Spring 2011

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Master of Science in Molecular Medicine

Thesis/Project Catalogue

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Faculty of Medicine

NTNU

Master Thesis in Molecular Medicine

Name of Group: **Cell biology, Dept Cancer Research and Molecular Medicine**

Name of Research Community: **Research group on immunology of infection**

T cell function in HIV-infected individuals with mycobacterial co-infections

Background

Co-infection with Human immunodeficiency virus (HIV) and *Mycobacterium tuberculosis* (MTb) presents a major problem on a global scale. In 2008, MTb killed 1.8 million people, of which an estimated 0.5 million were HIV-positive individuals. HIV patients experience increasing immunodeficiency due to loss of CD4+ T helper cells and are prone to opportunistic infections by a range of pathogens. The majority of complications are caused by co-infections with mycobacteria, namely MTb and MAC-disease (*Mycobacterium avium* complex). Due to the early onset of highly active antiretroviral therapy (HAART), MAC disease is usually not diagnosed amongst HIV patients in Norway. But co-infection with MTb disseminates a serious, cost-intense and emerging problem.

Hypotheses and Objective of study

T cell effector functions in patients co-infected with mycobacteria and HIV are impaired, influence each other, and mycobacteria-directed T cell responses are involved in a poorly understood paradoxical syndrome in HIV-patients called IRIS (immune reconstitution inflammatory syndrome). Only little is known on the role of opportunistic infections on T cell reconstitution under HAART. The overall objective of this project is to characterize T cell responses to mycobacterial and HIV antigens in healthy versus HIV-infected individuals.

This master project will be part of a 3-years research project funded by NTNU and Helse Midt-Norge starting in January 2011. Specifically, cells from peripheral blood of HIV-patients before and after onset of HAART as well as healthy controls will be isolated. The cells will be tested for antigen-specific T cell functions directed towards mycobacterial and HIV antigens *in vitro*. Methods for T cell analysis are established in the lab and will include flow-cytometric characterization of antigen-specific T cell effector functions (intracellular staining for effector cytokine production, T cell subtyping, cell proliferation assays), cytokine analysis (ELISA / multiplex) as well as isolation of mRNA for real-time PCR assays. Results from this project will lead to an improved understanding of HIV- and HIV/mycobacteria co-infected individuals.

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Master Thesis in Molecular Medicine

Name of Group: **Trondheim Bioencapsulation group**

Name of Research Community: **IKM, DMF**

Whole blood assay – revealing inflammatory mechanisms towards alginate microcapsules

Alginate microcapsules or microbeads have a potential in cell-based therapy for diabetes treatment. Pancreatic islets can be encapsulated within alginate microcapsules and still be secreting and producing insulin. Upon transplantation the insulin producing tissue will be able to respond and to normalize the blood glucose level in the patient. The purpose of the microcapsule is to provide protection from the host immune system. Although this concept has proved its function, there are challenges related to biocompatibility. This is manifested as overgrowth reaction on the capsules surface, which impairs the free passage of nutrition's/oxygen/waste products and therapeutic protein over the capsule membrane. The overgrowth problem is variable and the mechanisms behind only partly understood. What is known is that capsules compositions affect the outcome and it varies with the choice of animal model. There is presently a question of how well animal models might describe the outcome in the human body.

The goal with our studies is to understand the inflammatory mechanism behind overgrowth, in order to design optimal alginate microbeads for a functional cure to diabetes.

Inflammation can be studied by using human whole blood. Whole blood contains almost the entire network of proteins (complement, coagulation, cytokines) and cells involved in inflammatory reactions. A lepirudin-based whole blood assay is established in our lab and will provide the basis for the studies. Different types of alginate microcapsules (containing polycations) and microbeads (alginate only) considered for future transplantation will be evaluated, as well as different types of alginates and capsules that might clarify the underlying mechanism to overgrowth.

Methods: ELISA (Complement, cytokines, growth factors), Flow cytometry (leukocytes receptor activation), Confocal laser scanner microscopy (Complement C3 surface activation), alginate microcapsules formation

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Master Thesis in Molecular Medicine

Name of Group: **Cell biology, Dept Cancer Research and Molecular Medicine**

Name of Research Community: **Research group on immunology of infection**

Background Mycobacteria constitute a major global health problem with *M. tuberculosis* killing close to two million people each year (http://www.who.int/). There is a lack of universally effective vaccines, therapy is expensive and long lasting, drug-resistant mycobacteria are emerging, and there is a rise of HIV patients co-infected with *M. tuberculosis*. Thus, there is continued search for new therapies and vaccines and an intense effort to understand the biology of the host-pathogen interactions with mycobacteria. Pathogenic mycobacteria take residence in host macrophages and cause life long infections in humans. Initially, mycobacteria interact with phagocytic receptors such as the Mannose receptor (MR), and pattern-recognition receptors like the Toll-like receptors (TLRs) mediating inflammatory signaling. Mycobacteria manipulate macrophage responses to avoid killing, disturb antigen presentation and gain access to host-derived nutrients. A catabolic process called autophagy normally aimed at degrading damaged organelles and intracellular protein aggregates, seems to be involved in destruction of mycobacteria in autophagolysosomes.

Hypotheses and Objective of study

We hypothesize that activating the chronically infected macrophage with for instance Interferon gamma (IFN-γ) or stressing the mycobacteria through iron deprivation or exposure to antibiotics will initiate autophagy and PRR signaling from the mycobacterial phagosome. The proposed Objective will be addressed by standard and experimental research methods in molecular medicine with *in vitro* infection models of macrophages by *Mycobacterium avium*, a low-virulent mycobacterium. We will address the role of individual host molecules (TLR2, MR, autophagy-related proteins) using established knockout mouse macrophages or with siRNA techniques in primary human or mouse cells. Macrophage infections, mycobacterial trafficking and autophagy will be visualized using confocal microscopy and/or quantified by high throughput imaging using the Olympus Scan^R system. Differential PRR signaling pathways will be analyzed using ELISAs and real-time PCR, and mycobacterial survival quantified from plating CFUs or by PCR. This proposal can be for one or several master students and the final project description will be specified upon agreement with the student(s).

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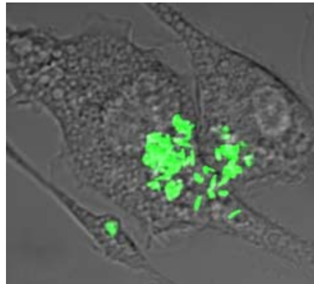
Master Thesis in Molecular Medicine

Name of Group: **Cell biology, Dept Cancer Research and Molecular Medicine**

Name of Research Community: **Research group on immunology of infection**

Mycobacteria are intracellular pathogens, whereof M. tuberculosis *currently infects 2 billion people, killing 1.8 million people yearly. Due to expensive and lengthy drug treatments, drug resistance and no efficient vaccines, novel treatment modalities, novel drugs and drug formulations and novel vaccine candidates are urgently needed. To be more efficient in developing new cures, a better understanding of the microbe and the interaction with host immune system is needed. Our group focuses on low-pathogenic mycobacterial variants with effort on describing the intracellular niche which they inhabit, how they obtain nutrition, how they interact with the trafficking machinery of the host cell, how they evade our immune system and how they eventually become recognized and killed. The overall objectives are to understand the requirements and mechanisms for mycobacterial killing, either by antibiotics or by the immune system itself.*

This thesis in molecular medicine will be based on trafficking and delivery of lipid based materials to the intracellular bacteria to define pathways of lipid transport, host transport molecules involved and preferred substrates and formulation. Much of the work will be based on state-of-the-art subcellular imaging (Laser scanning confocal microscopy and high through-put screening flow cytometry and scanning microscopy (Scan^R)) as well as some basic molecular and cell biological techniques such as siRNA treatment for gene silencing, cell labelling and cell culturing, ELISA. The project is suitable for candidates with understanding of immunology and interest in imaging, and can potentially be divided in two parallel tasks for students wishing to work in pairs.



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Master Thesis in Molecular Medicine

Name of Group: **Medical microbiology**

Name of Research Community: **LBK**

Short description of the assignment/thesis (background, hypothesis and methods):

Is DNA microarray useful for genotyping of meticillin resistant Staphylococcus aureus (MRSA)?

Staphylococcus aureus is part of the normal flora of the anterior nares of the nose in many healthy persons. However, it may also cause skin and soft tissue infections and is one of the most frequent causes of severe invasive infection. Resistance of S. aureus against antistaphylococcal drugs has been associated with treatment failure and increased mortality. Infection with such bacteria, termed meticillin resistant S. aureus (MRSA), may due to a colonizing strain of the same person (endogenic) but may also be due to spread from other persons. MRSA is a recognized cause of outbreaks of infections in hospitals and other health institutions. Molecular genotyping of MRSA is important to uncover the source and stop the spread of such outbreaks. Several methods for genotyping of MRSA are available, but have limitations in the ability to differentiate between certain groups of MRSA.
The aim of the current project is to study the usefulness of DNA microarray for genotyping of MRSA and compare this method with spa-typing and other available methods like pulsed-field gel electrophoresis (PFGE) and multilocus variable number of tandem repeats assay (MLVA).
The student will analyse MRSA strains within selected spa-types by a published S. aureus DNA microarray, PFGE and MLVA, and will compare the discriminatory power of microarray with the other two methods.

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Master Thesis in Molecular Medicine

Name of Group: **Group of Cell Biology**

Name of Research Community: **Research Community TOLL**

Short description of the assignment/thesis (background, hypothesis and methods):

Inflammation, asthma and small pollution particles

Inflammation is an underlying condition of many diseases that represent important public health problems ranging from e.g. asthma and COPD to cancer. Particle exposure affects important regulators of the inflammatory processes. Depending on the size and type of particle different intracellular mechanisms of phagocytising cells of the immune system may be involved. This may result in different inflammatory and clinical outcomes. Particles or crystals may act via the cytoplasmic NOD like receptors, the NLRs including the inflammasome, resulting in activation of interleukin (IL)-1β and IL-18. Particle size is important as small particles more than larger ones exert adjuvant effects on allergic responses in animals.

Macrophages need to be primed in advance for the particles to activate the inflammasome, and in real life humans are often exposed to various microorganisms and allergens together with inhaled particles. Priming may occur via the Toll-like receptors (TLRs). TLR4 which binds LPS is found both on the plasma membrane and in endosomes. LPS and particles may affect the receptors in both compartments and the effects may depend on whether the LPS is bound or not bound to the particles. Activation of TLR in different compartments induces signalling via different routes which ends up in production of different cytokine profiles. The combined resulting inflammatory response will then depend on the combination of TLR activation, particle endocytosis and inflammasome activation.

The working hypothesis is that the inflammatory responses initiated via these intracellular mechanisms depend on particle size and concomitant exposure to microbial compounds

We have indications from preliminary experiments with whole blood that small particles more than larger ones acti the complement system and induce production of cytokines and chemokines. Therefore, we also want to study the interaction between the complement cascade and the inflammasome in inflammation induced by small particles.

Magnetic, fluorescent and functionalised particles in the size range from 100 nm to 1 μm will be used and compared with diesel exhaust particles. The inflammatory mechanisms will be revealed by using whole blood and blood cells from adult healthy persons. Major analysis methods will be ELISA, Bioplex and flow cytometry.

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Master Thesis in Molecular Medicine

Name of Group: **Bioinformatics and Gene Regulation**

Name of Research Community: **DNA Repair and Genome Stability, Molecular Biology**

The Bioinformatics and Gene Regulation research group is developing and using software for analysis of data from molecular biology. The group is mainly doing research on eukaryote gene regulation, using computational data analysis together with experimental data generation and verification. Active research areas are in particular transcription factors, microRNAs and genome structure, including epigenetics.

Transcription factors are proteins that bind to regulatory regions in the genome and control gene expression. Binding sites for transcription factors are described by motifs representing short fragments of DNA. Binding site motifs may be determined experimentally or by modelling, but modelling gives several false hits in a typical genomic sequence. We are working on improved modelling and analysis of transcription factor-based gene regulation by using a combination of large experimental data sets and better prediction methods. This can be used to analyse regulatory relationships between genes. Relevant problems include studies of cell cycle-regulated genes and genes involved in DNA repair.

In addition to binding sites for traditional transcription factors the genome also contains binding sites for structural proteins that define the physical organisation of the genome and demarcate functional subunits within the genomic sequence. This is an important aspect of gene regulation, and we are also developing tools for classification of functional genomic regions. Detailed analysis of such regions can give us valuable information about the interplay between genome organisation and gene regulation.

MicroRNAs (miRNAs) are a recently discovered class of approximately 22 nucleotide long RNA genes that regulate protein coding genes. MicroRNAs constitute about 2% of the currently known human genes, but these miRNAs may regulate more than 60% of the human protein coding genes. Many miRNAs have been implicated in developmental disorders and diseases such as cancer. MicroRNAs regulate protein coding genes by binding to the genes' transcribed RNA and preventing the RNA from being translated into protein. How a miRNA recognizes its target genes is still a focus of intense research. Our group develops and uses computational and experimental tools to study how miRNAs individually and cooperatively recognize and regulate target genes, how miRNAs and transcription factors jointly regulate gene expression, and how genomic alterations such as single nucleotide polymorphisms (SNPs) affect gene regulation. We are particularly interested in how miRNAs and transcription factors regulate and affect processes such as DNA repair, cell proliferation, cell differentiation, and virus infection.

Our available projects range from pure experimental work to pure bioinformatics analyses. For the latter projects, some programming experience may be required. Interested students should contact Finn Drabløs or Pål Sætrom to discuss project-specifics.

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Master Thesis in Molecular Medicine

Name of Group: **Human Reproduction Group**

Name of Research Community: **IKM, DMF**

Trophoblast immunity in development of pregnancy complications

The placenta harbors a setting where cells from two different individuals must act in concert. The placenta must ensure 1) that growth conditions for the fetus are good; 2) that the maternal immune system tolerates the “foreign” fetus – and on top of this; 3) it must be able to mount an immune response against invading pathogens. This complexity may cause problems.
It is known that pregnancy complications, such as pre-eclampsia and fetal growth restriction (FGR), may be based on the formation of an insufficient placenta. In the beginning of pregnancy, this is not a problem. But towards term, the fetus requires an optimal placenta for full nutrition and oxygen supply. At this point, an insufficient placenta will not fulfill its tasks, giving a “system overload” resulting in activation of inflammatory processes harmful for both the mother and her fetus.
The Pattern Recognition Receptors (PRRs) represent first line immune cell activation pathways and they are activated by both external (invading microbes) and endogenous inflammatory (stress and tissue injury signals) mediators. The recent discovery that fetal cells in the placenta (trophoblasts) express these receptors reflects their role as placental immune cells.
Our hypothesis is that PRR activation of trophoblasts during placental development may cause an imbalance in the interaction between maternal and fetal cells, resulting in an insufficient placental development, underlying subsequent complications as pre-eclampsia and/or fetal growth restriction.

The Human Reproduction Group at IKM approaches this hypothesis by analyzing PRR expression and function in cultured trophoblasts and placental tissue. PRR immunity is studied by RNA/DNA isolation, real-time qPCR analysis, flow cytometry, cytokine assays, confocal microscopy, siRNA gene silencing and other immunological techniques.
This project gives the basis for *two related master projects* based on the study of placental and systemic inflammation in pregnancy in relation to development of pre-eclampsia and/or FGR:
I PRR immunity in trophoblasts studied in response to endogenous signals (from cell stress and injury).
II Role of cholesterol crystals in trophoblast immunity and pre-eclamptic placentas.

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Master Thesis in Molecular Medicine

Name of Group: **Myeloma group (Cell biology group)**

Name of Research Community: **Cancer Research and Molecular Medicine (Gastrosentert 2nd floor)**

Interactions between genetic aberrations and growth of multiple myeloma cells

Multiple myeloma is a neoplasm of the plasma cells in the bone marrow. In Norway, 300 are diagnosed with the decease every year. The cancer is non-curable and the overall survival is five years.
All MM patients are cytogenetically abnormal. MM can be divided in two groups based on chromosome numbers (hyperdiploid myeloma, HRD) and on immunoglobulin heavy chain translocations (non-hyperdiploid myeloma, NHRD). Doing basic myeloma research usually means doing experiments with myeloma cell lines (HMCLs). A lot of conclusions have been drawn based on observations from experiments with these HMCLs grown in monocultures in the laboratories. There are more than a hundred HMCLs around the world, and they are important tools in the study of MM. Virtually all HMCLs used in laboratories are derived from NHRD tumors. HMCLs do not fully represent MM, since only approximately half of the MM patients have a NHRD tumor. The bias that HMCLs are from NHRDs has to be considered when HMCLs are used as models of the human disease. The reason for the lack of HRD HMCLs is perhaps that HRD tumors are strictly dependent on mitogenic cytokines and the bone marrow microenvironment. It appears that NHRDs more likely become independent of their microenvironment compared to HRDs, and this confers a more aggressive disease allowing some NHRDs to grow *in vitro* and become HMCLs. However, we have been able to establish two HMCLs from HRD myeloma patients. We now want to use these to find one or a few factors that enable the HRD cells to grow *in vitro,* and hopefully have the key to be able to establish long sought for HRD HMCLs. These undetermined factors might also be important in understanding the HRD MM, and be potentially drug targets.

We would like the student to test the effect of the microenvironment on the different HMCLs and primary cells from patients by using different growth media (human, cow, goat, rabitt ect.). Both look at the growth itself (proliferation /apoptosis) and the expression of different genes and proteins varying with the growth and growth conditions (qPCR/sequencing/Western Blots).

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Master Thesis in Molecular Medicine

Name of Group: **Group (faggruppe)**

Name of Research Community: **Research Community (fagmiljø)**

Short description of the assignment/thesis (background, hypothesis and methods):

Prostate carcinoma is the most common cancer among men in Norway, and the incidence is increasing. However, the patient cohort is highly heterogeneous. In most cases the process takes an indolent course, with only a slow progression of the tumour, which remains localized for many years. Only a minority of the patients experience a highly aggressive tumour with rapid extension beyond the confines of the gland, as well as the development of distant metastases, especially in skeletal sites. Currently, the biological behaviour of prostate carcinoma is evaluated based on histological classification according to the Gleason system. Although the Gleason grading has shown its usefulness over many years, it has a number of limitations and drawbacks, not least due to its dependence on subjective factors. The grading is evidently dependent on the actual sample, which also constitutes a source of variation in these very heterogeneous tumours. More precise and more objective criteria for determining the biological potential of an individual tumour are therefore highly in demand. Hopefully, detailed molecular analysis of tumours might shed light on this issue. An intriguing question that warrants exploration is the possibility that the patient’s genetic makeup and exposure history may to some extent determine the biological nature of the individual tumour.

The principal objectives of the proposed study will be to identify a set of reliable miRNA (short RNA regulator strands about 20 bp) indicators, to help assess as precisely as possible the biological potentials of individual tumours of the prostate, in order to determine the prognosis of the patient, thereby serving as a guide to the choice of appropriate therapy. The work will be carried out onpParaffin embedded prostate cancer tissue.

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Master Thesis in Molecular Medicine

Name of Group: **Molecular Microbiology**

Name of Research Community: **Medical Microbiology**

Detection of prosthetic joint infection by molecular methods.

Background: The frequency of prosthetic hip joint infection (PJI) is approximately 2 %. Conventional microbiological culture is hampered with the risk of failing to demonstrate bacterial growth, mainly due to problems related to the biofilm mode of growth. Sonication using ultrasound is believed to augment the yield by disrupting the biofilm allowing the bacteria to grow in culture. Molecular techniques, e.g. PCR have to some extent improved the diagnosis of PJI, but contamination during the entire process is a serious problem.

Hypothesis: Detection of bacteria associated with the prosthetic surface in PJI is feasible after disruption of the biofilm by using molecular methods.

Methods: Materials for the project will be: 1) interface membranes surrounding the implant in patients undergoing revision arthroplasty; 2) implants experimentally infected in an animal model. Detection of bacteria after sonication of removed material will be pursued by means of fluorescence in-situ hybridization (FISH) and polymerase chain reaction (PCR). Broad-range hybridization probes and PCR primers will be employed on the clinical specimens, and specific oligonucleotide probes / primers in the experimental infection model. The results will be compared to results obtained by conventional culture.

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Master Thesis in Molecular Medicine

Name of Group: **Laboratory Medicine**

Name of Research Community: **Immunology and Transfusion Medicine**

Proteoglycan-related adhesion mechanisms of neutrophil granulocytes

Neutrophil granulocytes play a central role in inflammation. In order to enter tissues, they use adhesion molecules to adhere to the blood vessel wall. We have previously found that proteoglycans may contribute to such adhesion in certain settings, but the mechanisms are not well known.

The aim of the project is to further clarify the role of proteoglycans in neutrophil adhesion.

Fresh human neutrophils will be isolated from blood samples from volunteer blood donors. Using blocking antibodies, the adhesive functions of various proteoglycans will be investigated in tissue culture experiments, including adhesion to plastic surfaces (which is relevant in settings with artificial surfaces such as in hemodialysis or use of cardiopulmonary bypass) as well as to endothelial cells. The project will provide an excellent opportunity for developing good skills in tissue culture, and is best suited for two students working in cooperation.

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Master Thesis in Molecular Medicine

Name of Group: **Laboratory Medicine**

Name of Research Community: **Immunology and Transfusion Medicine**

Establishment of PCR-based methods for genotyping of mediators of inflammation

Atherosclerosis is the main cause of cardiovascular disease, including myocardial infarction and stroke. Inflammation is central in the pathogenesis of atherosclerosis. Thus, genetic differences in molecules related to inflammation influence the risk of cardiovascular disease. We hypothesize that genetic differences in HSP70-1 (heat shock protein-70-1) and MMP-8 (matrix metalloproteinase-8), two central mediators of inflammation, are related to the risk of cardiovascular disease.

The aim of the project is to develop PCR-based methods for genotyping of two SNP (single nucleotide polymorphisms) in the gene for HSP70-1 and three SNP in the gene for MMP-8, for use in future clinical studies on risk factors for cardiovascular disease.

The project involves design of PCR primers, optimization of PCR conditions, analysis of restrictrion fragment length polymorphism, and analysis of PCR fragments based on allele-specific primers. Genotype frequencies will be analyzed in a set of samples from blood donors. The study will provide an excellent opportunity for developing skills in one of the most basic methods used in molecular genetics.

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Master Thesis in Molecular Medicine

Name of Group: **PDT-group**

Name of Research Community: **Department of Cancer Research and Molecular Medicine, Unit for Molecular Medicine**

Effects of photodynamic therapy, using blue and red light, on different cancer cell lines.

Photodynamic therapy (PDT) is a clinical cancer treatment based on the photochemical reactions which occur after a photosensitizer has absorbed light. Photochemical reactions can induce cell death through oxygen requiring reactions and thereby give a therapeutic effect. Several photosensitizers and precursors are approved for clinical use; all of them absorb light within the visible range. After administration, a photosensitizer or its precursor will accumulate or be produced fairly selectively by high proliferating cells such as cancer cells due to different metabolism and uptake between normal cells and neoplastic tissue/cells. PDT is well established within dermatology and is in use in several other clinical fields. Improvement of light sources and increasing research increases the foothold of PDT as generally used treatment modality. The most widely used form of PDT clinically is aminolevulinate (ALA) based PDT.

Our group uses mainly hexyl aminolevulinate (HAL), which is approved for bladder cancer diagnosis under the name Hexvix (PhotoCure, Oslo, Norway). Since our research is translational, we have collaborations with colleagues both domestic and abroad, with companies and within different special field. We are doing several studies, ranging from proteomic studies to animal studies.

The master project will be at cellular level and in close collaboration with a PhD-student. The work is meant to be a part of a study leading to a publication and is adequate for 1-2 master projects. We will study effects of blue light versus red light and the effect of light intensity on cell death pathways. This is highly relevant for the Clinics, for future studies and for comparison of results from different studies. Both results confirming different effect of red and blue light and the relevance of intensity and results which do not confirm differences, are results which we can publish, provided the laboratory work is at accepted level.

The master student will learn several methods in the lab and must learn some theory about both PDT and cell death pathways. For the apoptosis/necrosis measurement we will use both flow cytometry and a caspase assay. Cell survival will be measured by a colorimetric assay. And finally, the student will of course do HAL-PDT on cells.

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