving of this goal would ***replace*** the animal studies by *in vitro* assay and ***reduce*** a number of animals, which are sacrificed for development of RMT tracers.

For the moment, there are a large number of *in vitro* assays, which can predict tumour-targeting properties of RMT conjugates (affinity, specificity, cellular processing and retention). Such assays have been widely used in our research concerning development of targeting conjugates. At the same time, *in vitro* assays for prediction of hepatic and renal assays are missing. Analysis of the literature indicates that development of such assays is feasible. For example, opossum kidney (OK) cell line derived for proximal tubule has been used for elucidation of renal uptake mechanism for ^{111}In-labelled octreotide. A number of studies on physiology, toxicology and pharmacology utilised immortal hepatoma cell lines, as *in vitro* models. These studies show that

molecular mediators of uptake (scavenger receptors, transporters, channels) remained to be expressed in renal proximal tubule- and hepatocyte-originating cell lines *in vitro*. This creates pre-conditions for development of *in vitro* assays for uptake and retention of radiolabelled RMT conjugates in liver and kidneys.

Research Group VI: DNA Damage and Repair

Principal Investigator: Bo Stenerlöw

When a cell is exposed to ionizing radiation, or to other DNA damaging agents such as cytotoxic drugs, DNA double-strand breaks (DSBs) in the chromosomal DNA are critical. The cellular repair capacity is the major parameter affecting cell survival after exposure to ionizing radiation, and incorrectly repaired or unrepaired DSBs might lead to chromosomal aberrations that are lethal for the cell. The last decades research on DNA repair have lead to many novel insights in cellular repair but several important aspects of radiation-induced DSB are still unresolved, *e.g.* it is still unclear how primary damage is detected, how this initiates signal transduction and activate DNA repair proteins and how DNA repair mechanisms are affected by radiation quality (*i.e.* clustered damaged DNA sites generated by high LET radiation). A thorough understanding of the mechanisms for radiation-induced DNA damage and regulation of the DNA repair systems may have important implications for radiotherapy and the general aim is to provide novel knowledge about cellular processes that have the potential to increase the efficacy of radiation treatment of tumors.

Members of the group during 2011

Ann-Sofie Gustafsson, Ph.D. student
Sara Häggblad Sahlberg, Ph.D. student
Diana Spiegelberg, Ph.D. student
Bo Stenerlöw, Professor, group leader

Publications 2009-2011

1. Ståhl, S.V., Fung, E., Adams, C., Lengqvist, J., Mörk, B., **Stenerlöw, B**., Lewensohn, R., Lehtiö, J., Zubarev, R. and Viktorsson, K., Proteomics and pathway analysis identifies JNK-signaling as critical for High-LET radiation-induced apoptosis in non-small lung cancer cells. *Molecular and Cellular. Proteomics*, **8**, 1117-1129 (2009).
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4. Waldeland, E., Hole, E. A., **Stenerlöw, B.**, Grusell, E., Sagstuen, E. and Malinen, E., Radical formation in lithium formate EPR dosimeters after irradiation with protons and nitrogen ions. *Radiation Research,* **174**, 251-257 (2010).
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6. Häggblad Sahlberg, S., Spiegelberg, D., Lennartsson, J., Nygren, P., Glimelius, B. and **Stenerlöw, B,** The effect of a dimeric Affibody molecule (ZEGFR:1907)2 targeting EGFR in combination with radiation in colon cancer cell lines. *International Journal of Oncology*, **40**, 176-184 (2011).

Funding 2009 - 2011

The Swedish Cancer Society (per year)	850.000 SEK
Swedish Radiation Safety Authority (SSM)	250.000 SEK

Project 1: Repair of clustered damaged sites in DNA

Ann-Sofie Gustafsson
Bo Stenerlöw

Recent and planned radiation therapy modalities use high-LET (LET: linear energy transfer) radiation, in terms of accelerated ions or radioactive nuclides emitting α-particles or Auger-electrons in order to effectively treat malignant tumors: a relatively low dose of high-LET radiation has a high cell killing efficiency. However, the number generated DSB is similar to that induced by conventional gamma radiation and this strongly implicate that DSB is a highly heterogeneous type of DNA damage: the dense deposition of energy from high-LET radiation results in both complex DSBs (*i.e.* DSBs associated with additional DSBs, SSBs or base lesions within 20-30 bp) and clustered DNA breaks within 1-2 Mbp of chromatin. It is evident that clustered lesions 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.

Project 2: Regulation of non-homologous end-joining

Ann-Sofie Gustafsson
Bo Stenerlöw

The main repair pathway of radiation-induced DSBs is non-homologous end-joining (NHEJ). The rapid binding of broken DNA ends is a key event in repair of DSB and cells defective in NHEJ are extremely sensitive to ionizing radiation. The function of this initial step and the following protein interactions may largely affect the outcome of repair. Although the major protein complexes involved in NHEJ 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 NHEJ proteins interact and how they may regulate other repair pathways and cellular processes.

Project 3: EGFR family and downstream signaling

Sara Häggblad Sahlberg
Diana Spiegelberg
Bo Stenerlöw

The epidermal growth factor receptor EGFR (erbB1) mediates resistance of tumour cells to both chemo- and radiotherapy when mutated or overexpressed. Molecular blockage of EGFR signaling is an attractive therapeutic strategy for enhancing the cytotoxic effects of radiotherapy. EGFR-signaling and function activated by ionising radiation has been linked to essential mechanisms of DNA-DSB repair induced by radiation, but still there is only limited information how these interactions are regulated. Regarding HER2 there is no information about direct interactions with the repair machinery. The MAPK and Akt pathways are important regulators of the EGFR-family response and following radiation exposure, activation of MAPK and Akt promotes proliferation and survival. We here study the function of Akt in DNA damage response in relation to EGFR, HER2 and other receptors, including investigation of triggering signals of the response (e.g. DNA damage and/or membrane/receptor activation).

Research Group VII: Radionuclide molecular imaging of receptor tyrosine kinases expression in cancer

Principal Investigator: Vladimir Tolmachev

Current approach to improve therapy of disseminated cancer is based on molecular recognition of proteins aberrantly expressed in malignant cells (molecular targets). Radionuclide molecular imaging of tumour-associated targets can be used for patient stratification, finding patients who would most likely benefit from particular targeting therapy due to sufficient target expression. This would make cancer treatment more personalized. The goal of our research is to improve sensitivity and specificity of radio-

nuclide molecular imaging. The focus is on an optimal imaging agent format, affinity and labelling strategy. Radiolabelled conjugates with appropriate properties are evaluated for radionuclide therapy.

During last years, the investigations are focused on Affibody molecules, which is a new class of small phage-display selected proteins. Affibody molecules utilises a pre-organised peptide structure, Affibody scaffold, which provides exceptionally high affinity of antigen binding. They can be selected for specific binding to a variety of targets (e.g. receptors and antigens). Their small size ensures quick blood clearance and good tumour penetration. Receptor tyrosine kinases, which are often overexpressed in cancer and are used as molecular targets for therapy, are the main class of molecular targets in our research.

Members of the group during 2011

Vladimir Tolmachev, Associate professor, group leader
Mohammed Altai, PhD Student
Irina Velikyan, PhD, guest researcher
Joachim Feldwisch, PhD, guest researcher

Publications 2009-2011

1. Tolmachev V, Mume E, Sjöberg S, Frejd FY, Orlova A. Influence of valency and labelling chemistry on in vivo targeting using radioiodinated HER2-binding *Eur J Nucl Med Molecular Imaging,* 2009;36:692-701. IF: 5.036

2. Tolmachev V, Friedman M, Sandström M, Eriksson TJ, Rosik D, Hodik M, Ståhl S, Frejd FY, Orlova A. Affibody molecules for EGFR targeting *in vivo*: aspects of dimerization and labeling chemistry. *Journal of Nuclear Medicine,* 2009; 50:274-283. IF 7.002

3. Orlova A*,* Wållberg H, Stone-Elander S, Tolmachev V. On the selection of a tracer for PET imaging of HER2-expressing tumors: direct comparison of ^{124}I-labelled Affibody molecule and trastuzumab in a murine xenograft model. *Journal of Nuclear Medicine*, 2009; 50: 417-425. IF 7.002

4. Ekblad T, Tolmachev V, Orlova A, Lendel C, Abrahmsén L, Eriksson Karlström A. Synthesis and chemoselective intramolecular cross-linking of a HER2-binding Affibody. *Biopolymers-Peptide Science, 2009; 92:116-23.* IF: 2.572

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6. Ekblad T, Orlova A, Feldwisch J, Wennborg A, Eriksson Karlström A, Tolmachev V. Positioning of (99m)Tc-chelators influences radiolabeling, stability and biodistribution of Affibody molecules. *Bioorganic & Medicinal Chemistry Letters 2009; 19: 3912-3914* IF: 2.661

7. Tolmachev V, Wållberg H, Andersson K, Lundqvist H, Orlova A. The influence of Bz-DOTA and CHX-A''-DTPA on the biodistribution of ABD-fused anti-HER2 Affibody molecules: implications for ^{114m}In-mediated targeting therapy. *Eur J Nucl Med Molecular Imaging, 2009; 36:1460-8.* IF: 5.036

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11. Tolmachev V, Rosik D, Sjöberg A, Sandström M, Wållberg H, Hansson M, Wennborg *A,* Orlova A. Imaging of EGFR expression in murine xenografts using site-specifically labelled anti-EGFR [^{111}In-MMA-Cys]Z_{2377} Affibody molecule: aspect of injected amount. *Eur J Nucl Med Mol Imaging,* 2010; 37:613-22. IF: 5.036

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Funding 2009 - 2011

Swedish Research Council (Vetenskapsrådet) Personal research position,(6 year grant)	3,000,000 SEK
Swedish Research Council (Vetenskapsrådet): (3 year research grant)	1,050,000 SEK
Swedish Cancer Society (Cancerfonden) (3 year grant)	2,400,000 SEK
Vice-Chancellor of Uppsala University: 3 year grant)	1,500,000 SEK

Project 1: A new method for characterisation and treatment of HER2-expressing cancer. Radionuclide tumour targeting using new Affibody molecules

Recently, we have developed a new class of small proteins, Affibody molecules Z_{HER2}, which bind selectively to cancer cells expressing HER2 and enables to visualize tumour xenografts in mice. Pilot clinical data using radiolabelled anti-HER2 Affibody tracer has confirmed its utility for radionuclide imaging in cancer patients. The goals of the proposed research are:

- To develop radiolabelled Z_{HER2}-based tumour-targeting conjugates for *in vivo* visualisation and quantification of expression of HER2 in breast, ovarian, prostate, urinary bladder and other cancers.
- To develop Z_{HER2}-based tumour-targeting conjugates for radionuclide therapy of HER2 expressing tumours.
- To obtain knowledge and experience for design of Affibody molecules-based agents targeting other tumour-associated antigens.
- To evaluate if radionuclide imaging of HER2 expression in breast, ovarian, urinary bladder and other cancers can provide valuable diagnostic information for patient management in relation to immunohistochemical and FISH based HER2 determinations in biopsies and surgical specimen. Clinical studies.

Project 2. Affibody molecules: A new class of tracers for molecular imaging. Optimisation of targeting properties of anti-tumour Affibody molecules

The goal of this project is to further improve sensitivity of radionuclide imaging using the Affibody molecules by optimising their biodistribution and minimizing uptake in non-specific compartments, especially excretory organs. An emphasis is on incorporation of peptide-based chelators for radionuclide ^{99m}Tc into the sequence of Affibody molecules and modification of biodistribution by variation of chelator composition.

In the case of success, this would enable to develop tumour-targeting Affibody molecules with an improved sensitivity and pre-determined biological properties. The use of a generator-produced ^{99m}Tc would reduce costs of imaging procedures. The information obtained within this project could be used for radionuclide labelling of other small scaffold affinity proteins for tumour targeting, facilitating the application of these proteins in medicine and biology.

Undergraduate Teaching

The Department of Radiology, Oncology and Radiation Science is involved in undergraduate teaching of medical students, radiographers, technicians, and engineers.

Section of Radiology

Within the Section of Radiology lectures and seminars are given in the following subjects within the medical education program:

Subject	**Study Points**
Professional Development	0.36
Circulation and Respiration	0.09
Communication, Nerves and Psyche	0.36
Professional Development II	0.04
Clinical Anatomy	0.37
Integration Period I	0.21
Cardiovascular Disease I	1.15
Integration Period II	0.29
Cardiovascular Disease II	0.12
Anaesthesiology and Diagnostics	0.06
Integration Period IV	0.09
Skin- and Joint Diseases	0.09
Endocrinology and Metabolism	0.13
Integration period V	1.47
Urinary Tract Diseases	0.33
Neurology	0.03
Psychiatry	0.03
Ophthalmology and Ear-Nose-Throat	0.03
In total:	***5.24***

Approximately 498 lecture and seminare hours were given during the year 2011 (equivalent to 1.380 evaluated lecture hours).

We also have an elective course in Radiology, for 5 students, twice a year, where lectures and seminars of approximately 149 hours per semester are given. This is approximately 298 lecture and seminar hours per year, equivalent to 546 evaluated lecture hours per year.

Supervision of 7,5 study point project work within Uppsala University Medical School

1. Anna Frisk: Fantompunktioner i CT-genomlysning. En jämförelse mellan två punktionsmetoder; punktionshjälpmedlet SeeStar och frihandsteknik. Supervisor: Anders Magnusson, 2009.
2. Jon Isacson: DT-biopsi i fantomstudie: Nåljusteringar och stråldos-jämförelse mellan frihandsteknik och punktionshjälpmedel (SeeStar). Supervisor: Anders Magnusson, 2009.
3. Richard Nordenskjöld: Coronary Artery Segmentation. Supervisor: Joel Kullberg, 2009.
4. Anders Södergård: Peroralt kontrastmedel vid datortomografisk undersökning av buken - en jämförande retrospektiv studie av Omnipaque® och Gastrografin® rörande passagehastighet och distribution. Supervisor: Anders Magnusson, 2009
5. Daniel Örtoft: En jämförelse mellan olika behandlingar på akut diagnostiserade uretärstenspatienter. Från diagnos till första kontrollundersökningen. Supervisor: Maria Lönnemark, 2009.
6. Thomas Bäckebo: Akutläkares utredning av patienter med icketraumatisk huvudvärk innan remiss till DT hjärna. Supervisor: Hampus Eklöf, 2010.
7. Diana Dackell: Bedömning av läckage efter högersidig colonkirurgi. En retrospektiv genomgång av undersökningar mellan 2006-01-01—2008-10-16, av såväl radiologiska undersökningar som kirurgiskt material för att hitta korrelation mellan kliniska fynd och påvisat läckage vid colonröntgen. Supervisor: Michael Torkzad, 2010.
8. Frederik Janryd: Five year follow-up of electibe endovascular aneurysm repair (EVAR) of abdominal aortic aneurysm (AAA) at a single centre (Uppsala Akademiska sjukhus). Supervisor: Rickard Nyman, 2010.
9. Lars Rocksén: Evaluating parameters used to examine large renal pelvic calculi before percutaneous nephrolithotomy. Supervisors: Maria Lönnemark, Anders Magnusson, 2010.
10. Henrik Sjöström: Endovaskulär stentgraftbehandling av traumatiska thorakala aortaskador. Supervisor: Rickard Nyman, 2010.
11. Mia Stoor: Frekvensen av allvalriga sjukdomar hos patienter utredda med ”akut DT hjärna” för huvudvärk vid akutmottagningen vid Akademiska sjukhuset. Akuta och senare patologiska fynd på hvudvärkspatienter som utretts med DT hjärna. Supervisor: Hampus Eklöf, 2010.

Supervision of 30 study point project work within Uppsala University Medical School

1. Marijela Bosnjak: En retrospektiv studie av utfallet vid användande av Pro-Star® vid förslutning av A. femoralis efter endovaskulära ingrepp (EVAR och TEVAR). Supervisor: Rickard Nyman, 2011.
2. Ishita Huq: Neuroangiografi. Supervisor: Raili Raininko, 2011.
3. Axel Trägårdh: Ureteral calculus. Which patients do not need radiologic follow-up?

Education of Radiographers/Technicians

Another area of education is the three-year study program of radiography. The study program consists of 10 courses with the following subjects:

Subject	**Study Points**
Radiography I	15
Technology and Medical Radiation Physics	7,5
Radiology	7,5
Nursing Care Related to Radiography	7,5
Technololgy, Radiation Protection and Radiobiology	7,5
Nursing Related to Conventional Radiography	15
Nursing Related to Angiography	7,5
Nursing Related to Magnetic Resonance Imaging	7,5
Nursing Related to Radiographic Examinations	15
Scientific Report in Caring Sciences	15
In total:	***180***

During the spring term 2011, 8 students, out of the admitted 20 students, were examined and received a diploma as Radiographers.

During the year 2011 the Section of Radiology was also involved in commissioned education within the field of Basic Radiology, Neuroradiology and Uroradiology. Each course was given during one whole week with approximately 45 lecture hours per week and 24 – 27 students per course.

Section of Oncology

The Section of Oncology is involved in teaching activities in the medical education program:

Subject	Study Points
Tumours - Oncology Integration Period VII Oncology	1.40 0.14 0.27
In total:	1.81

Specialist education in oncology for nurses

Another field of education is within the field of specialist education of nurses in oncology.

Subject	Study Points
Nursing in Oncology Diseases I Nursing in Oncology Diseases II	7.5 7.5
In total:	15

During the year 2011 8 students were enrolled in both courses, but have not yet finished the study program.

Section of Biomedical Radiation Science

Master Program in Medical Nuclide Techniques

During 2011 7 students were enrolled in the Master Programme in Medical Nuclide Technique.

Courses within the Engineering Program

Within the civil engineering program “Molecular Biotechnology” the Section of Biomedical Radiation Science gives a course in Nuclide Techniques. The course is included in the third year of the program and approximately 15 students were registered during 2011. During fall 2011 a course in Medical Technology and Radiation Biology was held for students enrolled in the Graduate Engineering Program.

Awards and Appointments 2011

Olof Eriksson received the Berzelius Award, from the Kungliga Vetenskapssocieteten in Uppsala, for his thesis: Imaging Islets of Langerhans by Positron Emission Spectroscopy.

Olof Eriksson received the Hwasserska Prize, from Upsala Läkareförening, for having presented the best thesis within the Medical Faculty, Uppsala University, during the period of 2010/2011.

In 2011, the Section of Radiology was awarded a Prize for giving the best elective course within Uppsala University Medical School. The Prize is awarded by the Uppsala Medical Student Organization. The Prize was awarded for both the spring and fall semester of 2011.

List of Authors

Section of Radiology

Håkan Ahlström, Professor

Elna-Marie Larsson, Professor

Per Liss, Assistant Professor

Christl Richter-Frohm, Financial Coordinator

Section of Oncology

Gunilla Enblad, MD, PhD, Ass. Professor

Bengt Glimelius, Professor

Birgitta Johansson, PhD, Senior lecturer

Peter Nygren, Professor

Section of Biomedical Radiation Science

Bo Stenerlöw, Professor