Interested in recruiting a PhD student or postdoc

Project title: The role for the interaction between smooth muscle cells and mast cells in airway hyperresponsiveness in asthma

Supervisor: Mikael Adner Associate Professor; Unit of Experimental Asthma and Allergy, Research Institute of Environmental Medicine ,Karolinska Institutet, (mikael.adner@ki.se)

Background: Asthma is a chronic inflammatory disease where the asthmatic individuals suffer from recurrent exacerbations of wheezing, chest tightness, breathlessness and coughing, and have airway hyperresponsiveness (AHR) a main characteristic. The mast cell plays a central role in both allergic and non-allergic asthma, which when activated, can cause airway smooth muscle contractions. It is known that antigen stimulated mast cell causes both early- and late-phase allergic reactions by airway narrowing mediated primarily due to release of histamine and leukotriene. After the initial secretion of newly synthesized eicosanoids and preformed mediators, the mast cell continues to secrete cytokines, chemokines and growth factors. How this successive mast cell release of mediators, of which the composition is incompletely defined, affects airway smooth muscle cells has not yet been studied.

Hypothesis and aims: The overall hypothesis of the project is that asthmatic inflammation influences the interaction between mast cells and airway smooth muscle, and that this effect is important for airway obstruction in asthma. The main focus of the experiments is to define the mechanisms behind the alterations in smooth muscle using isolated airways from both humans and animals, and subsequently to validate the relevance of these newly defined mechanisms to airway hyperresponsiveness in animal models of asthma.

Work plan: Experiments will be performed in isolated human small airways using our unique access to human lung tissue, as well as *in vivo* in a new animal model of asthma. The *in vitro* portion in this project will be conducted at our laboratory and the *in vivo* component will be conducted at our animal platform. We have developed an organ culture technique that generates controlled experimental conditions to systemically define the actions of mast cells during inflammatory conditions in human isolated small airways. As guinea pigs have a remarkable similarity to humans with regard to both mast cell distribution and pharmacology in the airways, we will use this species for the *in vivo* experiments. To mimic as closely as possible the allergic reactions in humans in the guinea pig, we have developed a new asthma model for using allergens known to affect humans, namely house dust mite and cat allergen.

Significance: The molecular interplay between mast cell mediators and airway smooth muscle cells is proposed to be the central mechanism behind the clinical manifestation of AHR, which currently stands out as the fundamental pathological feature underpinning asthma. The organ culture technique creates controlled experimental conditions to define the actions of mast cell mediators proposed to have a central role in the functional remodeling of asthmatic airways. This specifically involves analysis of how mast cells interact with airway smooth muscle cells in the peripheral part of the airway tree which is considered to be a critical site in the pathobiology of asthma. Due to the advantages of the guinea pig model of asthma, the possibility to validate how the in vitro generated data are linked to AHR is available. The project therefore has great potential to generate a more complete understanding of the development of AHR and define new targets for treatment of asthma.

Interested in recruiting a PhD student or postdoc

Project title: Molecular mechanisms behind asthma-induced airway smooth muscle hyperreactivity

Supervisor: Mikael Adner Associate Professor; Unit of Experimental Asthma and Allergy, Research Institute of Environmental Medicine ,Karolinska Institutet, (mikael.adner@ki.se)

Background: Asthma is a chronic inflammatory disease in which the asthmatic subjects suffer from recurrent exacerbations of airflow obstruction due to contractions of the airway smooth muscle (ASM). A central component of the airway hyperresponsiveness in asthma is the ability of ASM to regulate airway tone and the diameter of the airway lumen. This is the rationale for the frequent use of drugs such as β_2-adrenoceptor agonists, as well leukotrienes and muscarinic receptor antagonists, which directly targets and inhibits bronchial smooth muscle contraction. It has been shown that the contractile properties of ASM cells can be changed by inflammation. In addition to their contractile capacity, the ASM can cause inflammation and remodeling of the airway by secreting inflammatory mediators and growth factors. However, the signaling pathways that drive the alteration of the ASM properties are still undefined.

Hypothesis and aims: The overall hypothesis of the project is that inflammation-induced alteration of the ASM contractility is an important part of airway hyperresponsiveness in asthma. The main focus of the experiments is to define the mechanisms behind the alterations in ASM in isolated human small airways. This will be achieved by using a culture method of human small airways as the main method together with dispersed smooth muscle cells to step-wise define key factors in chronic airway inflammation that alter ASM function Work plan: Airway inflammation will be induced by culturing bronchial ring segments in the presence of specific inflammatory mediators and the properties of the airway smooth muscle will be defined by measuring the effects of individual contractile and relaxant substances. The signaling pathways that are involved consist indeed of many molecules ranging from those linked to inflammatory receptor signaling cascades (e.g. MAPK, p38 and Jun/AP-1 signaling), to expression and translation regulation, and further to those that affect G-protein receptor signaling pathway (e.g. the respective receptors, PKC and Rho-kinases). To define the importance of these pathways a combined approach will be used. Hence, activity of the pathways will be investigated through expression analysis (microarray analysis/RNA sequencing), mass spectrometry and phosphorylation analysis. Furthermore, to detect and also confirm certain pathways different pharmacological inhibitors, such as receptor antagonists, enzyme inhibitors, sequestering antibodies as well as silencing RNA, will be used.

Significance: This project takes advantage of our long-standing experience with integrated models and, in particular, our unique regular access to human lung tissue. Moreover, the human bronchi we will use in our experiments are obtained from the peripheral part of the airway tree which is assumed to be a critical site in the pathobiology of asthma. The organ culture technique creates controlled experimental conditions to systemically define the actions of different molecules proposed to have a central role in the functional alterations of asthmatic airways. The molecular interplay between inflammatory mediators and airway smooth muscle cells is proposed to be the central mechanism behind the clinical manifestation of airway hyperresponsiveness, which is a fundamental pathological feature in asthma. The project therefore has great potential to generate an understanding of the mechanisms that are driving the development of airway hyperresponsiveness and to define new targets for treatment of asthma.

Interested in recruiting PhD students and postdocs

Project title: Understanding regulatory T cells to find new therapeutic targets

Supervisor: John Andersson, PhD, Department of Medicine Solna, Karolinska Institutet,
email: john.andersson@ki.se homepage: http://ki.se/en/meds/immunology-and-allergy

Background and current projects: The immune system is the body's defense against infectious organisms. Furthermore, the immune system contributes to the progression of most of today's non-communicable diseases including cancer and cardiovascular diseases. We study $CD4^+FOXP3^+$ regulatory T (Treg) cells that suppress immune activation and modulate the outcome of both inflammatory diseases and cancer. Treg cells depend on the transcription factor FOXP3 and mutations in the FOXP3 gene leads to a fatal lymphoproliferative disorder known as IPEX. The ultimate objective of our research program is to find new possibilities to control immune responses in humans by targeting Treg cells. Treg cells have been extensively studied, however, two aspects of Treg cell biology remain unresolved. First, the transcription factor FOXP3 is required for Treg cell function, but the regulation and function of FOXP3 isoforms remain almost entirely unknown. Second, Treg cells inhibit immune responses by suppressing dendritic cells (DCs), but the exact mechanisms that Treg cells utilize remain controversial.

How does alternative splicing of FOXP3 impact immunity? The transcription factor FOXP3 is essential for Treg function. FOXP3 exists in several distinct isoforms; however, the regulation and functional consequences of FOXP3 isoform expression remain poorly understood. We have found that FOXP3 isoforms have different or even opposing functions, and that different diseases are characterized by distinct patterns of FOXP3 isoform expression. What factors induce alternative splicing of FOXP3 mRNA? How do FOXP3 isoforms confer their different functions? We are using a combination of genetic and biochemical approaches to answer these questions.

How do Treg cells suppress dendritic cells? The exact mechanisms and cellular targets of Treg cell-mediated suppression remain controversial. *In vitro* studies suggest that Treg cells have the capacity to directly suppress a large number of cell types including T cells and DCs. Many recent studies aiming to elucidate how Treg cells function have focused on Treg cells ability to suppress DCs as it is clear that Treg cells interact with DC *in vivo*. In order to define the exact mechanisms of suppression we have generated conditional knockout mice and are now combining *in vivo* studies with transcriptional profiling of *in vitro* suppressed DCs.

Methods currently used: Flow cytometry and cell sorting, magnetic bead-based cell isolation, primary cell culture, suppression assays, lentiviral transduction, western blot, immunoprecipitation and quantitative RT-PCR. We have also initiated several studies where we use RNA-Seq to define the global transcriptional profile of specific cellular states.

What we are looking for and what we can offer: We are interested in recruiting 1-2 PhD students or postdoctoral fellows with a background in immunology, medicine, cell biology, biochemistry, molecular biology or bioinformatics. We greatly value social skills, an interest in learning new things and a drive to do good science. We can offer a friendly atmosphere in a well-functioning laboratory with state-of-the art equipment.

Interested in recruiting a PhD student

Project title: For transdifferentiation to insulin-producing β-cells

Supervisor:

Olov Andersson, Assistant Professor, Department of Cell and Molecular Biology, Karolinska Institutet.
Email: olov.andersson@ki.se Group home page: http://ki.se/en/cmb/olov-anderssons-group

Qualifications of applicant:

Masters degree in Biomedicine, Molecular Biology, or a similar subject.

Short project description:

Diabetes can be controlled with insulin injections, but a cure is still lacking. One potentially curative approach is to increase the number of insulin-producing β- cells. Using a novel chemical screening approach in transgenic zebrafish for discovery, and transitioning to mouse and human studies for validation, we aim to identify and characterize enhancers of α- to β-cell transdifferentiation. In addition to expanding our whole-organism screening of small molecules in zebrafish, the PhD-student is to follow up on the tentative hits from our pilot screening to date. As a second independent approach, we are performing singlecell RNA-sequencing to identify genetic signatures for α- to β-cell transdifferentiation. The identified genes can be used as both markers and potential divers of α- to β-cell transdifferentiation. We can quickly test the functionality of identified genes by overexpressing them in the transgenic zebrafish monitoring α- to β-cell transdifferentiation. If treatment with the identified small molecules and genes (enhancers of α- to β-cell transdifferentiation) also lead to an improved regulation of glucose homeostasis in zebrafish, we will start translating the findings using mouse and human islets. Depending on the nature of the hit we might inject the small molecule or a secreted protein into diabetic mice for subsequent assessment of glucose-control and generation of bihormonal (insulin+ glucagon+) cells, which are indicative of transdifferentiation. In sum, by performing whole-organism screens, characterizing mutant zebrafish, translating findings to mice and human islets, we will identify factors that could be used to treat diabetes.

Interested in recruiting a postdoctoral fellow

Project title: Microvascular Oxidative Stress in Cardiovascular Disease and Type 2 Diabetes

Supervisor: Mattias Carlstrom, PhD, PharmD, Associate Professor in Physiology
Department of Physiology and Pharmacology, Karolinska Institutet
Email: mattias.carlstrom@ki.se Group Home page: http://ki.se/en/fyfa/reactive---oxygen---species---and---nitric---oxide---signaling---in---renal--- and---cardiovascular---function
Research Gate: https://www.researchgate.net/profile/Mattias_Carlstroem

Type of recruitment: Postdoctoral fellow (12---24 months)

Qualifications of applicant: Basic knowledge in physiology, pharmacology and molecular biology is needed. Previous experience and training with the use of rodent models, assessment of renal, cardiovascular and metabolic functions *in vivo*, and *ex vivo* studies of microcirculatory function is a great asset. Some knowledge in redox signaling, oxidative stress, immunohistochemistry is also desirable. Previous experience or training in clinical trials is also an asset.

Short project description: Adequate minute---to---minute regulation of blood perfusion within a given organ is maintained by the microcirculation. In the kidney, the afferent arterioles importantly contribute to renal autoregulation, and hence control glomerular perfusion and filtration as well as blood pressure control. In the pancreas, the arterioles are regulating islet perfusion and hence s---cell insulin release. The mechanisms for microcirculatory regulation are multifactorial, but are influenced by metabolism--- and endothelium---derived factors, including adenosine, angiotensin II (ANG II), nitric oxide (NO) and superoxide. Impaired arteriolar functions have been suggested in aging and obesity---related disorder such as hypertension, chronic kidney disease and type 2 diabetes (T2D). Further mechanistic understandings are necessary to develop new and cost---efficient treatment strategies against these global health problems. We aim to investigate the role and interaction between adenosine and ANG II receptors influences renal, cardiovascular and metabolic functions. In particular, studies address how receptor interaction influences oxidative stress and NO signaling. We also investigate novel strategies (*e.g.*, supplementation with inorganic nitrate and nitrite) to stimulate NO generation in the microcirculation. A comprehensive methodological platform is available (see table below) and this translational project includes *in vivo* animal studies, sophisticated *ex vivo* vascular studies (*i.e.,* myograph studies & isolated/perfused arterioles), cellular and molecular analysis, and also human studies. Novel insight from this project may have both nutritional and therapeutic implications in the treatment of cardiovascular disease and T2D.

Interested in recruiting a postdoc

Project title:

Antibody-mediated disease progression and spreading in rheumatoid arthritis, with a focus on mechanism identification

Supervisor:

Anca I. Catrina, MD Ph.D. Professor
Rheumatology Unit, Department of Medicine, Karolinska University Hospital, Karolinska Institutet
Contact: Anca.Catrina@ki.se ; Meng.Sun@ki.se

Project description

Rheumatoid arthritis (RA) is a chronic, inflammatory disorder that may affect many tissues and organs, but principally attacks diarthrodial (synovial) joints, leading to chronic synovial inflammation and progressive bone destruction. In most cases, the inflammatory process initially affects single joint, with relatively rapid expansion to others joints.

Antibodies against citrullinated proteins/peptides (ACPAs) are present in the majority of RA patients. The presence of these antibodies has been often detected before the onset of joint inflammation suggesting a role for anti-citrulline responses in the initiation of RA. Synovial fibroblasts (SFs) are cellular key players in promoting synovial inflammation and bone destruction, invading into and degrading cartilage and bone. Interestingly in one mouse model, human synovial fibroblast isolated from RA synovial biopsies were shown to be able to transmigrate through blood stream, suggesting a potential role for these cells in disease spreading between joints.

Bone destruction is associated with presence of antibodies against citrullinated proteins (ACPAs) that are highly specific for RA. We have recently demonstrated that ACPAs promote osteoclast development in an IL-8 dependent autocrine mechanism. In the proposed project, we aimed to identify the molecular mechanism that responsible for disease progression and spreading, focus on both osteoclast and synovial fibroblasts.

Interested in recruiting PhD student

Project title:
Understanding the function of T helper cells in the development of allergies

Supervisor:
Dr. Jonathan Coquet, Assistant Professor
Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet
Email: jonathan.coquet@ki.se Home page: http://ki.se/en/mtc/jonathan-coquet-project

Qualification of applicant:
We are recruiting a doctoral student for a period of up to 4 years. The applicant is to have completed a Masters degree, specialising in Immunology. It is important that the applicant have an interest in T helper cell biology, cytokines and intracellular signalling networks. Preferably, the applicant also has experience working with mice and has knowledge of cell processing techniques and flow cytometry.

Project description:
Central to the development of asthma is the activation of T helper cells. These cells promote airway inflammation and asthma by secreting soluble cytokines that in turn activate airway epithelial cells, induce mucus secretion in the airways, induce smooth muscle cell contraction and lead to the recruitment of innate immune cells, such as eosinophils into the airways. The differentiation of T helper cells into pathogenic cells capable of causing disease is what interests us in my lab. In particular, we ask, 'What genes and proteins are involved in this differentiation?' And furthermore, 'What can be done to counteract the development of asthma?'

Recently, we have been using cutting-edge technology to identify novel targets that are involved in T helper cell differentiation and programming. We are currently working on a number of interesting targets, not before analysed for their role in asthma. We will analyse the function of these genes in small animal models and using in vitro assays of human peripheral blood cells.

Our overall aim is to identify many genes that are important for the development of pathogenic T helper cells in asthma, and to target the function of these genes, as a strategy to alleviate the symptoms of asthma. We are excited to have a new doctoral student join our group and contribute to this exciting project.

Interested in recruiting a postdoc or a visiting researcher but also a PhD student would fit the project well

Project title: Effects of type 2 diabetes on synaptic plasticity and neurogenesis after stroke, and the therapeutic potential of dipeptidyl peptidase-4 inhibitors

Supervisor: Assistent Professor Vladimer Darsalia, (Vladimer.Darsalia@ki.se)
Department of Clinical Science and Education, Södersjukhuset, Karolinska Institutet
Research group home pages: http://ki.se/en/people/vladar and http://ki.se/en/kisos/stroke-neurodegeneration-and-diabetes

Qualification of candidate: The qualifications for a visiting researcher or postdoc should be documented with previous expertise in neuroscience and/or diabetes/metabolic research. The qualification for a PhD student should be according to the "entry requirement" at the KI.

Project description:

Background

Type 2 diabetic (T2D) patients show a severely impaired recovery after stroke. The pathological mechanisms behind this are still mostly unknown despite the growing medical need due to the increase of the diabetic population.

We hypothesize that *synaptic plasticity* and *neurogenesis* (endogenous mechanisms involved in stroke recovery) are impaired by T2D, but can be normalized by the treatment with dipeptidyl peptidase-4 inhibitors (DPP-4i). DPP-4i are clinical T2D drugs that have also shown neuroprotective properties in animal models.

Aims

To determine whether:

1) T2D impairs *synaptic plasticity* and *neurogenesis*
2) These effects correlate with decreased stroke recovery
3) DPP-4i can improve stroke recovery

Methods

We induce stroke by middle cerebral artery occlusion in T2D mice. The number and morphology of interneurons (*synaptic plasticity*) are quantified by IHC/stereology methods. Striatal *neurogenesis* is assessed by quantifications of newly-born neurons. The recovery is evaluated by behavioural tests. The DPP-4i Linagliptin is given after stroke for 5 weeks and the same parameters as above are assessed.

Preliminary Results

These results strongly support our hypothesis by showing that T2D reduces the number of striatal interneurons, impairs motor recovery and neural stem cell proliferation after stroke.

Significance of the Project and Learning Outcomes.

This project could provide insights for understanding the mechanisms of impaired stroke recovery in T2D and contribute to the development of effective treatments.

The project is unique since it provides the opportunity for the student/postdoc to work together with a team of diabetes experts, neuroscientists and forensic pathologists at the KI. Moreover, the project will also provide the unique chance to learn advanced techniques in diabetes and neuroscience research. Finally the project is run in collaboration with industrial partners. Thus the recruited researcher will also have the great opportunity to be exposed to the *modus operandi* of the industry.

Interested in recruiting a PhD student

Project title: Validate animal models of psychosis and depression with regard to biomarker profile

Supervisor: Göran Engberg, PhD, Professor, Dept of Physiology & Pharmacology
Goran.Engberg@ki.se ; Link to group home page:

Qualifications of applicant:
We are looking for highly motivated candidates with an M.Sc. in neuroscience or other relevant area. Experience or interest in working with animal models and rodent behavior, as well as statistical analysis, is a significant merit. Excellent communication skills and ability to interact socially and scientifically with other Ph.D. students and post docs in our laboratory as well as with collaborators in various networks are essential.

Project Description:
Psychiatric illnesses, such as major depressive disorder, schizophrenia, and bipolar disorder, are leading causes of disability, affecting millions worldwide and often causing recurrent chronic symptoms, heightened risk of suicide and cardiovascular comorbidity. There is now mounting evidence, including pioneering research from our group, that immune activation is a causal factor, underlying part of the pathology seen in psychiatric patients. Our research points to the kynurenine pathway as a putative pathogenic link between the immune system and aberrant brain neurotransmission and behavior. In this pathway several neuroactive metabolites are produced: kynurenic acid (KYNA) is an astrocyte-derived neuroprotective and blocks the N-methyl-D-aspartate (NMDA)-receptor; quinolinic acid (QUIN) is an excitotoxic NMDA receptor agonist. Our research combines cutting-edge technology and state-of-the-art biochemical and genomic analysis of well-characterized patient cohorts with innovative drug discovery programs. Preclinical models will be used to evaluate a drug candidate's promise for clinical research, including preliminary pharmacokinetics, efficacy, pharmacodynamics, validation of normalization of KYNA, QUIN/KYNA ratio, initial assessment of therapeutic windows, combinability and tolerability. There are several animal models of depression; the chronic mild stress protocol, administration of kynurenine (2 mg/kg, i.p.) or the bacterial endotoxin lipopolysaccharide (LPS) and the Flinders Sensitive Line rat. All these models are based on face validity and thus, display depressive-like behavior, and also, we have data showing that excessive amounts of QUIN are produced in these models. Interestingly, administration of LPS (0.83 mg/kg, s.c.) increases mouse brain levels of QUIN, and at the same time decreases the levels of picolinic acid (PIC), another metabolite of the kynurenine pathway. We will validate these four animal models with regard to both depressive-like behaviors, to changes in brain KYNA, QUIN, and PIC levels and the response to existing anti-depressant drugs. The aim is to develop animal models that are designed to also reflect underlying pathophysiological mechanisms in depression.

Furthermore, in our lab, we have developed two transgenic animal models of psychosis with face and construct validity, i.e. (1) the G-protein-coupled receptor kinase 3 (GRK3) knock out (KO) mice, showing elevated brain levels of IL-1β, kynurenine and KYNA as well as disrupted PPI and enhanced amphetamine-induced locomotion, and (2) the kynurenine 3-monooxidase (KMO) KO mice, which show increase in brain KYNA levels, exaggerated amphetamine-induced locomotion, and impaired social interaction and cognition. Putative animal models will be tested at baseline but also following challenges with psychotomimetics or immune stimulating agents. Our animal models showing face, construct and predictive validity with regard to behavior, underlying pathophysiological mechanisms, e.g. levels of kynurenines, and response to antipsychotic/ antidepressant drugs will be used as screening models for candidate drugs identified in an ongoing drug discovery project (together with SciLife Lab). This translational and back-translational approach is designed to systematically and rationally clarify the pathogenic role of genetic and/or distinct biochemical aberrations in schizophrenia. Preclinical rodent tasks for depressive and psychosis-like behavior as well as cognition are well-established in our lab.

Interested in recruiting a PhD student

Project title:
Investigating pathophysiological mechanisms in schizophrenia – focus on neuroinflammation

Supervisor:
Sophie Erhardt, PhD, Professor in Experimental Psychiatry
Dept of Physiology & Pharmacology. Email: sophie.erhardt@ki.se
Link to group home page: http://ki.se/en/fyfa/neuropsychoimmunology

Qualifications of applicant:
We are looking for highly motivated candidates with a MSc. in neuroscience or computational science. Experience or interest in working with bioinformatics tools for pathway reconstruction and network analysis, as well as multivariate statistics is a significant merit, as is biomedical training with experience from clinical research. Excellent communication skills and an ability to interact socially and scientifically with other students and post docs in the laboratory and with collaborators in various networks are essential.

Project description:
Schizophrenia is a highly heritable disorder, in most cases leading to chronic, severe loss of function. The unfavorable outcome of therapy in schizophrenia is related to our lack of insight into pathophysiological mechanisms, preventing treatment directed at causative targets. Furthermore, the absence of disease biomarkers hampers patient stratification as well as detection of patients early in the disease phase. We hypothesize that brain immune activation is underlying cause of schizophrenia.

In the present project we have enrolled first-episode patients with schizophrenia and age- and gender-matched healthy volunteers. All individuals are recruited via the Karolinska Schizophrenia Project (KaSP) which is a clinical research program involving collection of detailed clinical data, cerebrospinal fluid, blood, and brain imaging using MR and PET. So far 70 patients and 49 controls have been included in the study. We have performed whole genome sequencing (WGS) using IGN (with 30x coverage per sample on a Illumina HiSeq 2500 v4, PE 2x125bp) as well as transcriptomics (RNA-seq) on all individuals. The clinical characterization includes symptom levels as well cognitive performance and physiological parameters such as prepulse inhibition. From fall 2014, peripheral blood mononuclear cells (PBMCs) and fibroblasts are generated from all subjects for functional studies. All subjects are monitored and re-examined after 1.5 years and then on a 5-year basis. Furthermore, samples for a detailed analysis of immune cell phenotypes has been analyzed using the cyTOF platform.

Our overall goal is to find new targets for treatment in schizophrenia as well as biomarkers for clinical use, via identifying pathway-specific biochemical abnormalities.

Interested in recruiting a postdoc

Project title: Physical exercise as an intervention to increase cognitive performance and decrease metabolic risk factors in young persons affected by first time psychosis.

Supervisor: Yvonne Forsell, Adjunct Professor, Specialist in Psychiatry, Karolinska Institutet, Department of Public Health, Epidemiology and Public Health Intervention Research. Yvonne.Forsell@ki.se **Link to group home page** http://ki.se/en/phs/epidemiology-and-public-health-intervention-research-ephir

Type of recruitment and qualifications of applicant: Post doc 12-24 months. Documented knowledge of cognitive tests, metabolic risk factors and advanced statistical methods are required.

A short project description – The Fitforlife project

The aim is to increase autonomy in young persons affected by first episode psychosis by targeting both psychological (cognitive function, body awareness) and physiological (metabolic risk factors) functioning using regular physical exercise.

Psychosis starts in young age and it is often accompanied by life-long social impairment and decreased level of functioning. The affected persons have an increased mortality due to elevated suicide rates but also to a wide range of somatic disorders. During the past decades' psychosocial interventions has emerged focusing on increasing resilience to stress and building social support. These strategies often involve support for life style changes but very rarely organized physical exercise. Physical exercise has effects on a lot of problems seen in psychosis such as cognitive dysfunction, stress intolerance, metabolic risk factors. Few studies in this area have used objective measures of outcome and most of them include very few participants. When Fitforlife is finished in end of 2016 it will include 70 persons (18-40 years) from psychiatric open care units. This is an unique high number in this type of research. Data includes cognitive tests, blood samples, functional measurements before and after 12 weeks of organized regular physical exercise. Medical records are available. Fitforlife is a cooperation between KI (Dep. of Public Health, EPHIR and Center of Molecular Medicine) and Swedish School of Health and Sports Medicine.

Postdoc: Will mainly be focused on analysis of cognitive data (Cogstate, Stroop test, TMT-A and TMT-B) and biological data (blood lipids, inflammatory markers). The post doc will work in a team including competences in psychology, microbiology, advanced statistics, intervention research and psychiatry. If the postdoc wish there will be opportunities for lab work. An individual development plan will be made in cooperation with the post doc. The plan will include relevant courses, congresses and development of teaching skills. The post doc will have regular meetings with the main supervisor and the EPHIR group.

Interested in recruiting a Postdoc (24 months)

Project title: Study on human endometrial stem cell niche factors, its application in endometrial regeneration

Supervisor's name: Professor Kristina Gemzell Danielsson
Chair Div. of Obstetrics and Gynecology, Dept. of Women´s and Children´s Health
Contact: Lalit.Kumar@ki.se ; Kristina.Gemzell@ki.se
Home page: http://ki.se/en/kbh/reproductive-health-reproductive-medicine-research

Qualifications of applicant: PhD. Experience in the relevant field

A short project description

Endometrial regeneration and adequate endometrial thickness are essential for human embryo implantation and maintenance of pregnancy. Several studies have shown that endometrial thickness contribute to the success of a pregnancy. Thin endometrium lacks sufficient glandular and stromal structure. It is widely accepted that there exists a relationship between endometrial stem cells (enSC) and fertility and there are strong evidences showing enSC consist about 1-5% of total endometrial cells.

Stem cell niche maintain the phenotype of stem cells to retain their regenerative capacity as well as differentiation into other cell types. A recent study with human endometrial stem cells show that TGF-beta differentiate enSC into endometrial stromal cells, *in vitro*. Also there are reports showing co-administration of estrogen and progesterone significantly expand endometrial epithelial progenitor cells. In this project, we will use enSC isolated from women to Identify niche factors that are involved in maintenance, expansion and differentiation of enSC *in vitro*. To address this, we will use the following technologies - stem cells isolation and in vitro cell culture, FACS, RNA-sequencing technology and immunostaining to identify enSC niche factors along with bio-informatics tool. The knowledge obtained from this study will be important to develop niche based treatment for endometrial regeneration.

Interested in recruiting a Visiting Researcher 3-12 months

Project title: Controlled Nitric Oxide Delivery in Vascular Reperfusion Therapy

Supervisor's Name: Dmitry Grishenkov, PhD, Docent (dmitry.grishenkov@ki.se)
Department of Clinical Science, Intervention and Technology (CLINTEC), Division of Medical Imaging and Technology

Qualification of applicant: PhD degree

Short project description:

Background. Cardiovascular disease (CVD) accounts for 1/3 of total global deaths. The most widespread CVD is ischemic heart disease. It is the leading cause of death in both genders, equally diagnosed in developed and developing countries with mortality exponentially increasing with age. Efforts of healthcare system should be primary focused on prevention, timely detection, efficient differentiation and instant treatment of the disease.

Goal. Current project introduces a new class of micro devices providing integrated diagnostic and therapeutic applications, i.e. *theranostics*, of ischemic heart disease using microbubble-based ultrasound contrast agent loaded with nitric oxide (NO). A gas core makes microbubbles efficient ultrasound contrast agent. Application of therapeutic gas, in our case NO, opens new possibilities for local, specific drug delivery triggered by ultrasound.

Work plan. First, the dry powder of novel polymer-shelled microbubbles and commercially available phospholipid-shelled SonoVue microbubbles will be acquired. Then gas core will be substituted with NO and amount of loaded gas quantified. The passive and ultrasound mediated active release of gas through shell membrane will be assessed. Mathematical modelling will be performed to evaluate the mechanisms and physical principals behind triggered ultrasound mediated gas release through the thick- and thin-shelled membranes of polymer and SonoVue microbubbles. This will provide the feedback to optimise and tune the quantity of loaded therapeutic gas as well as structural composition and geometry of the contract agent itself.

Impact. The translational clinical significance of this study is to develop a simple combined tool for diagnostics and treatment of acute myocardial ischemia in patients with atherosclerosis or diabetes with impaired bioavailability of NO. Keeping in mind that systemic treatment with NO or NO-donor has a very narrow therapeutic window and may provoke critically low blood pressure, novel approach for NO transport, local delivery and triggered administration of specified doses is of high immediate clinical interest.

Interested in recruiting a PhD student or postdoc

Project: Molecular Epidemiology of Aging

Supervisor: Sara Hägg, PhD, Associate Professor in Molecular Epidemiology
Email: Sara.Hagg@ki.se Home page: http://ki.se/en/people/sarhag
Department of Medical Epidemiology and Biostatistics (MEB) Karolinska Institutet, Stockholm (http://ki.se/en/meb/startpage)

Entry requirements

Applicants should have an MSc in epidemiology, biomedicine, biostatistics, bioinformatics, genetics or equivalent. Experience from doing prior related research is a merit as well as skills of using standard data analysis software (e.g., SAS, STATA, or R).

Duties

The work for the intended PhD-position includes analyzing biomarker data such as genotypes, proteomics, metabolomics and telomere length assessments and associations with aging and aging-related diseases. Moreover, causal inference studies using genetic data will be undertaken as well as discordant twin analyses. The student will also take part in the epidemiology program at our department including mandatory courses in epidemiology and biostatistics.

Division

The research in our group focuses on molecular epidemiology of aging, using genetic-, molecular-, cognitive- and register-based data among others. Within the group, we are working in the fields of gerontology and genetics using methods such as genome-wide analyses, Mendelian Randomization, life-course trajectories, gene-environment interactions and twin approaches. Most cohorts used in the research are sub-studies from the Swedish Twin Registry but we will also start working with the UK biobank. Currently, the group consists of a PI, three postdoc's, five PhD-students and one master student.

Interested in recruiting PhD student, postdoc or a visiting scientist

Research area: Clinical Immunology, Immunogenetics, Cancer Genetics

Supervisor/host: Qiang Pan Hammarström, MD, PhD, Professor
Department of Laboratory Medicine, Huddinge Qiang.Pan-Hammarstrom@ki.se
Website: http://ki.se/en/labmed/research-group-qiang-pan-hammarstrom

Qualification of applicants:

The applicant is eligible to apply if he or she has obtained a MD or PhD in the fields of Biology, Biochemistry, Genetics, Oncology and Immunology.

Project I: *Regulation of immunoglobulin class switch recombination in human B cells*

The project is aimed at understanding the complex molecular mechanisms involved in immunoglobulin class switch recombination and somatic hypermutation and their involvement in the pathophysiological processes leading to immunodeficiency, allergy and cancer development in humans.

Project II: *Discovery of therapeutic targets in B cell lymphoma by next generation sequencing*

The project is aimed at identifying potentially treatable molecular targets in mature B cell lymphomas (with focus on diffuse large B cell lymphomas and mantle cell lymphomas) by high-throughput, next generation-sequencing omic- technologies such as whole genome and exome sequencing and RNA-seq. Functional studies will be followed, using standard molecular and cellular technologies, including Cas9/CRISPR system.

Interested in recruiting a PhD student

Project title: Identification and analysis of new immune target structures in cartilaginous joints of importance for development of arthritis

Supervisor: Prof Rikard Holmdahl, Division of Medical Inflammation Research, Department of Medical Biochemistry and Biophysics, Karolinska Institutet.
Contact: Angel.Yao-Mattisson@ki.se Webb page http://www.inflam.mbb.ki.se/

Qualification of candidate: To qualify, the applicant must have successfully passed an education in medicine or biological science including a master education, which also shows scientific ability. Laboratory experience and excellence is a requirement, in particular in immunology and biochemistry. Experience in experimental animal research is needed. Computer skills and bioinformatic knowledge are needed. Fluent English is a requirement.

Project description: The project aims to identify and analyze new immune target structures in cartilaginous joints of importance for development of arthritis. It will be primarily done using mouse models for rheumatoid arthritis. The role of the newly identified epitopes will be tested using genetically tailor-made animal models. Antibody binding as well as T cell activity will be studied in detail in vivo and in vitro. Results will be compared with immune response in human RA. The goal is to identify new epitopes with known functional properties, which will improve diagnosis and understanding of rheumatoid arthritis.

Interested in recruiting a postdoc or a visiting researcher

Project title:
Development of a vaccine to prevent rheumatoid arthritis in the Asian population

Supervisor: Prof Rikard Holmdahl, Division of Medical Inflammation Research, Department of Medical Biochemistry and Biophysics, Karolinska Institutet.
Contact: Angel.Yao-Mattisson@ki.se Webb page http://www.inflam.mbb.ki.se/

Qualification of candidate: To qualify, the applicant must hold a PhD in medicine or biological science, and with a strong track record including high quality publications. Laboratory experience and excellence is a requirement, in particular in immunology and biochemistry. Experience in experimental animal research is needed. Computer skills and bioinformatic knowledge are needed. Fluent English is a requirement.

Project description: The project aim to validate and functionally analyze new types of vaccines to prevent the development of autoimmune diseases. The work will be mainly done using genetically humanized animal models. These are unique models in which we have made mice expressing human MHC class II, DR molecules of different alleles together with human invariant chain. In particular we will study the *0405 allele which is the major gene associated with rheumatoid arthritis in Asians. We have made antigen-specific vaccines based on the molecule that will be tested for proof of concept in the mouse models. The work will include analysis of peptides binding to the *0405 molecule an their ability to trigger an autoimmune response in vivo. The precise mechanism of immune tolerance will be studied. The specific T cells will be tracked in vivo by tetramer complexes of *0405 and the specific peptides. Furthermore the mechanisms of action and subphenotypes of the effect will be analyzed. This will include studies on how the selected peptides induce pathogenicity or regulatory protection. The goal is to translate these findings to humans and initiate clinical trials.

Interested in recruiting PhD student, postdoc or a visiting scientist

Project title: **Mechanical forces control morphogenesis and cancer**

Supervisor: Professor Lars Holmgren, Department of Oncology and Pathology, Karolinska Institutet, SE-17176 Stockholm, Sweden, Lars.Holmgren@ki.se
Group home pages: http://ki.se/en/people/larhol http://ki.se/en/onkpat/lars-holmgrens-group https://se.linkedin.com/in/lars-holmgren-74648bb

Qualification of applicant: experience in molecular and cell biology techniques required.

Background: Transmission of mechanical force via cell junctions is an important component that molds cells into shapes consistent with proper organ function. Of particular interest are the cadherin transmembrane proteins that play an essential role in connecting cell junctions to the intra-cellular cytoskeleton. Understanding how these biomechanical complexes orchestrate intrinsic and extrinsic forces is import for our understanding of the underlying mechanisms driving morphogenesis and invasion. We have previously identified the Amot protein family, which are scaffold proteins that integrate polarity, junctional, and cytoskeletal cues to modulate cellular shape.

Methods: Analysis of protein expression in human and mouse tumors. Using genetic inactivation approaches in endothelial cells, zebrafish and mice we have characterized the function of the protein family in normal development as well as in tumor progression.

Results: Expression analysis shows that p60 AmotL2 is regulated by hypoxia and is induced in colon, breast, prostate and glioma cancer patients. We provide a novel mechanism how tumor cells escape the mechanical constraint exerted by neighboring cells and become plastic and highly invasive.

***References**: AmotL2 disrupts apical-basal cell polarity and promotes tumor invasion*. Mahdi Mojallal, Yujuan Zheng, Sara Hultin, Stéphane Audebert, Tanja van Harn, Per Johnson, Claes Lenander, Nicolas Fritz, Christin Mieth, Martin Corcoran, Marja Hallström, Johan Hartman, Nathalie Mazure, Thomas Weide, Dan Grandér, Jean-Paul Borg, Per Uhlén, and Lars Holmgren. Nature Communications, 2014 Aug 1;5:4557.

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VE-PTP regulates VEGFR2 activity in stalk cells to establish endothelial cell polarity and lumen formation. Hayashi M, Majumdar A, Li X, Adler J, Sun Z, Vertuani S, Hellberg C, Mellberg S, Koch S, Dimberg A, Koh GY, Dejana E, Belting HG, Affolter M, Thurston G, Holmgren L, Vestweber D, Claesson-Welsh L. Nature Communications. 2013;4:1672.

A tight junction-associated Merlin-angiomotin complex mediates Merlin's regulation of mitogenic signaling and tumor suppressive functions. Yi C, Troutman S, Fera D, Stemmer-Rachamimov A, Avila JL, Christian N, Persson NL, Shimono A, Speicher DW, Marmorstein R, Holmgren L, Kissil JL. Cancer Cell. 2011 Apr 12;19(4):527

Interested in recruiting a PhD student

Project title: **Organoid models for manipulation and modelling of bile duct cancer from human induced pluripotent cells using CRISPR**

Supervisor: Tomas Jakobsson, Assistant Professor
Department of Laboratory Medicine, Division of Clinical Chemistry
Email: tomas.jakobsson@ki.se

Qualifications of applicant:
Molecular biology and cell biology

Background
To study complex human diseases, that not are observed in animal models, you are today limited to *in vitro* cell cultures which most often do not reflect human physiology. A major technological breakthrough is the development of the *in vitro* organoid model (1) in order to mimic human physiology. In this research proposal we will apply a physiological model (organoids) and the tools to introduce multiple mutations simultaneously using CRISPR (2) in order to investigate the development of bile duct cancer, cholangiocarcinoma (CCA). CCA most often result in poor prognosis and there are today limited therapeutic options. To study the impact of these mutations, frequent inactivating mutations in PBRM1, *BAP1* and *ARID1* has been reported to be associated with worse survival (3), human normal cholangiocyte organoids will be edited using CRISPR. Edited organoids will be compared to patient derived CCA organoids in order to evaluate the disease model and the impact of the inactivating mutations for the development of CCA.

Project description
Generation of cholangiocyte organoids.
The first aim of this project is to generate cholangiocyte organoids (CO) from hIPSCs. To achieve this, we will use defined differentiation protocols. hIPSCs will be differentiated into definitive endoderm and hepatoblasts using defined growth factors. To mature hepatoblasts into CO a three-dimensional culture composed of matrigel and collagen will be used.

Examining bile duct cancer using CRISPR/Cas9 in organoids.
The second aim is to use the CO model to define the key genetic changes and molecular mechanisms for the development of cholangiocarcinoma using CRISPR/Cas9. To study the impact of these inactivating mutations, human normal CO, with a clean genetic background, will be used to generate mutated chromatin remodeling enzymes using CRISPR. The edited organoids will be compared to patient derived cholangiocarcinomas organoids in order to evaluate the disease model and the impact of the inactivating mutations in PBRM1, *BAP1* and *ARID* for the development of cholangiocarcinoma.

Interested in recruiting a PhD student

Project title:
Mechanisms of apoptosis activation in lung cancer cells with suppressed/activated autophagy in response to cellular stress.

Supervisor: Vitaliy Kaminskyy, PhD, Research coordinator, email: Vitaly.Kaminsky@ki.se
Cosupervisor: Boris Zhivotovsky, Professor, Head of the Unit of Toxicology. Institute of Environmental Medicine. http://ki.se/en/imm/unit-of-toxicology

Qualifications of applicant:
PhD student is expected to have a strong interest in cell death research and have a good knowledge of cell and molecular biology methods, such as cell culture, light and fluorescent microscopy, western blotting, PCR, cloning, flow cytometry. Applications are welcome from ambitious and enthusiastic students with good knowledge of English in terms of both spoken and written.

Short project description:
The importance of autophagy has been established in the development of embryo and differentiation of different types of cells in the body; however, its role in tumor progression remains controversial. Autophagy is often activated in tumors as an intracellular mechanism that support tumors with energy and modulation of autophagy may potentially facilitate apoptotic response of cancer cells to therapy. The aim of this project is to explore the molecular mechanisms of sensitivity of lung cancer cells to apoptotic stimuli induced by growth factor deprivation, starvation and treatment with drugs used for lung cancer therapy. In particular, we aim to study the mechanisms of activation of caspase system, involvement of mitochondria functions in this process and the role of antioxidant defense systems. Recently, we established lung cancer cell lines with knockout of several autophagy-related genes that are characterized by suppressed early or late stages of autophagy process. In addition to these cell lines with suppressed autophagy, human-derived lung adenocarcinomas and xenografts will be used to study the effect of autophagy modulation in the development of tumors. A specific role of autophagy modulation in cellular metabolic pathways and their link to activation of apoptosis in lung cancer cells will be revealed. Obtained results will provide us with new data for understanding of the role of autophagy in response of lung adenocarcinomas to treatment. Modulation of autophagy will explore new molecular pathways involved in survival of lung adenocarcinomas as well as establish conditions when alterations in autophagy machinery may play a role in alternative pathway for sensitization of lung adenocarcinomas to treatment. Improved knowledge of the molecular mechanisms of cell death and factors which influence the susceptibility of cells to treatment will be beneficial for the design of drugs and their combination that can be used to modulate the cell death process. Thus, in this project we will reveal new molecular mechanisms of how activation/suppression of autophagy might be potentially used to reduce lung cancer growth and how modulation of autophagy may improve treatment of lung adenocarcinomas.

Interested in recruiting a PhD student

Project title: **"Functional interdependencies of noncoding and protein-coding transcriptomes in liver cancer"**

Supervisor: Claudia Kutter, PhD, Assistant professor, SciLifeLab fellow
Karolinska Institutet, MTC and SciLifeLab Stockholm
Email: claudia.kutter@ki.se orcid.org/0000-0002-8047-0058
Group home page: ki.se/en/mtc/claudia-kutter-group scilifelab.se/researchers/claudia-kutter/

Qualifications of applicant: The applicant will apply transcriptome- and genome-wide approaches (such as RNA-sequencing and epigenome profiling techniques) to study the processing and regulation of transfer RNAs (tRNAs) in cultured cells, carry out validation experiments involving biochemical and molecular biological tools. The work implies computational methods and implementing analytical pipelines to infer underlying molecular mechanisms. A strong background in genomics, molecular biology, genetics, and/or biochemistry is required. Experience in eukaryotic RNA biology, gene regulation, transcriptome-wide studies and mammalian tissue culture techniques are important. Prior knowledge in bioinformatics (implementing analytical pipelines) and R programming for statistical computing and graphics is an asset. The ideal candidate should be collaborative, scientifically adventurous, curiosity-driven, and should bring independent and original ideasinto the project. The applicant should have good communication skills and be proficient in spoken and written English.

Project description: The genetic code is an abstraction of how mRNA codons and tRNA anticodons molecularly interact during protein synthesis. We recently showed that Polymerase III (Pol III)-driven tRNA gene expression evolves rapidly during mammalian evolution[1], and needs to be tightly controlled during mouse organ development[2] and in proliferating liver cancer cells[3] to control protein translation. The aim of this project is to: (I) identify Pol III-transcribed noncoding RNAs and their influence on protein-coding gene regulation in healthy and diseased liver cells by using state-of-the-art ChIP- and RNAsequencing in human primary hepatocytes, multiple human liver cancer cell lines and biopsies of liver cancer patients.
(II) investigate alteration of Pol III transcription of tRNA genes as a source of newly acquired regulatory potential by altering the expression levels of tRNA genes systematically. This will be achieved by inserting and excising tRNA genes from the genome of hepatic cell lines by using genome engineering methods (clustered regularly interspaced short palindromic repeats [CRISPR/Cas]).
(III) identify regulatory partners in the processing of tRNA fragments during in liver cancer cell lines by using advanced RNA-protein interaction assays.
The findings of this research project will contribute to our understanding of the molecular mechanisms employed in liver cancer – a disease that is dramatically increasing (especially in China) with poor diagnosis and treatment.

1. Kutter C. *et al.*, **Nature Genetics** (2011) 43(10), 948-955
2. Schmitt B.M. … **Kutter C., Genome Research** (2014) 24(11), 1797-1807
3. Rudolph K.L.M. … **Kutter C**.† and Odom D.T.†, **PLoS Genetics** (2016) 12 (5), e1006024

Interested in hosting a PhD student

Project title: "Surgical treatment and prognosis of gastric cancer".

Main supervisor: Jesper Lagergren, Professor of Surgery (jesper.lagergren@ki.se) .
Co-supervisors: Shaohua Xie, PhD in Epidemiology (shaohua.xie@ki.se) and Karl Wahlin, PhD in Biostatistics. All work in the Upper Gastrointestinal Surgery group, Department of Molecular Medicine and Surgery, Karolinska Institutet.

Link to group home page: Please read more about us and our research activities on the homepage http://ki.se/en/mmk/upper-gi-surgery.

Qualifications of applicant: Relevant medical background. Documented knowledge in epidemiology and biostatistics are required, preferably a master degree in these subjects. Personal characteristics include curiosity, engagement and good collaboration skills. Excellence in oral and written English is required (English is the language of our group).

Project description: Gastric cancer is common disease in several countries, including China. It is the 5th most common cancer and the 2nd most common cancer death globally. The overall 5-year survival is poor (lower than 20%). The mainstay treatment is surgery. It is important to identify factors that can concretely improve the prognosis. The PhD project will examine the surgical treatment and prognosis in gastric cancer. We will use data sources available almost uniquely in Sweden to conduct large and population-based cohort studies of high scientific validity.

The project will examine four specific research questions in separate studies:
1) Which are the main causes of death (except for gastric cancer) among all patients diagnosed with gastric cancer in Sweden?

2) What are the recent time trends in prognosis in patients diagnosed with gastric cancer, both for those having undergone surgery and not?

3) How do various levels of annual hospital volume of gastric cancer surgery influence all-cause and disease-specific mortality?

4) How does minimally invasive surgery compare with conventional open surgery for gastric cancer regarding all-cause and disease-specific mortality?

The data for this project originate from linkages of high-quality and nationwide Swedish registries, i.e. the Patient Registry (containing data on diagnoses and surgical procedures), Cancer Registry (containing data on cancer diagnoses with information on date of diagnosis, site and stage) and Causes of Death Registry (containing data on dates and causes of death).

Chinese collaboration: Our group has a network grant from the Swedish Research Council and the National Natural Science Foundation of China for collaborative research with Chinese researchers in upper gastrointestinal cancer. Our group includes two Chinese researchers, one postdoc and one PhD student.

Interested in hosting a PhD student

Project title: "Improved survivorship after oesophageal cancer surgery".

Supervisor: Pernilla Lagergren, Professor of Surgical Care Science, Surgical Care Science group, Department of Molecular medicine and Surgery, Karolinska Institutet.
Email: pernilla.lagergren@ki.se
Link to group home page: Please read more about us and our research on the homepage http://ki.se/en/mmk/surgical-care-science

Type of recruitment: Doctoral student for 48 months of full-time work. This corresponds to a PhD in medicine at Karolinska Institutet.

Qualifications of applicant: Completed undergraduate medical exam, e.g. surgeon, physician, nurse. Knowledge in epidemiological and biostatistical methods is a merit. Important personal characteristics include curiosity, engagement, and good collaboration skills. Excellence in oral and written English is required (English is the language of our group).

Project description: Oesophageal cancer is common worldwide, particularly in China, and is afflicted by poor prognosis. The cardinal symptoms are dysphagia (difficulties swallowing) and weight loss. Curative treatment includes extensive surgery (oesophagectomy) usually proceeded by neoadjuvant chemoradiotherapy. The surgery is often followed by severe complications and the recovery is extraordinarily long and complex, and often incomplete, highlighting the great need for research on strategies to better support and rehabilitate these patients following surgery. This PhD project will use data from a Swedish nationwide and population-based cohort study, named OSCAR (Oesophageal Surgery on Cancer patients – Adaptation and Recovery). OSCAR is a uniquely comprehensive study on this topic, including all patients who have undergone surgery for oesophageal cancer in Sweden. The patients are interviewed 1 year after surgery and respond to several well-validated patient-reported outcome measures during a personal visit by a research nurse. Patients are then followed up repeatedly (at 1½, 2, 2½, 3, 4 and 5 years) after surgery with established questionnaires.

Specifically, the project will examine:
1) If and how the patient's age, gender, education level, marital status and social network influence the postoperative illness perception;
2) If and how comorbidities and life events occurring after the surgery influence the postoperative recovery in health-related quality of life;
3) If and how an optimistic personality (defined by validated set of questions) influences the postoperative recovery of health-related quality of life;
4) If and how selected patient-reported outcomes influence the postoperative long-term survival.

Interested in recruiting a Visiting researcher or Postdoc

Project: Characterize the role of nuclear IGF-1 receptors (IGF-1R) in cancer and sarcoma cells for future clinical treatment studies.

Main Supervisor: Olle Larsson, Prof., MD, Ph.D
Co-Supervisors: Felix Haglund, MD, Ph.D and Yingbo Lin, Assist. Prof., Ph.D

Cancer Center Karolinska, Dept. of Oncology and Pathology, Karolinska Institutet.
Home page: http://ki.se/en/onkpat/olle-larssons-group
Contact Person: Dr. Yingbo Lin, Yingbo.lin@ki.se

Qualifications of applicant:

Visiting researcher or Post Doc: Possess a Ph.D in biomedicine, molecular biology or relevant field; a good publication record in peer-reviewed journals; expertise in biochemistry and molecular biology techniques and cell culture; highly motivated and able to undertake independent research project; fluent in both written and spoken English, bioinformatics background is a plus but not compulsory.

Project description:

Background: IGF-1R has a well-established role in carcinogenesis, but the underlying mechanisms are still poorly known. A new potential player is nuclear IGF-1R. Nuclear expression of IGF-1R in cancer has been shown to correlate to poor outcome in patients, and may therefore be important for malignant cell growth. We have previously showed that SUMOylation of IGF-1R is important for the nuclear translocation. Currently, we found that IGF-1R may regulate DNA repair mechanisms and proliferation through interaction with e.g. PCNA. Our results provide with increased understanding of IGF-1R signaling, which may contribute to development of improved cancer biomarkers and therapies.

Workplan/Methods: We will continue characterizing functions of nuclear IGF-1R in tumor cells and clinical specimen. Our group applies a wide range of methods including cell cultures with functional assays, immunoblotting, immunoprecipitation, qRT-PCR, sequencing, immunohistochemistry, in situ PLA and next generation sequencing including bioinformatics.

Interested in recruiting a PhD student or postdoc

Project title: Psychosocial factors and health: register-based studies from Nordic countries

Supervisor: Krisztina László, PhD, assistant professor at the Department of Public Health Sciences; email: krisztina.laszlo@ki.se

Qualifications of the applicant: good knowledge of the English language; at least basic knowledge of statistics and epidemiology; some experience in programming and database management would be a great advantage.

Short project description:

Project 1: We have a Nordic research collaboration which involves merging register based data from three Nordic countries. The data from this collaboration will allow investigating whether exposure to bereavement during different stages of life, i.e. in the prenatal period, during childhood, during pregnancy, and in early adulthood is associated with an increased risk of adverse health outcomes. A strong focus of our group is on cardiovascular diseases and perinatal outcomes. We will use data from the Nordic Perinatal Bereavement Cohort, including: births in Denmark during 1978-2008; in Sweden during 1973-2014; and 90% of the births in Finland during 1987-2007 (N≈7.4 million children and their ≈7.5 million parents). Information on death of study participants' family members, pregnancy-related characteristics, sociodemographic factors and health-related factors for index persons and their family members was/will be obtained through individual record linkage between several population-based registers. The project is a collaboration between Aarhus University, Denmark, the National Institute for Health and Welfare, Finland and Karolinska Institutet, Sweden. A detailed description of the study design can be found in: Li et al. Cohort profile: the Nordic Perinatal Bereavement Cohort. Int J Epidemiol. 2011;40:1161-7. Further information about the study and the involved researchers can be found at www.progeuro.au.dk. This international collaboration offers good training possibilities for PhD students and postdocs and opportunities for international exchange and networking.

The aim of the **project 2** is to investigate the association of several stressful life events and of specific psychiatric diseases with prognosis in patients with (a) acute myocardial infarction, (b) stroke and (c) heart failure. The three study populations will consist of:

1. patients with a diagnosis of acute myocardial infarction included in the Swedish Patient Register (since 1987) and/or the Register of Information and Knowledge about Swedish Heart Intensive Care Admissions;
2. patients with a diagnosis of stroke included in the Swedish Patient Register (since 1987) or in the Swedish National Quality Register for Stroke Care;
3. patients with a diagnosis of heart failure included in the Swedish Patient Register (since 1987) or in the Swedish Heart Failure Registry.

To obtain information on personal and familial health related factors, on mortality of index persons and of their relatives, on socioeconomic factors and on clinical measurements we will apply for linking the cohorts to several population-based registries and to the Swedish quality registries for acute cardiac care, stroke, and heart failure, respectively.

Interested applicants are welcome to contact Krisztina László to discuss – based on the above description, our funded projects and other interests in the research group – about a potential research plan for the study period at Karolinska Institutet. It is possible to combine parts of the two above presented projects.

Interested in recruiting a PhD student or postdoc

Project title: **Health effects of short and long-term separation from parents early in life**

Supervisor: Krisztina László, PhD, assistant professor at the Department of Public Health Sciences; email: krisztina.laszlo@ki.se

Qualifications of the applicant: good knowledge of the English language; at least basic knowledge of statistics and epidemiology; interest in social epidemiology; some experience in database programming would be a great advantage.

Short project description: The aims of the project are to investigate whether:

1. early start of daycare and the average weekly time at daycare are associated with epigenetic changes in genes regulating stress response, cortisol levels, health behavior, mental ill health and academic achievements, all assessed in adolescence.
2. death of a parent during childhood is associated with risks of hypertension, coronary heart disease and stroke later in life;

Question 1 will be investigated using data from KUPOL (Swedish acronym for "Kunskap om Ungas Psykiska hälsa Och Lärande", i.e. "Knoweldge about Adolescents Mental Health and Learning"), a longitudinal study involving 3671 Swedish adolescents born 2000-2001. The study participants and their parents completed on three occasions during 2013/2014-2016/2017 extensive questionnaires concerning – among others – parental socioeconomic factors, psychological factors in the family, school related factors, the adolescents' mental health and health behavior etc. One of the parental questionnaires inquires also about the age (in months) when the child started daycare and the average weekly hours the child was at daycare between the ages 1 to 2, 2 to 3 and 3 to 6 years. In the first and third wave of data collection, a subsample of the cohort gave three saliva samples that will permit assessment of epigenetic changes in genes regulating response to stress and assessment of morning and afternoon cortisol levels. For a part of the cohort we have permission to retrieve information from several health and socioeconomic population-based registries including data on pre- and perinatal factors, familial socioeconomic factors, specific medications and hospital-based diagnoses for adolescents and their parents, as well as diagnoses from the regional child and adolescent psychiatry care units. A more detailed description of the study can be found in the publication: Galanti et al. School environment and mental health in early adolescence - a longitudinal study in Sweden (KUPOL). BMC Psychiatry. 2016;16:243 and on the website http://kupolstudien.se.

To study ***question 2*** we will use data from two different cohorts: (1) the Nordic Perinatal Bereavement Cohort, including all children born in Denmark during 1978-2008; in Sweden during 1973-2014; and 90% of the births in Finland during 1987-2007 (≈7.4 million children) and (2) the Swedish 1969-70 conscription cohort, including almost 50000 men born 1949-51. The Nordic Perinatal Bereavement Cohort is a collaboration between Aarhus University, Denmark, the National Institute for Health and Welfare, Finland and Karolinska Institutet, Sweden. Information on death of study participant's family members, prenatal, sociodemographic and health-related factors for index persons and their family members was/will be obtained through individual record linkage between several population-based registers. A detailed description of the study can be found in: Li et al. Cohort profile: the Nordic Perinatal Bereavement Cohort. Int J Epidemiol. 2011;40:1161-7 and at www.progeuro.au.dk. Men in the Swedish 1969-70 conscription cohort completed extensive questionnaires about social, familial, lifestyle and health-related factors and participated in a clinical examination by a team of physicians, psychiatrists and psychologists. Blood pressure was assessed at the clinical examination, while information on coronary heart disease and stroke up to 2008 is available from the Swedish Patient Register and the Cause of Death Register.

Interested applicants are welcome to contact Krisztina László to discuss based on the above description about a potential research plan for the study period at Karolinska Institutet. The research plan may be combined with other projects presented by Krisztina László on the website of the China Scholarship Program.

Interested in recruiting a PhD student or postdoc

Project title: **Ovarian cancer-microenvironment communication as a target to overcome metastatic burden and drug resistance**

Supervisor: Kaisa Lehti, PhD (kaisa.lehti@ki.se)
Department of Microbiology, Tumor and Cell Biology (MTC), Karolinska Institute
Group home page: http://ki.se/en/mtc/kaisa-lehti-group

Type of recruitment: doctoral student/post-doctoral fellow

Qualifications of applicant:

We are looking for ambitious student/postdoc with strong enthusiasm towards science. A successful candidate has MSc or PhD degree and strong background in cancer biology, molecular and cell biology, cellular biochemistry and/or genetics. A good command of English is also expected from successful candidate. Clinical experience and/or basic understanding of bioinformatics is considered as an asset.

Project description:

The position is in the fields of molecular cell biology and translational cancer research. The project goal is to identify key mechanisms of tumor cell-microenvironment communication that underlie metastasis drug resistance, and relapse in epithelial ovarian cancer. The project will investigate how the cancer-specific genetic alterations, epigenetic regulation, and transcriptional programs relate to the microenvironment-dependent dynamics of e.g. signaling receptors, adhesion molecules, transmembrane proteinases, and cytoskeleton. This will be done by integrating unique genomic data of cancer patients with hypothesis-driven functional and molecular mechanistic research. State-of-the-art molecular biology, proteomics and functional genetic approaches including the most relevant cellular, ex vivo and in vivo models, as well as clinical human tissue material will be utilized for this research. By identifying key molecules and mechanisms in tumor dynamics, metastasis, and drug responses, the project will contribute to the development of new prognostic indicators and strategies for better treatments.

Interested in recruiting PhD student, postdoc or a visiting scientist

Project title: Signaling Complexes at the β-Arrestins: Cross-talk between Receptor Tyrosine Kinases and G-Protein Coupled Receptors. From basic studies to clinical applications in cancer.

Supervisor: Leonard Girnita, M.D., Ph.D., Associate Professor of Pathology, Group leader.
Department of Oncology-Pathology, Karolinska Institutet
Email: leonard.girnita@ki.se, Group webpage

Qualification of applicant: This project will require a student with a Masters degree in medicine, biomedicine or cell molecular biology. Experience with animal experimentation is a bonus. Ability to work as a team member in an international English speaking work environment is an essential requirement.

Project description:

Multilayered crosstalk between G protein–coupled receptors and growth factor receptors has a fundamental role in coordinating downstream signaling molecules that are ultimately responsible for the development and maintenance of the malignant phenotype.
The overall objective of this program is to investigate the function and determine potential utility of the signaling complexes involved in the GPCR/RTK cross-talk as potential biomarkers or molecular targets in cancer. This is based on the underlying hypothesis that the signaling complexes coordinated by β-arrestins (β-arr) and involving kinases, non-coding RNAs (ncRNA), ubiquitin ligases and/or deubiquitinating enzymes, contributes to tumorigenesis and the progression of cancer, and could be targeted in therapies.

The specific goals are:

1. WP1. Carry out a comprehensive analysis of the β-arr complex in normal cells and different progression stages of cancer. Validation of the β-arr signaling complex as a potential biomarker for metastasis.
2. WP2. Develop alternative strategies for cancer treatment with focus on clinical applicability: Un-Biasing β-arr/GRK signaling through GPCRs as a novel approach to cancer treatment.

Key publications:

1. Huiyuan Zheng, Claire Worrall, Shen Hongchang, Tarik Issad, Stefan Seregard, Ada Girnita and **Girnita L.** Selective recruitment of G protein coupled receptor kinases (GRKs) controls signaling and trafficking of the Insulin-like Growth Factor 1 Receptor. Proc Natl Acad Sci U S A. 2012 May 1;109(18):7055-60.

2. Zheng H, Shen H, Oprea I, Worrall C, Stefanescu R, Girnita A**, Girnita L.** β-Arrestin-biased agonism as the central mechanism of action for insulin-like growth factor 1 receptor-targeting antibodies in Ewing's sarcoma. Proc Natl Acad Sci U S A. 2012 Dec 11;109(50):20620-5.

3. Girnita L, Worrall C, Takahashi SI, Seregard S, Girnita A. Something old, something new and something borrowed: Emerging paradigm of insulin-like growth factor type 1 receptor (IGF-1R) signaling regulation. Cell Mol Life Sci. 2013 Nov 26.

4. Jia M, Andreassen T, Jensen L, Bathen T, Sinha I , Gao H , Zhao C , Haldosen LA, Cao Y , **Girnita L** , Moestue SA , Dahlman-Wright K Estrogen receptor α promotes breast cancer by reprogramming choline metabolism Cancer Res. 2016 Jul 25.

Interested in recruiting post-docs and visiting researchers

Supervisor: Nailin Li, MD, PhD, associate professor
Department of Medicine-Solna, Clinical Pharmacology Group, Karolinska Institutet, Karolinska University Hospital-Solna
Email: Nailin.Li@ki.se Tel: +46-8-51773996

Project I:

Platelet-regulated CD4+ T effector cell responses and their impact on atherosclerosis

Atherosclerosis is an inflammatory and thrombotic disease, in which both CD4 T cells and platelets play critical roles. We have recently shown that platelets distinctly regulate immune responses of different CD4+ T cell subsets. Aim of the project is thus to elucidate the impact of platelet-regulated CD4+ T effector cell responses on the development of atherosclerotic lesions. We are investigating the mechanisms underlying platelet regulation of CD4+ T effector responses of T helper (Th1 and Th17) cells and regulatory T (Treg) cells. Using murine models of platelet-specific deficiency of CD4+ T cell regulators, we will study how platelet deficiency affects CD4+ T effector responses in vivo and how the deficiency influences atherosclerotic lesion formation in a pro-atherosclerotic mouse model. The work may lead to novel therapeutic developments for atherosclerotic disease management.

Project II:

Platelet angiogenic activity and its role in cancer metastasis

Platelets are closely engaged in angiogenesis, apart from exerting their principal functions in thrombosis and haemostasis. We and others have recently shown that platelets differently release pro-angiogenic and anti-angiogenic factors upon different stimuli. We are therefore investigating the mechanisms underlying the distinct packaging of pro-angiogenic and anti-angiogenic factors into separate alpha-granules, the storage pool of proteins in platelets, and the signalling mechanisms controlling selective release of pro-angiogenic and anti-angiogenic factors. Through intervention of the signalling mechanisms, we will study how pro-angiogenic and anti-angiogenic activities of platelets can modulate angiogenesis in cancer, and subsequently regulate cancer growth and metastasis.

Interested in recruiting a postdoc or a visiting researcher but also a PhD student would fit the project well

Project title: **Pathophysiology and therapies against the neurological complications of diabetes: a translational project**

Supervisor: Associate Professor Cesare Patrone, Department of Clinical Science and Education, Södersjukhuset, Karolinska Institutet. Email: Cesare.Patrone@ki.se
Research group home pages: http://ki.se/en/people/cespat and http://ki.se/en/kisos/stroke-neurodegeneration-and-diabetes

Qualification of candidate: The qualifications for a visiting researcher or postdoc should be documented with previous expertise in neuroscience and/or diabetes/metabolic research. The qualification for a PhD student should be according to the "entry requirement" at the KI.

Project description:

Introduction/Aims

Type 2 diabetic (T2D) patients often show cognitive, sensorimotor and olfactory deficits. The pathophysiological mechanisms behind these cerebral complications are mostly unknown and the medical need is rapidly growing due to the global epidemic of T2D. We hypothesize that specific brain regions and neural cells are damaged during the early stages of T2D and that this process can be arrested by an early treatment with anti-T2D drugs targeting the glucagon-like receptor 1(GLP-1R).

We aim to:

1. Identify specific brain areas and cells affected by T2D in rodents.
2. Validate the rodent findings in the human brain.
3. Determine whether GLP-1R agonists can tackle the identified neuropathologies in rodents.

Methods

Quantitative biochemical and immunohistochemical analyses of neural cell types are performed in the main brain areas controlling cognitive, sensorimotor and olfactory functions in different T2D models mimicking different aspects of the T2D pathology. Electrophysiology, HPLC and olfactory studies will complement the analyses. The project is translational and the most relevant findings will be validated in post-mortem human brains (ethical applications approved). In the efficacy studies, we will use the GLP-1R agonist exendin-4.

Results in support of the Project Hypothesis

We recently showed that T2D leads to specific neuronal loss in the *neocortex* of T2D rats (Hussain et al *J Alzheimers Dis* 2014). We also showed that specific types of neurons are decreased by T2D in the *piriform cortex* (Lietzau et al *Oncotarget* 2016). Moreover, our group has a robust experience in the development of therapeutic strategies, GLP-1R-mediated, for CNS diseases that we aim to apply to this project. See below our most recent published articles on the topic: Darsalia et al. *Clin Sci.* 2012; Darsalia et al. *Diabetes.* 2013; Kappe et al *J Neuroinflammation* 2012; Patrone et al *Lancet Diabetes Endocrinol*. 2014; Darsalia et al *Rev Endocr Metab Disord*. 2014; Darsalia et al. *PLoS One*. 2014; Darsalia et al. *J Cereb Blood Flow Metab.* 2015; Darsalia et al. *Diabetes Obes Metab*. 2016.

Significance of the Project and Learning Outcomes

Previous studies have mostly focused on the impact of T2D on Alzheimer's. However, T2D patients also suffer from other types of brain disorders and neurodegenerative diseases such as Parkinson's. Little research has been done in this area and our studies aim to fill this gap.

The project is unique since it provides the opportunity for the student/postdoc to work together with a team of diabetes experts, neuroscientists and forensic pathologists at the KI. Moreover, the project will also provide the unique chance to learn advanced techniques in diabetes and neuroscience research. Finally the project is run in collaboration with industrial partners. Thus the recruited researcher will also have the great opportunity to be exposed to the *modus operandi* of the industry.

Interested in recruiting a PhD student

Project title: Genome-wide study of the impact of translation regulation on cellular heterogeneity.

Supervisor: Vicente Jose Pelechano Garcia, PhD. Assistant Professor, Karolinska Institutet. Department of Microbiology, Tumor and Cell Biology. Science for Life Laboratory Fellow.
Email: vicent.pelechano@scilifelab.se Group home page: http://pelechanolab.com/

Qualifications of applicant:
The student will have the opportunity to learn and help develop a variety of experimental and bioinformatic tools. The successful applicant should have a theoretical background and experience in functional genomics, RNA biology and/or bioinformatics. Prior experience in any of those areas and interpreting NGS biological data will be beneficial. The successful candidate is expected to be highly motivated and take a strong lead on his/her project and start to develop independent ideas. The candidate should be able to communicate scientific results by writing up scientific papers and attending scientific meetings in English. The ideal candidate is also expected to participate in the general duties of the team and to effectively communicate with scientists of very diverse backgrounds in a highly interdisciplinary and international environment.

Project description:
One of the biggest challenges in biology is to understand how identical information encoded in a genome generates diversity between cells and tissues. Different cells in a population can present varying responses to the same stimulus. In some cases these differences are attributable to genetic mutations. However, in other cases, identical (clonal) cells can also display phenotypically heterogeneous responses. This phenotypic heterogeneity has a poorly understood origin but a significant impact on biology and human health. To understand how these divergent phenotypes arise, it is necessary to study the factors that control gene expression variability across cells, from the transcription process to translation and production of a functional protein.

We will use novel genome-wide approaches to investigate the transcriptional basis of the non-genetic heterogeneity driving divergent gene expression responses within a clonal population using *Saccharomyces cerevisiae*. Cells will be sorted according to their translational potential and characterized using methods that we have previously developed to investigate their transcriptome complexity (TIF-Seq) and ribosome dynamics (5PSeq). This will allow linkage of molecular phenotypes with cellular consequences, and highlight those variations with higher functional potential. Once we identify novel mechanisms implicated in the appearance of phenotypically divergent cells, we will characterize selected targets using biochemical and molecular biology tools. We will particularly focus on the dynamic study of translation and the role of small RNAs in the regulation of ribosome dynamics. Once fundamental mechanism are characterised in budding yeast, we will perform an evolutionary analysis and experimentally assay their impact in human biology and disease.

The proposed work will use experimental and computational tools to improve our knowledge of translation regulation and to what degree translation regulation underpins cell-to-cell differences and bet-hedging strategies.

Interested in recruiting a PhD student and/or a Postdoc

Project title:
Sino-Swedish collaboration on molecular epidemiology of liver cancer

Supervisor/host:
Amelie Plymoth, PhD, Lecturer and Study Director of Doctoral Education at Dept. of Medical Epidemiology and Biostatistics (MEB), Karolinska Institutet.
Contact: amelie.plymoth@ki.se Webb page: http://ki.se/en/people/ameply

Background of applicant:
Since the proposed doctoral education covers aspects of liver disease, microbiome and molecular epidemiology based research; it is suitable for students with backgrounds in the medical or public health area with laboratory experience.

Project description:
Liver cirrhosis and liver cancer (mostly hepatocellular carcinoma, HCC) represent the end stage of most chronic liver diseases and studies from others and us show a heavy burden of HCC in China, eastern Asia and West Africa, where it is the second most common cause of death from cancer. Worldwide, we also see evidence for an increasing incidence in women, a trend that underlines the growing impact of risk factors for HCC such as metabolic disorders associated with obesity, physical inactivity and/or diabetes type 2.

The Chinese population is aging with an increase in those aged over 60 years, the age at which HCC most frequently occur. Thus, the death toll by liver cancer in China, will continue to increase at least until circa 2050-60, when most subjects aged 60 would have been vaccinated against HBV at birth. Therefore, we are faced with one of the worst cancer epidemics worldwide, a threat to the world's sustainability and development efforts, with dramatic human, social and economic consequences. To face this challenge, improved diagnosis, surveillance and knowledge about therapy and associated outcomes in clinical practice are needed. Furthermore, we need to increase our knowledge about the molecular mechanisms linking chronic hepatitis with cirrhosis and liver cancer that are today only poorly understood. To do this, complementary approaches are needed, combining knowledge gained and evidence collected from different types of studies such as clinical, epidemiological and molecular studies. We have the capacity and expertise to perform these different types of studies. A work that is made possible by recent molecular biology technical advances and our molecular epidemiology laboratory, which focuses on genomics, proteomic and microbiome analysis, and most importantly by our longtime field, clinical and educational work in China. By using cutting edge microbial metaproteomic techniques we will be the first to study the chemical link between gut microbes and liver cancer in the high risk Chinese population as well as in the Swedish population.

Interested in recruiting a PhD student, postdoc or a visiting scientist

Project title:
Functional evaluation of therapeutic potential of leukemia-associated niche factors

Supervisor: Hong Qian, Ph.D, assistant professor, Group leader,
Center for Hematology and Regenerative Medicine (HERM), Department of Medicine Huddinge, Karolinska Institutet
Email: hong.qian@ki.se Group website: http://ki.se/en/medh/hong-qian-group

Qualifications of applicant: we are looking for a highly self-motivated person PhD student, postdoc or visiting researcher with a keen interest in bone marrow mesenchymal stem cells and hematopoietic microenvironment. Experience in working with cell culture techniques, multi-color flow cytometry, mice and bioinformatics is desired; and good ability to communicate in English (written and verbal) is required. The successful candidate will work as a doctoral student or postdoctoral researcher under the group leader (assistant Professor Hong Qian).

A short project description
Chronic myeloid leukemia (CML) is a myeloproliferative stem cell neoplasm characterized by presence of the BCR-ABL fusion gene encoding active tyrosine kinase. Although current treatments tyrosine kinase inhibitors (TKI) have dramatically improved the prognosis of CML, they do not eradicate leukemic stem cells (LSC) which maintain the disease. This has led to the life-long treatment and the high risk of relapse or disease advance after TKI discontinuation or development of TKI resistance. This might be attributed to residual LSC protected by bone marrow (BM) stroma, so called BM niche. Therefore, there is a great demand to identify new alternative treatments targeting BM niche and uncoupling leukemic cells from their protective niche. To do this, understanding the molecular pathways mediating the interactions between LSCs and their BM niche is a prerequisite. The BM niche contains multiple types of stromal cells and cytokines, growth factors as well as extracellular matrix proteins produced by the cells. We have identified several CML associated candidate factors that are dramatically deregulated in CML BM niche. The project aims to functionally evaluate the therapeutic potential of these molecules in the initiation or progression of CML. The potential findings from the project will advance our understanding of molecular interplay between CML leukemic cells and their BM niche, which may serve as new therapeutic targets for the treatment of CML.

This project is a continuation of an ongoing project in my group. We are currently testing the protocols for the function evaluation of the leukemia-associated molecules. The *in vivo* testing the therapeutic effects of the molecules will be done on a BCRABL CML mouse model which has already been imported to my group at Karolinska Institute.

Interested in hosting a PhD student

Project title: Relation of multimorbidity and polypharmacy with brain aging and cognitive decline in old age: a population-based MRI study

Supervision

Main supervisor: Chengxuan Qiu, PhD, Associate Professor and Senior University Lecturer, Aging Research Center (ARC), Department of Neurobiology, Care Sciences and Society (NVS), Karolinska Institutet. Email: chengxuan.qiu@ki.se; Personal page at KI: http://ki.se/en/people/cheqiu).

Co-supervisors: Kristina Johnell, PhD, Professor; Rui Wang, PhD, Postdoc; Amaia Calderón-Larrañaga, PhD, Postdoc; Laura Fratiglioni, MD, PhD, Professor, ARC, Department of NVS, KI.

Type of Recruitment

A four-year full-time doctoral (PhD) position in the major of medicine/geriatric epidemiology, supported by a scholarship from CSC (50%) and a project grant (50%).

Qualifications of the Applicant

The applicant should have (general requirements): (1) a bachelor degree or equivalent of education in medical science or biology or public health plus a master degree in biostatistics and epidemiology; (2) experiences or skills of using statistical software such as SAS, SPSS or Stata; (3) documents or certificates to demonstrate the proficiency in English language; and (4) good communication skills and ability to interact effectively and work productively with others in a multidisciplinary research group.

Project Information

Brief project description: (1) ***Background***: Multimorbidity (concurrent presence of two or more chronic health conditions) and polypharmacy (concurrent use of several medications) are highly prevalent among older adults. However, the associations of different patterns of multimorbidity (e.g. cardiovascular and neuropsychiatric disorders) with brain lesions and cognitive dysfunction, as well as the potential impact of medical therapy (e.g. cardiovascular and psychiatric medications) on these associations remain to be elucidated. (2) ***Purposes***: The overall aim is to explore the relationships of multimorbidity and polypharmacy with pathological brain aging and cognitive dysfunction among older adults. Specifically, the project seeks to investigate (i) prevalence and time trends of multimorbidity (with a focus on cardiovascular multimorbidity) and polypharmacy in an elderly population; (ii) the relation of multimorbidity and cardiovascular multimorbidity with brain lesions; (iii) polypharmacy in association with brain lesions; and (iv) impact of medical therapy on the association of multimorbidity with decline in global cognitive function. (3) ***Methods***: The overall goal and specific aims will be properly addressed in a series of studies based on the population-based Swedish National study on Aging and Care in Kungsholmen (SNAC-K, n=3363) in central Stockholm, and the embedded SNAC-K magnetic resonance imaging study (SNAC-K/MRI, n=555). At baseline (2001-2004) and subsequent follow-ups until 2016, data on demographics, lifestyles and health-related behaviors, health conditions, use of medications, and global cognitive function were collected following a standardized procedure. Markers of brain vascular and neurodegenerative lesions were assessed in the SNAC-K/MRI sample. Different statistical approaches will be utilized to address those specific research questions. (4) ***Relevance***: Understanding the relationships of multimorbidity and polypharmacy patterns with cognitive dysfunction in aging as well as potential neuropathological mechanisms may help achieve a longer and healthier life.

Aging Research Center (ARC) at Karolinska Institutet (KI) (http://ki-su-arc.se/; http://ki.se/en/)

ARC at NVS/KI is a multidisciplinary center devoted to aging and health. Researchers at ARC conduct scientific research, educate the next generation of aging researchers, and spread information about our research findings within and outside the scientific world. Our research group includes senior researchers, postdocs, doctoral students, and visiting scientists. We study the transitional process of health in aging from medical and psychosocial perspectives.

Interested in recruiting a PhD student

Project title: TIME COURSE OF ALLOIMMUNISATION DURING PREGNANCY: CONSEQUENCES FOR OPTIMISATION OF SCREENING AND PROPHYLAXIS

Supervisor: Marie Reilly, Professor of Biostatistics (Marie.Reilly@ki.se)
Dept. of Medical Epidemiology & Biostatistics, Karolinska Institutet

Qualifications of applicant: This project is suitable for a medical or health science graduate with good quantitative skills, a keen interest in population health issues such as screening and maternal/neonatal health, as well as an interest in research training in epidemiology and biostatistics. The project would ideally suit a graduate with a Master degree in epidemiology or public health, who has an interest in developing the skills for a career in a medical research environment. Experience of handling large population databases and statistical software tools (such as SAS) is desirable. Good communication skills and a capacity to collaborate are essential as the project is multi-disciplinary spanning clinical medicine, health services and epidemiology.

SUMMARY OF RESEARCH PLAN

Background: Screening for red blood cell antibodies, follow-up of alloimmunised pregnancies, and prophylaxis of Rhesus negative women immunised with anti-D antibody, are standard components of maternal care in many countries. Immunisation due to anti-D or other antibodies is rare, raising questions about the cost-effectiveness of screening and the potential for optimisation, of not just who but when to screen, monitor and treat. Despite the accumulation of extensive electronic records, protocols vary widely between (but also within) country.

Aim: To investigate how information on the time course of alloimmunisation can help optimise the identification, follow-up and prophylaxis of pregnancies at risk. The **specific aims** are to:

1. model the profile of alloimmunisation risk during pregnancy to identify a “risk window”
2. compare the timing and severity of immunisations due to prior transfusion or pregnancy
3. use repeated titres and concentrations to estimate the association between accumulated antibody exposure and adverse pregnancy outcome.
4. investigate if anti-D prophylaxis in late pregnancy provides protection through delivery.

Methods: Using a large population register, we will model the “risk-window” for optimal screening (Aim 1 and 2). Using a regional quality register, we will compare the severity of early alloimmunisations due to different prior exposures (Aim 2), and apply methods from toxicology to investigate how the accumulated antibody exposure impacts on fetal health (Aim 3). In a prospective cohort of 100 Rhesus-negative women carrying a Rhesus-positive fetus, a pharamokinetic study will investigate the protective levels of anti-D IgG at full-term following prophylaxis at week 28-30 (the current routine) and a booster at week 38.

Significance: Our findings can provide timely and relevant evidence for expert groups working on optimising and harmonising screening programs and contribute to the development of more equitable and cost-effective protocols.

Interested in recruiting a CSC scholar

PROJECT TITLE: TUMOR ASSOCIATED MACROPHAGES- AS PREDICTIVE, THERAPEUTIC AND MECHANIST TOOLS IN BREAST CANCER

SUPERVISOR/HOST: Charlotte Rolny, PhD. Associate Professor
Cancer Center Karolinska, Dept. of Oncology-Pathology, Karolinska Institutet
E-mail: charlotte.rolny@ki.se; Phone: +46 (0)707335006 (Cell) Office. +46(0)851773280
Web page: http://ki.se/en/onkpat/charlotte-rolnys-group

OVERALL AIM

In the past two decades, it has become evident that Tumor Associated Macrophages (TAMs) fuel tumor progression. Many questions remains to be answered in terms how the tumor-promoting phenotype of TAMs is generated and maintained. This research proposal aims to find novel therapeutic strategies that have the capacity to reprogram TAMs to acquire an anti-tumoral phenotype that will restrict tumor progression as well as elucidating if TAMs can be used as biomarkers in human cancers.

SPECIFIC AIMS

Aim 1: To elucidate if VEGF-C expressing macrophages can be used as a prognostic, predictive and/or mechanistic tools.
Aim 2: To identify new targets, which educates macrophages towards an anti-tumoral phenotype and hampers tumor progression.
Aim 3: To further investigate if SEMA3A can be used as prognostic and therapeutic tool.

BACKGROUND

TAMs can crudely be divided into two sub-groups that are either of an anti-tumoral M1-phenotype or of a pro-tumoral M2-phenotype. M2-macrophages (M2-Mϕs) fuel tumor progression by secreting factors that suppress cytotoxic immune cells. On the other hand, M1-Mϕ are thought to restrain tumor growth by secreting pro-inflammatory factors that activate and recruit immune cells with anti-tumoral properties, such as cytotoxic T cells and Natural Killer (NK) cells. We have recently unraveled a new mechanism whereby the guidance molecule Semaphorin 3A (SEMA3A) selectively enhances proliferation of anti-tumoral M1-Mϕwhile the proliferation of pro-tumoral M2-like Mϕs is restricted. Preliminary data indicate that SEMA3A regulates M1-and Mϕ proliferation via its receptor Plexin A4. Further support that SEMA3A is a key molecule in cancer was obtained in studies of samples from breast cancer patients where immunohistochemical levels of SEMA3A correlated with the expression of genes characteristic anti-tumoral immune cells. We also have preliminary data that We now have preliminary data indicating that SEMA3A mediated expansion of M1-like macrophages is mediated by its tyrosine kinase receptor Plexin A4. Therefore, it is timely to investigate the underlying mechanisms whereby Plexin A4 mediates selective expansion of M1-like Mϕs. We will also explore if SEMA3A can be used as a prognostic marker in other cancer types.

METHODS AND PLANNED STUDIES

We use murine breast cancer cell lines with different metastatic properties and state-of-the-art transgenic and chimeric mouse models in order to find novel candidate drugs that target TAMs to restrict metastatic dissemination. Firstly, we will elucidate TAM signatures that dictate the route of lymphatic or haematogenous metastatic dissemination by investigating the role of TAM derived VEGF-C. Secondly, we are investigating macrophage-derived candidate genes that are regulated by RNA translational control and are potentially involved in promoting tumor cell dissemination. Thirdly, we have identified the guidance molecule Semaphorin to be involved in selectively enhancing the proliferation of anti-tumoral macrophages we will now further investigating the underlying mechanisms whereby SEMA3A regulates macrophage proliferation and if SEMA3A can be used as a prognostic tool in human cancer.

Interested in recruiting a PhD student postdoc or visiting researcher

Project title: Second messenger cyclic di-GMP signaling in *Salmonella typhimurium*

Supervisor: Ute Römling, PhD, Professor of Medical Microbial Physiology
Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet, Stockholm,
Email: Ute.Romling@ki.se
Link to group home page: http://ki.se/en/mtc/ute-romling-group

Type of recruitment:
can be on all education levels from Master student to Visiting researcher

Qualifications of the applicant:
Master studies in Microbiology, Biochemistry, Biology, Veterinary Medicine, Medicine, Chemistry, and related subjects; PhD or post-doctoral education in these subjects.

Short project description:
My long-standing research interest is the molecular and epidemiological analysis of multicellular behavior (biofilm formation) in microorganisms with a focus on regulation of biofilm formation and related phenotypes by cyclic di-nucleotide second messenger signaling and the implication of extracellular matrix production. Furtheron, my group investigates the impact of biofilm formation on microbial-host interaction.
We have (re)discovered the bacterial second messenger cyclic di-GMP which mediates the transition between motility and sessility in 2004. Lateron, we also showed that cyclic di-GMP mediates the transition between acute virulence and biofilm formation in *Salmonella typhimurium* whereby low cyclic di-GMP levels promote acute virulence properties such as invasion and stimulation of pro-inflammatory cytokine production. Projects in my group broadly center around these topics.
We use microbiological, genetic, biochemical and other approaches to solve the research question. I welcome applicants with a keen interest and an outmost capability in tackling microbiological questions with a broad range of techniques and experimental approaches.

Some references
Ahmad I, Wigren E, Le Guyon S, Vekkeli S, Blanka A, El Mouali Y, Anwar N, Chuah ML, Lünsdorf H, Frank R, Rhen M, Liang ZX, Lindqvist Y, Römling U. The EAL-like protein STM1697 regulates virulence phenotypes, motility and biofilm formation in *Salmonella typhimurium*. Mol Microbiol. 2013, 90:1216-32.
Römling U, Galperin MY, Gomelsky M. Cyclic di-GMP: the first 25 years of a universal bacterial second messenger. Microbiol Mol Biol Rev. 2013, 77:1-52.
Lamprokostopoulou, A., Monteiro, C., Rhen, M. and Römling, U. (2010) C-di-GMP controls virulence properties of *Salmonella enterica* serovar Typhimurium at the mucosal lining, Environ Microbiol, 12, 40-53.
Simm, R., Morr, M., Kader, A., Nimtz, M. and Römling, U. (2004) GGDEF and EAL domains inversely regulate cyclic di-GMP levels and transition from sessility to motility, Mol Microbiol, 53, 1123-1134.

Interested in recruiting a postdoctoral fellow

Project title:
Defining the ability of Dendritic cells in priming CD4+ T cells to mycobacteria

Principle investigator:
Antonio G Rothfuchs, Associate Professor
Department of Microbiology, Tumor and Cell Biology (MTC), Karolinska Institutet

Contact: antonio.rothfuchs@ki.se , phone: +46-8-52485252.
Rothfuchs project webpage: http://ki.se/research/rothfuchs

Qualifications of applicant:
PhD in Immunology or Infection biology. Prior experience in mouse models and flow cytometry are important. Previous experience in tissue culture work and handling mycobacteria or other microbiological agents is a merit. Applicant must be fluent in English, have good communication skills and be able to work as part of a team.

Short project description:
During *T-cell priming* naïve T cells are activated by *Dendritic cells* (*DCs*) in lymph nodes. This fundamental process that arms T cells to fight-off pathogens and tumors is poorly understood during infection with *Mycobacterium bovis* Bacille Calmette- Guérin (BCG), the only available but ineffective vaccine against tuberculosis. ***Our aim is to define the contribution of DCs in priming CD4+ T cells to BCG***. Indeed, little is known about T-cell priming in the lymph node that drains the BCG infection (vaccination) site in the skin, and in particular how DCs and BCG bacilli relocate from the infection site in the skin to the lymph node. To begin addressing this we employed a BCG infection model in mice, and using a CFSE-based migration assay recently developed in our laboratory (Bollampalli et al, *J Vis Exp,* 2016, in press), discovered a migratory skin DC sub-population that actively transports BCG to the lymph node to trigger priming to the bacilli (Bollampalli et al, *PLoS Pathog*, 2015, 11:e1005206). It remains unclear though, if this DC subset directly primes T cells to BCG. Our studies also suggest that BCG may drain to the lymph node in the absence of DC transport, but the contribution of the latter to priming is entirely unknown. ***The goal of this project is thus to investigate the relative contribution of DC subpopulations in T-cell priming to BCG and also to determine if lymphatic drainage of BCG in the absence of DCs affects the outcome of such priming.*** Our experiments make use of a robust BCG infection model in mice, transgenic tools, multi-color flow cytometry and the ability to deliver BCG and DCs to the lymph node via intralymphatic injections. These studies offer new avenues for manipulating DCs for clinical benefit and for improving the efficacy of BCG and other vaccines of lowto- modest efficacy that rely on CD4+ T-cell responses; they are also relevant for the immunotherapy of cancer.

Keywords: Dendritic cells; T cells; mycobacteria; mouse models; intralymphatic injections.

Interested in recruiting a postdoctoral fellow

Project title: Oxygen sensing and Cancer

Supervisor's name: Susanne Schlisio, PhD (susanne.schlisio@licr.ki.se)
Ludwig Institute for Cancer Research and Department of Microbiology, Tumor and Cell Biology
Karolinska Institutet
Link to group home page: http://www.ludwigcancerresearch.org/location/stockholm-branch/susanne-schlisio-lab

Qualifications of applicant: PhD degree

Project description:
Our research concerns the mechanisms of how disruption of oxygen-sensing pathways can lead to cancer. Oxygen sensors enable the cell to adapt to low-oxygen environments and are critical for normal development and apoptosis. These events are often disrupted in the development of tumors. Oxygen sensing is mediated partly via prolyl hydroxylases that require molecular oxygen for enzymatic activity. Our work focuses on how prolyl hydroxylases execute apoptosis in neural precursors during development and how disruption of this process can lead to certain forms of nervous-system tumors, such as neuroblastoma.

Our first milestone paper was published in ***Cancer Cell*** describing a novel oxygen-sensing pathway mediated by prolyl hydroxylase EglN3. We demonstrated that EglN3 activity is required for apoptosis during neural development when levels of nerve growth factor (NGF) become limiting. We further showed that apparently unlinked genes implicated in pheochromocytoma act in a single common pathway impinging on EglN3 apoptotic activity. We provided evidence that all the genetic defects act by decreasing the likelihood of apoptosis of neural crest cells during development. The study gives particular insight on how mutations affecting succinate dehydrogenase components could be tumorigenic.

However, the mechanism of EglN3 apoptotic function remained unknown. We recently published the results of an unbiased genome wide RNAi screen that identified genes that are required for EglN3 to induce cell death. One of them is called 'KIF1Bβ', a gene that resides on human chromosome 1p36, which is commonly deleted in neuroblastomas.

Our current work on EglN3- and KIF1Bβ-mediated neuronal apoptosis points to interesting questions regarding the development of tumors arising from the same cellular origin and the implication of oxygen sensing pathways during development or in the adult in various diseases. The heart of our current research is:

1. *To understand how EglN3 regulates KIF1Bβ, and how this translates into cell death*
2. *To investigate whether KIF1Bβ is a neuroblastoma tumor suppressor* in vivo
3. *To study cancer metabolism and its direct impact on the prolyl hydroxylase function and apoptosis*

Interested in recruiting postdoc

Project title: **Understanding adult vertebrate regeneration**

Supervisor: Andras Simon, PhD, Professor, Department of Cell and Molecular Biology
Email Andras.Simon@ki.se; Lab website: www.simonlab.se

Qualification s of applicant: strong background in cell and molecular biology

Research summary:
Natural examples of regeneration, such as salamanders, may unravel novel strategies for cell replacement of damaged or lost tissues. We study regeneration mechanisms in an aquatic salamander, the newt, which has the widest repertoire of regenerative abilities among adult vertebrates.

We address how salamanders regenerate complex structures, such as entire limbs during their entire life span? Conversely, why do not mammals display comparable regenerative responses after injury?

We have two main experimental systems: brain and limb regeneration.

1. Brain regeneration:

In these projects we ask how the adult brain maintains its capacity to functionally replace lost neurons. We aim to identify cellular source(s) of new neurons, and to characterize molecular mechanisms controlling adult neurogenesis. In particular we are interested in how the brain senses the extent of cell loss in relation to the normal homeostatic state. A key current hypothesis of ours is that neurotransmitter signaling plays a central role in the control of neurogenesis both during homeostatic conditions and during regeneration. We study neurotransmitter signaling not only to reveal its impact on the production of new neurons but we also manipulate neurotransmitter signaling as a means to address lineage relationships between neural stem and progenitor cells in the adult brain.

2. Limb regeneration

The target tissue of our investigations in the context of limb regeneration is skeletal muscle. Skeletal muscle may contribute to limb regeneration in two ways; either by activation of quiescent stem cells or by dedifferentiation of differentiated muscle fibers. By various cell tracking strategies we try to compare these two processes to each other in terms of their relative contribution to the limb. We also characterize molecular processes involved in the generation of limb progenitors from skeletal muscle. At present we heavily focus on the balance between cell death andcell survival during the production of muscle progeny.

Key publications:
Sugiura et al, 2016, Nature
Hameed et al, 2015, Elife
Sandoval-Guzman and Wang et al, 2014, Cell Stem Cell
Simon, 2013, Nature
Berg et al, 2011, Cell Stem Cell

Interested in recruiting one PhD student, one postdoc and visiting researchers

Project title: Sino-Swedish Integrated Multisectorial Partnership for Antibiotic Resistance Containment (IMPACT)

Supervisor/host: Cecilia Stålsby Lundborg, Professor
Global Health - Health Systems and Policy (HSP): Medicines, Dept of Public Health Sciences
Cecilia.Stalsby.Lundborg@ki.se +46 (0) 8 524 833 66, + 46 (0) 70 210 26 73

Type of recruitment: one visiting researcher (professor level 3-6 months), one post-doc (12-24 months) and one doctoral student (48 months).

Qualifications of applicant:
The applicants should have an educational background of relevance to the project and also be interested in policy development and implementation. Further they should have knowledge in quantitative data analyses and preferably qualitative analyses. Data collection and intervention is now ongoing in the project. Both the visiting researchers and the doctoral student will spend their time in Sweden analysing data, taking part in academic activities and writing manuscript. Short term-visits to microbiology laboratories and practical work in a lab if appropriate can be arranged.

Abstract for the project
To minimize emergence and dissemination of antibiotic resistance (ABR) a holistic one-health approach is called for at national and international levels. This project aims to (i) increase basic knowledge of the complex routes of dissemination of ABR between sectors (humans, animals, the environment), (ii) increase basic knowledge of factors contributing to irrational use of antibiotics (ABs) in humans and animals, (iii) integrate this new knowledge with existing evidence to design and pilot interventions aiming to limit development and spread of ABR, and (iv) promote adequate infection prevention and control and access to effective ABs for humans and animals for improved public and animal health and consequently efficient, sustainable animal food production. Molecular investigations will map and correlate the occurrence of ABR clones in; humans (commensal, clinical isolates), animals (household, farm animals), food, drinking water and the environment (water, sewage, manure). Antibiotic residues will be mapped as well as AB use (humans and animals), perceptions, knowledge, attitudes and practice among key stakeholders (community members, farmers, health care providers, animal health advisors). The project continues an ongoing collaboration coordinated by Public Health Agency of Sweden and Zhejiang University and including a number of other collaborating partners including Karolinska Institutet and has its data collection and implementation in Shandong Province, China. Partners in the project have a multidisciplinary background including human medicine-, animal-, food- and environmental competence.

Interested in recruiting a PhD student

Project title:

Polycystic ovary syndrome: Importance of intrauterine environment and development of new treatments.

Supervisor and Principal Investigator (PI):

Elisabet Stener-Victorin, Senior Researcher, Associate Professor. Department of Physiology and Pharmacology, and guest professor at Heilongjiang University of Chinese Medicine, Harbin, China.
The PI has been main supervisor for 6 PhD thesis and co-supervisor for 8 PhD thesis.

Contact: Elisabet.stener-victorin@ki.se Phone +46 705643655
Link to group homepage: http://ki.se/en/fyfa/reproductive-endocrinology-and-metabolism

Qualifications of the applicant:

For this project it is desired that the applicant has a background in physiology (reproductive endocrinology and metabolism) and molecular biology. Knowledge of basic laboratory methods, primary cell culture, breading, animal handling, and basics in statistics and bioinformatics is of advantageous.

Short project description: Polycystic ovary syndrome (PCOS) is a common endocrine disorder with multiple severe health consequences for women who are affected. To date, there is no efficient treatment to offer and our understanding of the molecular mechanisms of PCOS is limited. Emerging evidence from maternal androgenized animal models and women with PCOS indicate that maternal androgen excess may predispose the development of a metabolic and anxiety-like phenotype of PCOS in the offspring. Maternal obesity is another common feature of PCOS causing an unfavourable intrauterine environment and is associated with maternal gestational diabetes and psychiatric problems in the offspring. In addition we currently investigate whether women with PCOS exhibit transcriptional and epigenetic changes in skeletal muscle and adipose tissue, and if muscle contractions caused by electrical stimulation can restore these changes.

The overall hypothesis is that high maternal androgens and maternal obesity transgenerationally remodels the epigenome (somatic or germline) and cause metabolic aberrations with impaired adipose stem cell differentiation, metabolic dysfunction and anxiety-like behaviour in the offspring, and that physical exercise/muscle contractions can prevent the development of these alterations. Information about which genes that are affected and reversed by exercise are potential targets for new drug development.

The present PhD project involve translational *in vitro* studies on primary human and mice target tissues/cells, and *in vivo* studies in different mice models with and without diet induced obesity and in women with and without PCOS to test our hypotheses in detail.

Interested in recruiting PhD student, postdoc or a visiting scientist

Title: GPR37 as a novel therapy target in Parkinson´s disease: A translational approach

Supervisor: Professor Per Svenningsson, CMM, Department of Clinical Neuroscience, Per.Svenningsson@ki.se
Group home page: http://www.cmm.ki.se/group/translationell-neurofarmakologi

Recruitment: Visiting researcher, postdoctoral fellow and/or doctoral student

Qualification of applicant: The studies relate to the role of 7TM receptor-mediated processes in the etiologies of Parkinson's disease. In particular, the role of GPR37 in neurodegeneration shall be studied. Various molecular and cellular assays for receptor trafficking, dimerization, aggregation, signaling and function will be employed. Successful applicants will generate data on the aforementioned topics that guide the development of novel approaches to be tested in animal models of Parkinsonism and patient samples. Independence and strong motivation are expected throughout the project. Applicants should have an interest in the field of Biomedical Science, Biophysics and/or Engineering. A strong background in molecular and cellular neurobiology, preferably in the neuroscience field, is advantageous. Command of the English language is highly preferred.

Short project description: The next breakthrough in the treatment of synucleinopathies, incl Parkinson´s disease (PD), will be aimed at interference of disease progression based on insights into the underlying pathogenic process. The pathological hallmark of PD are Lewy bodies (LBs), in which α-synuclein is the major constituent together with other PD-linked gene products (DJ-1, LRRK2, parkin, and GBA) and aggregated GPR37. GPR37 is exceptional among GPCRs having a high propensity for intracellular receptor accumulation and aggregation leading to neurotoxicity. However, unexpectedly, our results suggest that GPR37 is neuroprotective in dopaminergic when located at the plasma membrane. Consistently, prosaposin (PSAP), and its neurotrophic fragment prosaptide, were recently identified as agonists at GPR37. In chemical screens, we have recently found compounds that increase GPR37 levels at the cell surface. Pivotal to this programme is modeling and analysis of GPR37 together with the novel chemicals, which will grossly facilitate mechanistic understanding and drug development with potential use in diagnosis and treatment. Physical interaction studies between GPR37 and the recently identified chemicals will be performed. Novel applications and technological advancements of super resolution microscopy will be implemented for trafficking of GPR37 and its novel chemical interactors. These studies will also examine whether GPCR multimerization may be neurotoxic. Normal and cGPR37KO mice will be virally transduced by α-synuclein and treated with novel chemicals to elucidate whether GPR37 surface expression in critical for neuroprotection of synucleinopathies. Evolving from the autopsy studies that anti–GPR37 label LBs, we will develop GPR37 ligands as PET tracers for LBs in synucleinopathies.

Interested in recruiting a postdoc

Supervisor: Dr Kristiina Tammimies (http://ki.se/en/people/kritam)
Center of Neurodevelopmental Disorders at Karolinska Institutet, Division of Neuropsychiatry, Department of Women's and Children's Health, Karolinska Institutet
Division Center of Neurodevelopmental Disorders at Karolinska Institutet (KIND). KIND is a competence center for research, development and education within the area of developmental psychopathology. The center is established in collaboration between Karolinska Institutet and Stockholm County Council aiming at improving generating high-end basic research, clinical practice, and spread new knowledge to stakeholders.

Qualifications of the applicant

To qualify the applicant must hold at least PhD in Computer Science, Bioinformatics, Genetics or equivalent. The applicant must have excellent computer skills including programming (R, Perl, Python, etc.) and experience in cluster computing. Previous experience in the analysis of next generation sequencing data is an advantage. We look for highly motivated applicants that can work independently and have passion for genomics research. Good written and verbal communication skills in English are mandatory.
For more information: kristiina.tammimies@ki.se

Research group:

The position is available at KIND Genomics under supervision of Dr Kristiina Tammimies (http://ki.se/en/kind/kind-genomics). KIND Genomics is newly established group at KIND focusing on understanding genetic and biological factors associated with neurodevelopmental disorders such as autism spectrum disorder. We are using different genetics platform including DNA genotyping microarrays and next generation sequencing. We are conducting translational research by combining data from neuropsychology, neuropathology, neuroimaging and environmental factors with the genetic data to understand the biological mechanisms leading to neurodevelopmental disorders.

Project description

We have multiple on-going projects in which we analyze genomic information from individuals and families with autism spectrum disorder. This project aim in studying genotype-phenotype-outcome correlations across different NDDs. This will be done using genome-wide genetic data to identify genetic risk profiles (including causal rare mutations) associated with treatment outcome and predict developmental trajectories in individuals with NDD and children at high-risk for the disorders. Additionally, we will examine frequency of rare mutations in genes implicated in medical conditions identified as co-occurring conditions with NDDs using national patient registries and accessible genomic data sets. The results of this project will aid in taking the next steps in personalized genomic health services for NDDs.

Intent of hosting a PhD student

Project title: Risk factors for injurious falls in older adults: does gender matter?

Supervisor: Anna-Karin Welmer, PhD, Associate Professor; Aging Research Center, Department of Neurobiology, Care Sciences and Society (NVS), Karolinska Institutet
Phone: (+46) 8 690 68 66; fax: (+46) 8 690 68 89; e-mail: anna-karin.welmer@ki.se

Type of recruitment: A doctoral student

Qualifications of applicant: The student should preferably have a background in public health, biostatistics or epidemiology. In addition, we look for a student with good knowledge in biostatistics and use of statistical software (e.g., SAS, SPSS, or STATA).

Project description: Injuries resulting from falls are leading causes of long-standing pain, disability, and death in older adults. Women are more frequent fallers and at higher risk of an injurious fall than men. Little is however known about whether risk factors for injurious falls differ between older men and women. The goal of this project is to investigate whether gender-specific risk factors for injurious falls exist in the older population, in order to establish whether gender should be taken into account in fall-prevention programs. Specifically, we aim to examine possible gender differences in the associations between incident injurious falls and I) impairment in different domains of physical function, such as gait, balance and muscle strength, II) loss of vision and hearing, alone and in combination; III) physical activity and sedentary behavior; and IV) the number of medications, taking into account comorbidities and use of fall-risk inducing drugs. The first, second and third second aims will be achieved using data from the Swedish National study on Aging and Care in Kungsholmen, in which data on 3363 participants aged ≥60 years were gathered at the beginning of the study and every 3 or 6 years thereafter through interviews and clinical examinations. The fourth aim will be achieved by using data from nationwide registers, including the Swedish Prescribed Drug Register and the National Patient Register.
Description of the research group: This doctoral project will be conducted at the Aging Research Center, Karolinska Institutet, a multidisciplinary center with a focus on health in aging. The research group is multidisciplinary and consists of researchers with extensive expertise in fields such as rehabilitation, geriatric epidemiology, neurology, psychology, pharmaceutics, and statistics (www.ki-su-arc.se).

Interested in recruiting a postdoc

SUPERVISOR:
Weng-Onn Lui, Associate Professor
Department of Oncology-Pathology, Karolinska Institutet.
Email: weng-onn.lui@ki.se

QUALIFICATIONS OF APPLICANT:
We are seeking a highly motivated postdoctoral fellow, who has a strong background in molecular biology and cancer research. The applicant should have good communication skills and ability to interact effectively and work productively in a team of researchers. Previous experience in the fields of autophagy and RNA biology is favorable.

RESEARCH GROUP:
Our group focuses on fundamental biological mechanisms in cancer development, with a special interest in small RNAs along with other regulatory components.

PROJECT DESCRIPTION:
In this project, we will investigate novel function of TARBP2 (Trans-activation responsive RNA binding protein 2). TARBP2 is a double-stranded RNA binding protein, which is known to play an important role in miRNA processing. Besides miRNA precursors, TARBP2 can also bind to other RNA stem-loop structures, such as HIV-1 TAR RNA. TAR RNA element is a stable stem-bulge-loop structure that is present at the 5' end of all HIV-1 mRNAs, which plays important roles in both translational and transcriptional regulation. TAR RNA-like structures are also found in many human transcripts. This project will characterize putative targets of TARBP2 and elucidate the functions and mechanisms of TARBP2-mediated post-transcriptional regulation in human cancer.

Interested in recruiting a PhD student or a postdoc

Project title:
Studying the role of antibodies in health and disease using CRISPR screens

Supervisor:
Fredrik Wermeling, PhD, Assistant Professor
Department of Medicine, Solna, Karolinska Institutet
Email: fredrik.wermeling@ki.se , Group home page: www.wermelinglab.com

Qualification of candidate:
We are currently looking for PhD student and postdoc applicants with a background fitting with the proposed projects.

Short project description:
The Wermeling lab has an interest in antibodies in the context of autoimmune disease and cancer immune therapy. We also study hematopoietic stem cells and factors influencing development of myeloid cells. We put a lot of effort in studying these topics using in vitro and in vivo CRISPR screens.

Interested in recruiting a postdoc (24 months)

Title of the project: Cognitive impairment, cognitive restoration and early diagnosis in Alzheimer's disease: a multimodal study of the cholinergic system'

Main supervisor
Eric Westman, Associate Professor
Division of Clinical Geriatrics; Center for Alzheimer Research; Department of Neurobiology, Care Sciences and Society; Karolinska Institutet.

Co-supervisors
Lars-Olof Wahlund, Professor
Division of Clinical Geriatrics; Center for Alzheimer Research; Department of Neurobiology, Care Sciences and Society, Karolinska Institutet
Maria Eriksdotter, Professor
Division of Clinical Geriatrics; Center for Alzheimer Research; Department of Neurobiology, Care Sciences and Society, Karolinska Institutet
Daniel Ferreira, PhD
Division of Clinical Geriatrics; Center for Alzheimer Research; Department of Neurobiology, Care Sciences and Society, Karolinska Institutet.
Contact: daniel.ferreira.padilla@ki.se

Home page of the group
Division: http://ki.se/en/nvs/division-of-clinical-geriatrics
Group: http://ki.se/en/nvs/imaging-research

Brief description of the project
The overall aim of this project is to investigate the role of the cholinergic system in cognition by using novel neuroimaging and molecular techniques. The basal forebrain is composed of cholinergic cells with their neuronal bodies located at the basal forebrain. We will use a novel method based on structural magnetic resonance imaging (sMRI) to reconstruct separated parts of this region. Then we will model cholinergic projections to the hippocampus and different neocortical regions using diffusion tensor imaging (DTI) and functional magnetic resonance - resting state (fMRI-RS). We will also investigate other novel cholinergic markers such as ChAT activity and the Ach index based on electroencephalography (EEG). We will study associations with cerebrospinal fluid markers of amyloid burden and neurodegeneration, as well as genetic factors (ApoE e4). Finally, we will try to translate findings and knowledge acquired in this project to the clinical benefit. We will try to generate and will investigate the utility of a diagnostic index for early diagnosis of AD and differential diagnosis with other dementias and depression. The study sample includes healthy controls, individuals with subjective cognitive decline, mild cognitive impairment and pacients with Alzheimer's disease and other dementias. Around 2150 individuals will be included by combining five unique international cohorts already available at our group.
The fellow will work together with four co-supervisors with different expertise (neuropsychology, medicine, geriatrics, engineering). The fellow will also be in contact with many other researchers and students at our group and NVS Department, and will be able to attend numerous scientific activities at Karolinska Institutet.

Interested in hosting Visiting researchers, postdocs and PhD students

Project title: **The role of non-coding RNAs in human skin wound healing**

Supervisor's name: Ning Xu Landén**,** Assistant professor, Unit of Dermatology and Venereology, Department of Medicine, Solna, Karolinska Institutet
Email: ning.xu@ki.se
Link to group homepage: http://ki.se/en/people/ningxu

Type of recruitment: Visiting researchers (for 1 year-period), post-doctoral fellows (for 2 year-period), and doctoral students

Qualification of applicant:
1. Visiting researchers and post-doctoral fellows:
The candidate should have obtained a PhD degree within the area of molecular or cell biology and have deep interest in medical and biological problems. The applicant is preferred to have documented previous experience with RNA research, especially in the field of non-coding RNAs. Previous experience with tissue culture, molecular and biochemical techniques is desired. A high level of English, spoken and written, is a requirement.

2. Doctoral students:
The candidate should have a master degree within the area of medicine or molecular or cell biology and have deep interest in medical and biological problems. A high level of English documented by an internationally recognized test e.g. TOEFL or IELTS, is a requirement. The successful candidate need to be very motivated and able to work independently, and at the same time interact with scientists from other areas to coordinate complex projects. Previous experience with RNA research, tissue culture, molecular and biochemical techniques is a merit.

Project description: The immense economic and social impact of deficient wound healing e.g. chronic ulcers, post-surgical wounds care and skin scarring, calls for attention and allocation of resources to understand biological mechanisms underlying wound complications. Due to the complex nature of wounds, efficient targeted approach to enhance healing are essentially lacking today. The recent discovery of non-coding RNAs (ncRNAs) as powerful gene regulators provides hope to develop novel RNA-based treatments for a wide variety of diseases. However, the role of ncRNAs in human skin wound healing remains largely unexplored. The objective of our study is to reveal the role(s) of ncRNAs in skin wound healing and to explore the potential of RNA-based therapy for chronic wounds.

Interested in recruiting a postdoc

Project title:

Cognitive reserve counteracts the risk effect of cardiometabolic disorders on dementia.

Supervisor: Weili Xu, Associate Professor, Aging Research Center, Dept. of Neurobiology, Care Sciences and Society (NVS), Karolinska Institutet

Phone: (+46) 8 690 5848 **Fax:** (+46) 8 6906889 **E-mail:** weili.xu@ki.se

Qualification: The applicant should have PhD degree (obtained within last 5 years) in public health, epidemiology, nutrition, psychology, or biostatistics. The applicant should be familiar with epidemiological study designs, advanced statistical methods (SPSS, SAS or STATA), and basic knowledge of neuroscience.

Project description: The purpose of this project is to investigate whether higher education and stimulating lifestyle may counteract the deleterious effects of cardiometabolic diseases (diabetes, obesity and cardiovascular diseases) on cognitive decline, cognitive impairment and dementia. This project will use two large population-based studies: the Swedish National study of Aging and Care in Kungsholmen - SNAC-K on aging and care and the HARMONY study, a nationwide study on dementia in Swedish twins. The successful candidate is expected to play critical role in formulating scientific research hypothesis, testing the hypothesis using proper study design, analyzing the data, presenting and interpreting the results, and writing scientific reports and articles in English.

Work place: Aging Research Center (ARC), Department of Neurobiology, Care Sciences and Society, Karolinska Institutet

Description of the work group: Our research group consists of senior researchers, post-doctoral researchers, doctoral students, and guest researchers. We study the transitional process of aging and health from biomedical and psychosocial perspectives. More information about us at ARC can be found at: http://ki-su-arc.se/

Interested in recruiting a PhD student and/or a Postdoc

Project title:

Development and characterization of the novel long-acting anti-hyperglycemic GLP-1-IgG Fc fusion protein PPS 601 for treatment of type 2 diabetes

Supervisor: **Shao-Nian Yang**, MD, PhD, Associate Professor
The Rolf Luft Research Center for Diabetes and Endocrinology, Department of Molecular Medicine and Surgery, Karolinska Institutet, Karolinska University Hospital Solna
E-mail: shao-nian.yang@ki.se Phone: +46 8 517 794 56

Project

Glucagon-like peptide-1 (GLP-1) is a potent antihyperglycemic hormone. Unfortunately, this hormone is rapidly degraded and has a very short half-life in the circulation. Development of GLP-1 mimetics with longer half-lives and fewer adverse effects continuously receives great attention from clinicians and researchers including us. The overall purpose of this project is to develop and characterize the novel long-acting anti-hyperglycemic fusion protein PPS 601. The project objectives are: 1) to engineer PPS 601; 2) to characterize medicinal properties of PPS 601; 3) to mechanistically dissect anti-hyperglycemic effects of PPS 601; and 4) to clarify roles of PPS 601 on functional β cell mass in vivo, non-invasively, longitudinally and at single cell levels. Accomplishment of the project will pave a new avenue for overcoming diabetic hyperglycemia, produce significant socioeconomic benefits, and provide an in depth understanding of GLP-1-based medications, leading to conceptual advances in GLP-1-based therapy.

Interested in recruiting a postdoc or a PhD student

Project title: Epigenetic regulation of Hedgehog signaling. Role in medulloblastoma development

Supervisor: Peter G. Zaphiropoulos, Professor of Molecular Biology, Department of Biosciences and Nutrition, Email: Peter.Zaphiropoulos@ki.se

Type of recruitment: A post-doctoral fellow or a doctoral student

Qualifications of applicant:

- Strong commitment to curiosity-driven research
- Willingness to effectively collaborate with current members of the group
- Enjoying designing and accurately executing experimental approaches on the laboratory bench

Short project description:

Hedgehog signaling is a major developmental pathway whose deregulation has been implicated in many human cancers. About 25% of all cases of the pediatric brain cancer medulloblastoma are thought to result from hyperactivation of this signaling pathway.

Hedgehog signal transduction ultimately activates the GLI (Glioma-associated oncogene) family of transcription factors. We have demonstrated that the post-transcriptional process of RNA editing, an epigenetic mechanism, modifies the activity of the GLI1 transcription factor and its capacity to promote cellular growth.

Using RNAseq approaches we have obtained evidence that the RNA edited version of GLI1 differentially regulates gene networks when compared to the unedited GLI1. This has prompted us to employ the CRISPR/Cas9 technology to modify the endogenous GLI1 gene in such a way that only the RNA edited or the unedited version of GLI1 would be produced in medulloblastoma cells. We have recently demonstrated that medulloblastoma subclones with compromised GLI1 activity were generated using this technology. However, this has to be optimized to achieve an effective replacement of the endogenous gene with the edited or the unedited version of GLI1.

Ultimately, the impact of this epigenetic modification of GLI1 in cancerous growth, using xenograft tumor models, will be addressed.

Link to group home page: http://ki.se/bionut/zaphiropoulos

Interested in recruiting a PhD student or postdoc

Project title: Defining myeloid cell populations in chronic neurological diseases and immunotherapy

Supervisor: Xingmei Zhang, MD, PhD, Assistant Professor, Department of Clinical Neuroscience, Center for Molecular Medicine, Karolinska Institutet.
Email: xingmei.zhang@ki.se
Group home page: http://www.cmm.ki.se/en/group/applied-immunology/

Qualifications of applicant: Related background, ability to work collaboratively and a genuine interest in our work

Project description:

Multiple Sclerosis (MS) is an inflammatory autoimmune disease of the central nervous system (CNS) for which there is no current treatment for chronic disease states. Glioblastoma multiforme (GBM) is a common and lethal brain tumour with a median patient survival time of just 14.6 months.

Alzheimers Disease (AD) is a chronic neurodegenerative condition in which loss of nerve cell function leads to progressive cognitive impairment.

Effective treatments for these neurological conditions represent a currently unmet medical need. We will define the myeloid cell populations (resident microglia and infiltrating monocytes) in those pathological settings by using different mouse strains we have established that are able to specifically deplete monocytes or microglia for different periods of time. The general research aim of our research programme is to develop novel immunotherapies for treatment of these neurological diseases, which we address using a multifaceted approach including myeloid cell therapy, vaccination and tolerance induction.

Interested in recruiting a PhD student

Project Title: **Functional genomics of breast Cancer**

Supervisor: Chunyan Zhao, Associate Professor, Senior Researcher
Department of Biosciences and Nutrition, NOVUM, 141 83 Huddinge, SWEDEN
Email: chunyan.zhao@ki.se Homepage: http://ki.se/en/bionut/esr-estrogen-signaling-research-group-karin-dahlman-wright

Qualifications of applicant: highly motivated student with good communication skill

Project description:
Our group is using functional genomics approaches towards unravelling mechanisms of drug resistance in estrogen receptor (ER)-positive breast cancer and understanding molecular determinants of malignant cell behaviors in triple-negative breast cancer (TNBC). The ultimate goal is to develop novel and improved prognostic tools and therapies for patients with invasive breast tumors.

Currently there are three main projects in focus
1. Understanding the nature and composition of Fra-1 interacting protein complexes that define its target gene specificity and transcriptional properties. Recent published results from the group highlight that the AP-1 transcription factor Fra-1 is overexpressed in TNBC and has prognostic value, suggesting that the Fra-1 protein should be explored as a target for cancer therapy. Using newly developed proteomic approaches, we recently identified 116 proteins associate with DNA-bound Fra-1 within the TNBC cell nucleus. We hypothesize that several associated proteins are potential novel Fra-1 coactivators. We will further address 1) if the protein candidates coactivate Fra-1 dependent gene expression, and 2) whether depletion of the candidates renders TNBC tumors less aggressive.
2. Identification of the ER nuclear interactome to different ligands in ER-positive breast cancer cells
3 Identification of the ER nuclear interactome in tamoxifen resistant compared to tamoxifen sensitive breast cancer

Relevant publications

- Jia M, Andreassen T, Jensen L, Bathen TF, Sinha I, Gao H, **ZHAO C**, Haldosén LA, Cao Y, Girnita L, Moestue SA, Dahlman-Wright K. (2016) Estrogen receptor α promotes breast cancer by reprogramming choline metabolism. Cancer Res. 2016 Jul 25. pii: canres.2910.2015. [Epub ahead of print]
- Qiao Y, He H, Jonsson P, Sinha I, **ZHAO C** and Dahlman-Wright K. (2016) AP-1 is a key regulator of proinflammatory cytokine TNFα-mediated triple-negative breast cancer progression. J Biol Chem. 2016 Mar 4;291(10):5068-79.
- **ZHAO C**, Qiao Y, Jonsson P, Wang J, Xu L, Rouhi P, Sinha I, Cao Y, Williams C and Dahlman-Wright K. (2014) Genome-wide profiling of AP-1-regulated transcription provides insights into the invasiveness of triple-negative breast cancer. Cancer Res. 2014; 74(14):3983-3994.

Interested in recruiting a postdoc

Project title: **Database of partial sequences of common disease-related human IgGs**

Supervisor: Roman Zubarev, PhD, professor (roman.zubarev@ki.se)
Division of Physiological Chemistry I, Department of Medical Biochemistry and Biophysics
Link to group home page: http://chem1.mbb.ki.se

Qualifications of applicant: familiar with mass spectrometry, proteomics, de novo peptide sequencing, immunology

A short project description: The old paradigm in immunological sciences is that antigen specificity is determined by a completely random process which will result in unique antigen binding complementarity-determining regions (CDRs) in antibodies in different individuals. This paradigm has recently been challenged in a number of studies, including our "SpotLight Proteomics" paper (Lundström and Zubarev, submitted). There are reasons to believe that *the number of sequences of the variable region of human antibodies in the dynamic interval 1:N (n=1000, 10,000, etc.) is large but not infinite*. In SpotLight proteomics approach, blood (serum or plasma) is filtered through Melon Gel (MG), which binds all proteins but IgGs. The flow-through enriched with IgGs is then digested and analyzed by MS/MS using two complementary fragmentation techniques HCD and ETD. *De novo* sequencing program generates likely candidates; each of them is BLASTed, and the most-homologous protein assignment is retained, denoting peptide as "known". Some peptides do not produce any BLAST assignment; then the best-scoring *de novo* sequence is retained, denoted as "new". Both new and known peptides are then added to the sequence database, and conventional proteomics is then performed. The major bottleneck in the implementation of the SpotLight proteomics approach to various diseases is the limitations of *de novo* sequencing. To perform *de novo* sequencing each time a new cohort is analyzed is very time and labor consuming. Besides, due to the limited amount of information, the derived sequences are not very reliable. In contrast, database search is more sensitive than *de novo* sequencing and is also more accurate. The solution is to create and continuously expand **IgGome.dat** - a sequence database of reliable human antibody peptides appearing within the dynamic range 1:N (N=1000 for the first-generation database, n=10,000 for the second generation database, etc.). To this end blood plasma from several existing cohorts of different human diseases will be digested and de novo sequenced using precision mass spectrometry, in which we excel. This database will be an important reference material for blood proteomics, leading to discovering new biomarkers as well as true causes of common diseases.