List of research project descriptions for recruitment 2020-2021

No	Supervisor's name	Doctoral student	Visiting doctoral student	Postdoc	Visiting researcher	Department at KI	Project title
1	Aden, Ulrika			24 months	12 months	Department of Women's and Children's Health	Immunomodulation in neonatal hypoxic ischemia
2	Ahmed, Aisha Siddiqah	4 years				Department of Molecular Medicine and Surgery	Transcriptional Regulation in Chronic Osteoarthritis
3	Andersson, Olov	4 years				Department of Cell and Molecular Biology	Translational control of beta-cell regeneration for treatment of diabetes
4	Arnardottir, Hildur	4 years				Department of Medicine, Solna	Resolution of inflammation in abdominal aortic aneurysm: The role and actions of novel proresolving lipid mediators
5	Baranello, Laura			24 months		Department of Cell and Molecular Biology	TOPGOG: TOPoisomerase Dysregulation of Oncogenic Growth
6	Bergo, Martin	4 years				Department of Biosciences and Nutrition	Exploring BACH1-induced coordination of redox and metabolic pathways in cancer metastasis
7	Betsholtz, Christer	4 years				Department of Medicine, Huddinge	Elucidating mechanisms of endothelial cell fenestration
8	Bostanci, Nagihan		12 months		12 months	Department of Dental Medicine	Modelling of periodontal infection in a dynamic perfusion bioreactor
9	Cao, Yihai	4 years				Department of Microbiology, Tumor and Cell Biology	Hematopoiesis in tumors: A proof-of-principle study
10	Carlstrom, Mattias			24 months		Department of Physiology and Pharmacology	Targeting NADPH oxidase- and mitochondria-induced oxidative stress in cardio-metabolic disease and associated renal complications
11	Catrina, Sergiu		12 months	24 months	12 months	Department of Molecular Medicine and Surgery	Dissecting the mechanisms behind the inadequate hypoxia signalling in diabetes
12	Chang, Zheng	4 years				Department of Medical Epidemiology and Biostatistics	Management of ADHD and co-occurring cardiometabolic diseases
13	Chen, Gefei		12 months	24 months	12 months	Department of Biosciences and Nutrition	Mechanistic studies of amyloid aggregation associated with human diseases, molecular chaperone mediated inhibition and spider silk formation
14	Chuan-Xing, Li			24 months	12 months	Department of Medicine, Solna	Multi-Omics integrative analysis to understand chronic inflammatory lung diseases
15	Coquet, Jonathan			24 months		Department of Microbiology, Tumor and Cell Biology	Understanding the role of CD4 T cells in cancer immunity
16	Damdimopoulou, Pauliina			18 months		Department of Clinical Science, Intervention and Technology	In vitro activation of human ovarian follicles
17	Deng, Qiaolin	4 years		24 months		Department of Physiology and Pharmacology	Lineage and fata-map reconstruction of germ cells and their role in epigenetic inheritance of disease
18	Ehnman, Monika	4 years				Department of Oncology-Pathology	Prognostic education of non-malignant cells in the tumor microenvironment
19	Elsässer, Simon			24 months	12 months	Department of Medical Biochemistry and Biophysics	Capturing and modeling epigenome dynamics
20	Erlandsson Harris, Helena	4 years				Department of Medicine, Solna	Immunoprofiling of juvenile idiopathic arthritis
21	Ferreira Padilla, Daniel			24 months		Department of Neurobiology, Care Sciences and Society	Neuroimaging studies in Dementia
22	Fisone, Gilberto	4 years				Department of Neuroscience	Deep learning based analysis of behavior in mouse models of disease
23	Fogdell-Hahn, Anna	4 years				Department of Clinical Neuroscience	Immunogenicity of biopharmaceuticals
24	Fuxe, Jonas	4 years				Department of Laboratory Medicine	Exploring lymph nodes as an interface between cancer and the immune system
25	Fuxe, Jonas			24 months		Department of Laboratory Medicine	Exploring the role of the coxsackie- and adenovirus receptor in cancer metabolism
26	Gerling, Marco			18 months		Department of Biosciences and Nutrition	AI-aided digital pathology of gastrointestinal cancer liver metastases
27	Gustafsson, Nina			24 months		Department of Oncology-Pathology	Metabolic regulation of genome stability
28	Hartman, Johan	4 years				Department of Oncology-Pathology	Investigating breast cancer treatment resistance through bioinformatics
29	Hassan, Moustapha		12 months	24 months	12 months	Department of Laboratory Medicine	Personalized Medicine and Multimodal Imaging in Cancer

No	Supervisor's name	Doctoral student	Visiting doctoral student	Postdoc	Visiting researcher	Department at KI	Project title
30	Helleday, Thomas	4 years				Department of Oncology-Pathology	Combining DNA repair inhibitors and immunomodulating drugs to improve anti-cancer treatment
31	Holmdahl, Rikard			24 months	12 months	Department of Medical Biochemistry and Biophysics	Autoantibodies in rheumatoid arthritis with focus on cartilage proteins
32	Holmdahl, Rikard				12 months	Department of Medical Biochemistry and Biophysics	Oxidative regulation of autoreactive B cells
33	Jacobsson, Per-Johan	4 years				Department of Medicine, Solna	Plant based drugs against rheumatic disorders
34	Jiang, Xia	4 years	12 months	24 months	12 months	Department of Clinical Neuroscience	Using large-scale genetic data and complied analytical strategy to understand the etiology and sex disparity of multiple sclerosis
35	Kaipe, Helen			24 months		Department of Laboratory Medicine	Interactions between immune cells and cancer-associated fibroblasts in pancreatic cancer
36	Karlsson, Mikael	4 years				Department of Microbiology, Tumor and Cell Biology	Tumor associated macrophages as targets for immunotherapy
37	Karlström, Helena	4 years		24 months		Department of Neurobiology, Care Sciences and Society	Involvement of autophagy in small vessel disease using CADASIL Notch3 disease animal models
38	Kasper, Maria	4 years				Department of Cell and Molecular Biology	Uncovering body-site dependent skin cell diversity in health and disease
39	Kasper, Maria		12 months	24 months	12 months	Department of Cell and Molecular Biology	Skin and hair follicle regeneration
40	Kele (-Olovsson), Julianna (MV)			24 months		Department of Physiology and Pharmacology	Decoding and therapeutic exploration of extracellular niche in brain pathology
41	Kutter, Claudia			24 months		Department of Microbiology, Tumor and Cell Biology	Uncovering regulatory elements during organismal development and diseases
42	Kutter, Claudia				12 months	Department of Microbiology, Tumor and Cell Biology	Advancement of studying RNA and protein interaction at the single cell level
43	Larsson, Catharina	4 years				Department of Oncology-Pathology	Clinical and genetic studies of papillary thyroid carcinoma
44	Lavebratt, Catharina	4 years				Department of Molecular Medicine and Surgery	Gut-brain axis mediators in neuropsychiatric disorders
45	Leander, Karin			24 months		Institute of Environmental Medicine	Epidemiological studies of metabolic related determinants of cardiovascular event fatality
46	Lindqvist, Arne	4 years				Department of Cell and Molecular Biology	Regulation of recovery from a DNA damage checkpoint
47	Lu, Donghao	4 years	12 months		12 months	Department of Medical Epidemiology and Biostatistics	Impact of premenstrual disorders on women's health and working life
48	Lui, Weng-Onn	4 years		24 months		Department of Oncology-Pathology	Viral oncoprotein-mediated RNA regulation in Merkel cell carcinoma
49	Malin, Stephen	4 years	12 months	24 months	12 months	Department of Medicine, Solna	The molecular and cellular basis of pathological lipid accumulation in atherosclerosis and liver disease
50	Martinez Gonzalez, Itziar			24 months		Department of Microbiology, Tumor and Cell Biology	Role of Group 2 Innate Lymphoid Cells in a mouse model of atopic march
51	Melief, Jeroen			24 months		Department of Oncology-Pathology	Identifying compounds that enhance T cell-mediated recognition of human melanoma cells
52	Mulder, Jan	4 years				Department of Neuroscience	Mapping the distribution of protein coding genes in the mammalian central nervous system
53	Murrell, Benjamin			24 months		Department of Microbiology, Tumor and Cell Biology	Single-cell profiling of immune responses to SARS-CoV-2 vaccination.
54	Neufeld, Janina	4 years				Department of Women's and Children's Health	Brain mechanisms underlying detail-focused perception in autism and synesthesia – a twin study.
55	Nistér, Monica		12 months		12 months	Department of Oncology-Pathology	Crosstalk between mitochondrial dynamics and brain tumor biology
56	Näreoja, Tuomas	4 years				Department of Laboratory Medicine	Development of biomarkers and diagnostics of inflammatory osteolysis
57	Pan-Hammarström, Qiang	4 years	12 months	24 months	12 months	Department of Biosciences and Nutrition	Identification of regulatory modules and key factors that drive B-cell differentiation
58	Pawelzik, Sven-Christian	4 years				Department of Medicine, Solna	Iron metabolism and ferroptosis in calcific aortic valve disease.
59	Pelechano, Vicent		6 months			Department of Microbiology, Tumor and Cell Biology	Modelling mRNA life from synthesis to decay
60	Pelechano, Vicent				3 months	Department of Microbiology, Tumor and Cell Biology	Genome-wide investigation of mRNA life.

No	Supervisor's name	Doctoral student	Visiting doctoral student	Postdoc	Visiting researcher	Department at KI	Project title
61	Pelechano, Vicent		6 months			Department of Microbiology, Tumor and Cell Biology	Transcriptional complexity and RNA metabolism as a readout for personalised medicine.
62	Pereira, Joana			24 months		Department of Neurobiology, Care Sciences and Society	Dynamic Changes in Functional Brain Connectivity over the course of Alzheimer's Disease
63	Pettersson, Erik	4 years				Department of Medical Epidemiology and Biostatistics	Adverse outcomes in offspring of parents with psychiatric disorders: A population-based register study
64	Rodriguez-Wallberg, Kenny A.	4 years		24 months		Department of Oncology-Pathology	Investigation of risks inherent to assisted reproductive technologies in clinical and experimental studies
65	Rorbach, Joanna	4 years				Department of Medical Biochemistry and Biophysics	Immunometabolic mechanisms in human and murine models of mitochondrial dysfunction
66	Rosenqvist, Mina	4 years				Department of Medical Epidemiology and Biostatistics	Prenatal and early-life causes of neurodevelopmental disorders using genetically informative designs
67	Rundqvist, Helene	4 years		24 months		Department of Laboratory Medicine	Exercise induced immune modulation – consequences for tumor progression and responsiveness to checkpoint inhibition.
68	Sandberg, Rickard	4 years	12 months	24 months	12 months	Department of Cell and Molecular Biology	Investigating transcriptional dynamics using single-cell genomics
69	Sarhan, Dhifaf	4 years				Department of Microbiology, Tumor and Cell Biology	Studies of a newly discovered adaptive NK cells in solid tumors
70	Schlisio, Susanne	4 years				Department of Microbiology, Tumor and Cell Biology	Unlocking Vulnerabilities in malignant Paraganglioma and Neuroblastoma using single cell technology and integrated mass spectrometry
71	Selivanova, Galina			24 months		Department of Microbiology, Tumor and Cell Biology	Targeting p53 to kill tumor cells, reprogram cancer-associated fibroblasts and boost anti-cancer immune response
72	Seoane, Fernando	4 years				Department of Clinical Science, Intervention and Technology	Assessing of Motion-Cognitive Reserve with Virtual Reality and Wearable Sensing
73	Seoane, Fernando	4 years				Department of Clinical Science, Intervention and Technology	Feasibility study on applying Interactive Process Mining to Clinical Epidemiology Studies with Real World Data
74	Shen, Xia	4 years				Department of Medical Epidemiology and Biostatistics	Modelling high-dimensional genomics and omics data
75	Sidorchuk, Anna	4 years				Department of Clinical Neuroscience	Long-term prescribing of benzodiazepines in contemporary Sweden - predictors, consequences, and strategies to reduce unwarranted prescribing in primary care
76	Sindi, Shireen			24 months		Department of Neurobiology, Care Sciences and Society	Sleep and neuroimaging biomarkers: From healthy aging to Alzheimer's disease (SPIRE)
77	Sonkoly, Enikö	4 years		24 months	12 months	Department of Medicine, Solna	Investigation of non-coding RNAs in skin inflammation
78	Spalding, Kirsty	4 years		24 months	12 months	Department of Cell and Molecular Biology	Human adipose tissue senescence
79	Sundling, Christopher	4 years				Department of Medicine, Solna	A global perspective on the immune system for improved identification of biomarkers and resistance mechanisms in TB disease progression
80	Sundström, Erik			24 months		Department of Neurobiology, Care Sciences and Society	Multi-omics analysis of the developing human spinal cord in vivo and in vitro
81	Tietge, Uwe			24 months		Department of Laboratory Medicine	Identification and clinical validation of novel pathways linked to the atheroprotective effects of high density lipoproteins
82	Uhlen, Per	4 years		24 months		Department of Medical Biochemistry and Biophysics	Advanced 3D Imaging Analysis of Intact Tumor Volumes
83	Ungerstedt, Johanna			12 months		Department of Medicine, Huddinge	Functional consequences of TET2 mutation in chronic myelomonocytic leukemia, CMML
84	Wermeling, Fredrik	4 years				Department of Medicine, Solna	CRISPR-based studies of pathogenic neutrophil biology
85	Wikström, Jakob D	4 years				Department of Medicine, Solna	Metabolism in skin
86	Vu, Trung Nghia		12 months	24 months	12 months	Department of Medical Epidemiology and Biostatistics	Computational and statistical models to discover driver alterations in cancer
87	Xu, Dawei	4 years				Department of Medicine, Solna	Telomerase activation by TERT promoter mutations in carcinogenesis and implications in precision oncology
88	Xu Landén, Ning		12 months	24 months	12 months	Department of Medicine, Solna	Investigation the role of regulatory RNAs in human skin wound healing

No	Supervisor's name	Doctoral student	Visiting doctoral student	Postdoc	Visiting researcher	Department at KI	Project title
89	Zaphiropoulos, Peter			24 months		Department of Biosciences and Nutrition	Circular RNAs in cancer development
90	Öberg, Sara			24 months		Department of Medical Epidemiology and Biostatistics	Prescribed drug use in pregnancy: register-studies of safety and effectiveness

Table of contents

#1 Immunomodulation in neonatal hypoxic ischemia

Type of recruitment

Postdoc, 24 months
Visiting researcher, 12 months

Project title

Immunomodulation in neonatal hypoxic ischemia

Supervisor

Ulrika Aden, Professor
Department of Women's and Children's Health

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Qualifications of applicant

The applicant should have a PhD in Immunology, neuroimmuology, neuroscience or related areas. Previous experience in mouse models and in performing experimental procedures in mice is important.The candidate should have working experience and knowledge in Cell culture and molecular biology techniques such as DNA/RNA extraction, PCR. Previous experience in flow cytometry and tissue culture work, cryo- sectioning and confocal microscopy is also a merit. Applicants wishing to integrate computational and experimental biology approaches are especially encouraged to apply.

We are looking for a highly motivated person, with structured working manners and a good team member who has a strong interest in brain injury and development. A good ability to communicate in English (written and verbal) is required.

Background

Hypoxic ischemia (HI) or ischemic stroke is a major cause of neonatal brain injury which may lead to impaired psychomotor development. Subsequent inflammation has been identified to predict outcomes and proinflammatory cytokines exacerbates brain lesions in experimental models (see for example Aden at al 2010). Disruption of the blood brain barrier as well as activation of the microglia and brain infiltration with peripheral inflammatory cells play an important role as shown by us (Winerdal et al 2014) and others. Most studies have focused on immunological changes in the first few weeks following cerebral ischemia. We have also described long lasting inflammation up to five months after cerebral HI in mice. Modulating this immune response may be beneficial in terms of neurological outcome. One of the investigated modulators is Fingolimod, a sphingosine-1-

phosphate receptor agonist that promotes selective retention of T cells in lymphatic tissues, induces thereby lymphopenia, prevents lymphocyte influx into the brain and decreases inflammation. Studies in adult ischemic rodent models (Wei et al 2011, Brait W et al 2016) found reduced stroke size and improved neurological outcome.

Our goals are to characterize the early and late immune response in peripheral blood in neonates after brain injury, relate it to outcomes and examine a potentially protective therapy with a T cell modulator Fingolimod in mice.

Research project description

We aim to answer the following questions:

1. Is there a long term activation of immune cells in neonates after neonatal brain injury?
2. How does the long term immune activation relate to neurocognitive outcomes at 2 years of age in these patients?
3. What are characteristics of immune activation in neonatal mice in a model of HI brain injury?
4. Is modulation of the late T cell activation with FTY720 (Fingolimod) beneficial in the mouse model of neonatal ischemic brain injury?

Methodology

1. Patients: We aim to include newborns with neonatal stroke (n=20 per year in Stockholm), newborns with HI brain injury (n=20 per year in Stockholm) and 20 healthy infants as controls. The inclusion will be done by a clinically active member of the group. Blood samples will be taken within the first 7 days of life, at 3 months and 6-12 months of chronological age. When possible, the blood samples will be taken at the same time as clinical blood samples. The samples will be analysed via mass cytometry (CyTOF) and FACS (fluorescence-activated cell sorting).

CyTOF preparation of blood: About 100µl whole blood is collected for mass cytometry analysis, mixed with stabilizer and stored at -80°C until analysis. Samples are acquired on CyTOF2 mass cytometer. The files are exported from the CyTOF software, normalized, debarcoded and visualized. FACS analyses are done to further investigate the cells of interest.

Follow up of the infant's neurological development: Data on neurological development (Hammersmith exam), motor development (Bayley III and Peabody) and cognitive development (Bayley III) are extracted from clinical follow up charts at 3 months, 6-12 months and 2 years of age.

2. Animal model of HI injury: Ten day old mice (brain maturation similar to a full term infant) are anesthetized with isoflurane and local bupivacaine. HI is induced by electrocoagulation of the left common carotid artery via midline neck incision followed by exposure to 10% oxygen/90% nitrogen for 60 minutes at 36°C +-1°C (modified Rice-Vannucci model).
Assessment of outcome: The outcome of the mouse model will be evaluated by histopathological analysis of the mice brains. Brain volumes are compared between groups. Neuronal injury, reactive gliosis and myelination are evaluated via staining of microtubule-associated protein 2 (MAP-2). Neurological development will be assessed using beam walking and Rotarod for evaluation of balance and coordination, and open field activity to evaluate exploration and memory skills.

Fingolimod (hydrochloride) 1mg/kg (Cayman Chemical, 10006292, ref 5-9) is dissolved in 0.9% sodium chloride and administered intraperitoneally at 3 months after the lesion, based on our previous data (4).

Research group

The research Is lead by Ulrika Aden, professor of neonatology with a long standing research in neonatal brain injury. In the external evaluation of KI research groups ERA2010, we were scored as an excellent research group. We conduct translational research and the candidate would work in our experimental research group at Bioclinium, KI, which is part of the Women's and Children's Health experimental lab, a stimulating place with around 50 researchers and students and many basic techniques.

Experimental research group
Elena di Martino, post doc
Michel Bedin, post doc
Isabella Schme, neonatologist, research student
Guo Hang, post doc

Clinical research group:
Nelly Padilla, neonatologist post doc
Maria Örtqvist, physiotherapist, post doc
Gustaf Mårtensson, physicist, post doc
Hedvig Kvanta, physician, PhD student
Marika Strindberg, physician, PhD student
Eva Eklöf, psychologist, PhD student
Daniela Nosko, child neurologist, PhD student

Supplementary information

Key words

Neonatal, brain injury, neuroimmunology, FACS, T cells, stroke

#2 Transcriptional Regulation in Chronic Osteoarthritis

Type of recruitment
Doctoral student, 4 years

Project title
Transcriptional Regulation in Chronic Osteoarthritis

Supervisor
Aisha Siddiqah Ahmed, Dr.
Department of Molecular Medicine and Surgery

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Home page:

Qualifications of applicant
A successful candidate for this position should have experience of handling human material and experience of working with animal models and cells culture systems. Laboratory skills such as ELISA, Quantitative RT-PCR, Histology and Immunohistochemistry (IHC) are preferred.

The candidate must be fluent in English and have excellent writing skills. We are looking for a candidate who thrives working with others. The candidate will join a collaborative, hardworking and dynamic team.

Background
Chronic pain and pathological joint changes associated with osteoarthritis (OA) are major health concern globally. Despite decades of research, there is still no treatment that can reverse chronic pain, increase mobility and improve functional outcomes in patients suffering with OA. Previous studies have reported an association between inflammatory substances in the joint and increased joint pain. Our recent findings have indicated the pathological activation of transcription factor NF-kappaB (NF-κB) which regulates the synthesis of majority of inflammatory substances, in joint tissues, however, the phenomenon is not fully understood. The focus is to gain insight into the transcriptional regulation of inflammatory substances that underline the initiation and propagation of pain and inflammation in OA and find strategies based on NF-κB blockade.

Research project description
The objective of this PhD project is to identify molecular mechanisms associated with joint pain and inflammation which can be modified through the NF-κB system

inhibition. The experiments are designed first to gain insight into the transcriptional regulation of genes leading to pain and inflammation in patients suffering with knee OA. In addition, primary cells isolated from joint tissues will be studied for the activation of NF-κB signaling and its association on inflammatory and pain-related genes. Subsequently, NF-κB system will be antagonized with specific inhibitors and effects on the expression and interaction of inflammatory and pain-related substances will be studied in in-vitro and in-vivo models by biochemical and histological techniques.

Research group

The research group consists of Aisha Ahmed PhD, Senior Researcher at the Dept. of Molecular Medicine and Surgery, Karolinska Institutet and Paul Ackermann MD. PhD, Orthopedic surgeon and head of the Integrative Orthopedic Research Group at the Karolinska University Hospital. Aisha Ahmed and Paul Ackermann are jointly supervising two PhD students, working on projects related to pain and tissue regeneration. All research activities and supervision will take place at the Center of Molecular Medicine (CMM), Karolinska Institutet, sharing laboratory facilities with leading experts in the field of pain and inflammation.

Supplementary information

Key words

Osteoarthritis, Cartilage, Tendon, Transcription factor.

#3 Translational control of beta-cell regeneration for treatment of diabetes

Type of recruitment
Doctoral student, 4 years

Project title
Translational control of beta-cell regeneration for treatment of diabetes

Supervisor
Olov Andersson, Assistant professor
Department of Cell and Molecular Biology

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Qualifications of applicant

The zebrafish are amenable to efficient transgenesis and high-resolution imaging. We will make use of these properties to generate transgenic/mutant zebrafish for single-cell analysis of phenotypes. The successful applicants will have a strong background in cell and molecular biology and keen interest in beta-cell regeneration using model organisms.

The successful applicants may have experience in one or several of the following techniques/models:

1. Molecular, cellular and biochemical techniques, e.g. cloning, qPCR, Western blot and immunohistochemistry
2. Drug screening
3. Bioinformatics
4. Metabolism/diabetes research in mouse models
5. Organoid cultures
6. Zebrafish as a model system (note, not necessary)

Background

Diabetes can be controlled with injections of insulin, but there is currently no cure for this disease. An alternative to administering insulin is to increase the number of insulin-producing beta-cells in the pancreas, i.e. as a curative approach. Despite mechanistic differences, both type-1 and late stages of type-2 diabetes feature a reduction of the beta-cell mass. Experimental depletion of beta-cells in zebrafish and rodents is followed by significant recovery of the beta-cell mass, indicating that the adult pancreas in model organisms has cellular plasticity and can adapt to the need of insulin.

So which are the signals that can promote beta-cell formation, and how do they do so? For the last 10 years we have addressed this question by using the zebrafish model, which offers several advantages for studying pancreatic development owing to the simplicity of its organ structures (e.g. the zebrafish embryo has only one pancreatic islet) and ease of manipulation.

Research project description

To find drugs and identify pathways that can increase the number of beta-cells, we have taken a 'high-throughput chemical genetic' approach using a transgenic zebrafish model of diabetes.

The zebrafish model is ideal for high-throughput chemical screening in vivo, offering the opportunity to test small-molecule libraries efficiently. We screened 10 000 compounds, using >150 000 zebrafish larvae, for their effects on beta-cell formation. This, to my knowledge, is the largest in vivo chemical screen for beta-cells performed to date. Almost all of the compounds we identified increased the formation of beta-cell by increasing their proliferation. However, formation of beta-cells can occur through different mechanisms – mainly proliferation, neogenesis, and transdifferentiation – and one of the compounds increased regeneration of beta-cells via affecting the translation initiation complex. Therefore, this project aims to elucidate the mechanistic details of translational control of beta-cell regeneration. We will determine how pathways affecting translation, including mTOR and others, modulate general protein synthesis as well as increasing translation of a subset of mRNAs. By performing global translatome characterization (using Ribo-tag pulldown and RNA-sequencing) we aim to determine a translatome signature of beta-cell regeneration. Defining such signature will also allow us to determine what features these mRNA have in common, such as specific 5´UTR features. Subsequently we will determine whether individual genes in the translatome signature are sufficient and/or necessary for beta-cell regeneration. In summary, we aim to study translational regulation and identify novel drivers of beta- regeneration.

Research group

The lab currently composed of 2 senior lab-managers, 3 postdocs, 3 PhD students and 1 master student who are running numerous new projects that are progressing very well. Translating findings across species, and having the critical mass for such a broad research program, requires ambitious coworkers and a well-funded laboratory that has continuity. I believe that this team is uniquely positioned to support the prospective PhD-student to carry out the proposed experiments.

Supplementary information

Key words

beta-cell, insulin, diabetes, zebrafish, regenerative medicine, developmental biology

#4 Resolution of inflammation in abdominal aortic aneurysm: The role and actions of novel proresolving lipid mediators

Type of recruitment
Doctoral student, 4 years

Project title
Resolution of inflammation in abdominal aortic aneurysm: The role and actions of novel proresolving lipid mediators

Supervisor
Hildur Arnardottir, Assistant Professor
Department of Medicine, Solna

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Qualifications of applicant
The applicant must hold a Master's degree in molecular life sciences (or equivalent), degree in medicine or related disciplines at the start of the PhD period. We are looking for a highly motivated candidate that is able to work independently and in a structured manner. Previous research experience, especially in cellular and molecular biology techniques, cell culture, flow cytometry, immunohistochemistry or animal work is particularly meritorious. Additional experience working with eicosanoids and other bioactive lipid mediators in inflammatory systems or mass spectrometry is considered advantageous but not a must. Excellent communication skills in both verbal and written English are a requirement and an ability to interact socially and scientifically with other members of the laboratory and with collaborators in various networks are essential.

Background
Abdominal aortic aneurysm (AAA) is a life-threatening condition that arises when the aortic wall weakens and progressively dilates. This can result in eventual rupture if left untreated. Currently the only available treatment is invasive surgical options, therefore new therapeutic strategies are needed. Previous studies in animals and humans indicate a major role for chronic inflammation in AAA pathogenesis. The weakening of the aortic wall that occurs is characterized by loss of vascular smooth muscle cells (vSMC), chronic infiltration of immune cells and degradation of extracellular matrix, due to breakdown of elastin and collagen by metalloproteinases. A novel superfamily of lipid mediators called specialized pro-resolving mediators (SPM) actively counter-regulate pro-inflammatory responses

while also promoting healing and tissue repair. Successful resolution of inflammation is key to healing and long-term health. Emerging evidence indicate that impairments in the SPM pathways and their signaling contribute to chronic human diseases driven by inflammation, however little is known about these mechanisms in AAA. The aim of this project is to investigate SPM biosynthetic pathways and pro-resolution mechanisms in relation to aortic wall weakening and AAA progression, using patient sample and clinical data, animal models and LC-MS-MS profiling. The original and innovative nature of this

Research project description

Our group recently demonstrated that the proresolving receptor ALX/FPR2 is downregulated in human adventitia from aneurysmal lesions and that SPM biosynthetic pathways are dysregulated in calcified human aortic valves. Therefore it is important to elucidate unknown resolution pathways in human AAA. The overall aim of this PhD program is to investigate whether SPM biosynthetic pathways and pro-resolution mechanisms are disrupted in the aortic wall and whether impairment in these pathways and signaling contribute to the underlying pathophysiology and progression of AAA.

Firstly, we will establish the lipid mediator and SPM profiles in aortic tissues from AAA patients and non-AAA controls, as well as elucidate whether SPM biosynthetic or signaling pathways are disrupted in AAA patients. For this human samples will be collected from patients undergoing elective surgery for AAA or organ donors (controls). One part of the sample will be snap frozen and used for cutting edge LC-MS-MS based lipid mediator metabololipidomics profiling, which will provide a comprehensive lipid mediator profile with > 60 lipid mediators and SPMs. We will then further investigate human aortic tissues for the expression of key pro-resolution pathway markers, including receptors and biosynthetic enzymes, using immunohistochemistry and RTqPCR. Additionally, we will use bioinformatics tools in combination with an established global transcriptomics databank of human AAA tissue to study pro-resolution pathways in relation to AAA and to identify connected signaling pathways. For clinical translation, lipid mediators and existing array data will be used to evaluate associations to clinical parameters as well as other pathways involved in AAA (e.g. MMPs).

Using various pharmacological intervention strategies, we will dissect the pro-resolution mechanisms and SPM signaling pathways on a molecular level in primary cultures of vascular smooth muscle cells isolated from aortic tissue collected from AAA patients or organ donors (controls). First, the student will do a screening of different SPMs of interest to identify the most potent and relevant SPMs for vascular inflammation, e.g. phenotype, cell death and vascular structure and function. From those select SPMs will be chosen for further investigation.

In a mouse model of angiotensin-II induced AAA, we will investigate the effect of SPM treatment, using the most promising SPM candidate(s) identified from the in

vitro screening, on disease progression and potential regression as assessed by echocardiography, histology, and biochemical analysis.

No medical treatment has hitherto proved to be efficacious in slowing down AAA progression, which highlights the importance for innovative therapeutic strategies. The original and innovative nature of this project introduces a novel concept for understanding the pathology driving AAA, which may provide a novel platform for developing much needed pharmacological treatments.

Research group

The Translational Cardiology group belongs to the Cardiovascular Research Unit of the Department of Medicine Solna (MedS) and is a productive, well-functioning and innovative team of 8-10 members, headed by Magnus Bäck, MD, PhD, Professor of Cardiology. The research group consists of 1 PI, 1 assistant professor (main supervisor), 1 senior scientist, 4 PhD students, 1 technician and usually 1-4 master student each semester. The group has a high level of expertise in cardiovascular biology, resolution of inflammation and lipid mediator signaling, with advanced tools to study this topic, which will provide excellent support of knowledge, skills and competencies to the candidate to perform the translational phd project outlined. The lab is located in the NEO research building, a newly built hub for translational research on the south KI campus, We have established extensive local and international collaborations, which ensures access to all necessary resources to support this project.

Supplementary information

Key words

Inflammation, resolution, resolvins, lipid mediators, cardiovascular disease, abdominal aortic aneurysm.

#5 TOPGOG: TOPoisomerase Dysregulation of Oncogenic Growth

Type of recruitment
Postdoc, 24 months

Project title
TOPGOG: TOPoisomerase Dysregulation of Oncogenic Growth

Supervisor
Laura Baranello, Assistant Professor
Department of Cell and Molecular Biology

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Home page: https://ki.se/en/cmb/laura-baranellos-group

Qualifications of applicant
We are looking for an enthusiastic, hardworking and highly motivated candidate with interest in molecular biology or related sciences and a strong track record in term of publication and/or awards. The ideal candidate is expected to lead the project in collaboration with the PI (Laura Baranello) and the other fellow Donald Cameron and participate in common laboratory duties. The successful candidate should have excellent interpersonal and organization skills, communicate well and work in a team. A background in topoisomerase biology, expertise in standard biochemical approaches, ability to collect and analyse large amount of data as well as a good knowledge of both spoken and written English will be considered important in the evaluation.

Background
Topoisomerases (TOPs) are essential enzymes that resolve DNA torsional strain that accumulates during replication and transcription by cleaving and re-ligating DNA strands. Because cancer cells exhibit elevated levels of replication and transcription, they are particularly reliant on topoisomerase activity. As a result, topoisomerases are targeted by many of the most effective anti-cancer therapeutics. While many topoisomerase inhibitors are widely used in the clinic, the tolerated dose is limited by their toxicity caused by inhibition of topoisomerases in non-cancer cells. New strategies to target topoisomerases specifically in cancer cells will improve outcomes in cancer patients. Though originally considered a constitutively activated enzyme, our previous work demonstrated that the activity of topoisomerase is stimulated by interactions with oncoproteins to enable elevated transcription essential for cancer cells. Therefore we propose that targeting these interactions will halt oncogenic overexpression while preserving physiological topoisomerase activity, avoiding the toxicity

associated with current topoisomerase drugs. Using a plasmid-based fluorescent assay, we will screen for oncoproteins that stimulate topoisomerase activity and for compounds able to block these interactions. This project would yield novel tumor-specific and less genotoxic compounds to target cancer and improve patient outcomes.

Research project description

We will establish an assay to screen for agents that specifically prevent stimulation of TOPs but not inhibit their basal activity. The assay will rely on the fluorescent supercoiling reporter plasmid. This plasmid does not fluoresce when supercoiled but becomes fluorescent when relaxed, and therefore can be used as a quantitative measure of topoisomerase activity. The project will be structured in the following tasks:

1) Pilot experiments to establish conditions for the drug screen. We will perform a small-scale experiment to establish the optimal concentrations of TOP and candidate oncoprotein able to stimulate TOP, and the fluorescent reporter. We will then scale the fluorescence-based topoisomerase assay into a 384-well format mixing TOP, fluorescent reporter and oncoproteins.

2) Screen for detection of oncoproteins stimulating TOP activity. In collaboration with CDI Labs using their HuProt collection of human proteins, we will develop a boutique protein array of 100-200 oncoproteins. Imaging of fluorescent readout will be used to assess and identify oncoproteins able to stimulate TOP over its basal activity. All TOP-stimulating protein candidates will be validated by secondary screening and in vitro assays.

3) Screen for detection of drugs targeting stimulation of TOP activity. Once defined in step 2), the 5 most promising oncoprotein candidates able to augment topoisomerase activity will be tested against a library of pharmacologically-active compounds to screen for drugs able to block the protein-protein interaction and stimulation of the topoisomerase. All candidate drugs will be validated by secondary screening and in vitro assays.

4) In cell validation of the novel discovered compounds. Novel drug candidates identified by the screen will be characterized on a panel of 10 to 15 cancer cell lines by viability assays. The drug mechanism of action will be further elucidated in vivo using immunofluorescence imaging and immunoprecipitation assay to measure the disruption of oncogenic stimulation of topoisomerase.

Once developed, this method could provide a novel high-throughput platform for identifying compounds targeting other topoisomerase family members. This could have significant clinical implications with drug discovery not just for treating cancer, but also bacterial and viral diseases where topoisomerase activity is essential for pathogenicity. Therefore this project is highly feasible, medically important and has

the potential for rapid translational development that is likely to prove beneficial both for individual patients and for society at large.

Research group

The Baranello's lab is a stimulating and highly multi-disciplinary research group , with expertise spanning among cellular, molecular and biochemical techniques as well as genomics and bioinformatics approaches.

Specifically the group is composed by two postdoctoral fellows:

- Anika Wiegard: expertise in cell cycle analysis, confocal and fluorescent microscopy, nascent RNA and total RNA-Sequencing.

-Donald Cameron: expertise in protein biochemistry, confocal and fluorescent microscopy, drug screening and bioinformatics.

two PhD students:

-Vladislav Kuzin: expert in next-generation sequencing, with specific focus on ChIP-seq and bioinformatics.

-Jan Grosser: expert in next-generation sequencing, with specific focus on RNA-seq and bioinformatics.

one Master student- Sara Busquet: who will spend 5 months in my lab in 2021.

Supplementary information

The lab members meet once a week for discussing results and progresses, as well as recent literature. Interactions and collaborations between the members of the group are helpful and create an nice working environment. Laura Baranello has an "open door" policy and discussion with her are always welcome. The lab is located at Biomedicum, an interdisciplinary research platform, where the fellow will have access to state-of-the-art technologies and an excellent interdisciplinary research environment. The Baranello's group has monthly joint lab meeting with the groups of Camilla Björkegren (CMB/KI) and Lena Ström (CMB/KI). Finally, the department organizes monthly seminar where group leaders at CMB present their research to their colleagues.

Key words

Drug screen, cancer, oncoprotein, topoisomerase

#6 Exploring BACH1-induced coordination of redox and metabolic pathways in cancer metastasis

Type of recruitment
Doctoral student, 4 years

Project title
Exploring BACH1-induced coordination of redox and metabolic pathways in cancer metastasis

Supervisor
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Qualifications of applicant
Experience with in vitro and in vivo analyses of mouse or human cancer cell lines and mouse and/or organoid models of cancer. Experience with analyses of proliferation, apoptosis, senescence, epigenetics, sequencing, gene editing would be relevant. Excellent communication skills and ability to work both independently and in a group.

Background
The goal of this project is to understand how oxidative stress responses collaborate with metabolic adaptations to support tumor cell proliferation, migration, and metastasis, and to thus identify vulnerabilities that can be targeted for therapy.

The role of redox state in cancer is complex. On the one hand, levels of reactive oxygen species (ROS) are higher in cancer cells than in normal tissues and ROS can both cause DNA damage and stimulate oncogenic signaling pathways that promote cancer development. On the other hand, once a tumor has formed, high ROS levels constitute a barrier to tumor progression and metastasis; tumor cells therefore activate endogenous antioxidant pathways—a response mediated by the transcription factor NRF2.

Proliferating and metastatic tumor cells also require nutrients to support growth and survival. The cell redox state influences how nutrients are used and how cancers adapt their metabolism to support energy and biomass production. These metabolic adaptations must function in environments with high oxidative stress experienced during detachment, circulation, and metastatic colonization.

Interestingly, the ability of tumor cells to alter their metabolism and activate ROS detoxification pathways appear to be tightly linked.

We recently found that the transcription factor BACH1 links a response of lowering oxidative stress with glucose utilization and that this stimulates metastasis, but many questions remain.

Research project description

This PhD project will intially start with two specific aims.

Specific Aim 1: Identify mechanisms of antioxidant- and BACH1-induced cell migration, invasion and

metastasis—We will perform interactome-profiling to identify BACH1 partners necessary for DNA binding and transcriptional activation. We will use advanced live cell imaging to identify mechanisms underlying antioxidant- and BACH1-induced migration and the type of migration involved. Genetically-encoded biosensors will be used to determine which ROS molecules are involved; and FRET, genetics, biochemical and pharmacological approaches to determine how glycolysis drives invasion and metastasis. We will thereby obtain a comprehensive understanding of how antioxidants and BACH1 stimulate tumor progression.

Specific Aim 2: Identify redox- and metabolic-related adaptations in tumor progression and metastasis—We will analyze tumor metabolism in primary tumors and metastasis in mice with KRAS-induced lung cancer, in the presence and absence of wild-type and mutant p53, and in response to antioxidant administration and NRF2 activation (through Keap1 inactivation). We will also use genetic and pharmacologic interventions to perturb the redox state and metabolic parameters in cells and organoid systems and determine how this influences cell proliferation, migration, and metastasis. We will perform similar experiments in models of malignant melanoma and pancreatic cancer if time allows.

The prospective CSC-funded PhD student would begin by working on Aims 1 and 2. However, the project also contains additional aims, such as:

"Test the hypothesis that BACH1 and HIF1alpha interact under reduced and hypoxic conditions"

and

"Identify specific redox- and metabolism-related liabilities in tumor cells and develop new targeted cancer therapies".

Thus, the prospective PhD student will be part of a bigger picture and will be able to design side-projects, alternative projects, and backup projects in the event we

encounter technical difficulties that are impossible to solve; we will also be flexible if we encounter exciting serendipitous findings which prompt us to shift focus. Our long term goal is to graduate students who are well prepared for a competitive academic career.

Thus, this is an ambitious proposal but we believe it is both feasible and flexible. Moreover, we have exciting preliminary data and dedicated group members and collaborators at Karolinska Institutet, Harvard, MIT, Jena University, and INSERM, Paris.

Research group
https://medarbetare.ki.se/people/martbe3

https://news.ki.se/new-basic-understanding-of-how-lung-cancer-spreads

Supplementary information
The research group of Dr. Martin Bergö studies the role of redox balance and oxidative stress in cancer progression. In particular, the group is interested in redox-regulation during cancer metastasis. The group also studies the biochemical and medical importance of the posttranslational processing of CAAX proteins (e.g., RAS, RAC1, prelamin A). The group uses basic biochemistry techniques, cell culture and organoid models, genomics techniques, mouse models, and translational approaches.

Key words
Cancer, oxidative stress, redox, metastasis, lung, melanoma, mouse models, chemokines,

#7 Elucidating mechanisms of endothelial cell fenestration

Type of recruitment
Doctoral student, 4 years

Project title
Elucidating mechanisms of endothelial cell fenestration

Supervisor
Christer Betsholtz, Professor in vascular biology
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Qualifications of applicant
We are seeking a highly motivated person with a burning interest in basic science and scientific discovery in the area of cardiovascular biology and medicine. The successful applicant must have the appropriate undergraduate education for admission to PhD studies at KI, be fluent in English, have excellent communication skills and the ability to interact effectively and work productively in a team. Merit is previous lab experience and experience of international collaborations. Great advantage is experience in single-cell RNA sequencing data analysis, FISH, PCR and computer programming skills.

Background
A blood supply, orchestrated by the cardiovascular system, is essential for development and homeostatic functions. From being viewed largely as a conductive system for blood, it is now more and more obvious that the vasculature functions differ hugely between organs, a feature referred to as vascular organotypicity. At the center of this diversity are the endothelial cells, which line all types of vessels: arteries, veins and capillaries. Particularly the capillary endothelial cells are highly specialized in order to meet and match each organ's specific demands and roles, Therefore, the endothelial cells of different organs (and organ regions) show vast differences in e.g. permeability and trans-cellular molecular transport. One such specialization is the formation of fenestrations. Fenestrations are uniform transcellular pores organized in patches at sites where the endothelial cells are extremely thin, allowing the membranes of the two sides of the cells – luminal and abluminal – to come closely together and fuse to make pores. Fenestrated endothelial cells are found, for example, in kidney glomeruli, where they allow for blood ultrafiltration into urine, and in endocrine organs, where they allow hormones to passage from the producer cell into the blood. It is assumed that

specific molecular signals and structural proteins initiate and maintain fenestrations, however, these remain largely unknown.

Research project description

Several ongoing and planned scRNASeq projects provide an ever growing “atlas” of endothelial data from organs with non-fenestrated (e.g. brain, lung and heart) or fenestrated capillaries (e.g. liver, kidney, gut). For representative previous publications from our group, see Nature 2018 PMID: 29443965; Nat Comms 2020 PMID: 32769974) The generated data will be used for several projects on endothelial diversity, of which the fenestration project specified here is one. Endothelial scRNAseq data will first be integrated and analyzed by different bioinformatical tools and visualization techniques. Using molecular and anatomical hallmarks we will assign candidate groups of transcripts that correlate with fenestration across multiple organs and vascular beds, hence normalizing for other organotypic differences that would be expected besides fenestration. New data will then be collected from additional organs with fenestrated capillaries (e.g. thyroid, pituitary, choroid, islets of Langerhans, adrenal gland), in order to provide additional input data. Next we will select candidates for gain- and loss-of function studies in mice and zebrafish, often-used models for vascular research. The pathophysiological importance of the project is vast: loss of fenestrations in fibrotic liver disease inhibits liver function, and gain of fenestrations in e.g. diabetic retinopathy and brain tumors has deleterious consequences for eye and brain function.

Research group

Christer Betsholtz’s group (https://staff.ki.se/orgid/53072401) is located within the Karolinska Institute, within the Neo building, with full access to core facilities, collaboration, research courses and seminars. The laboratory is fully equipped for the project, has a single-cell sequencing facility and 16 members at different levels: PhD students, postdocs, researchers. The lab expertises cover not only molecular experiments for vascular related researches, but also experienced bioinformatics/computational analysis areas. The Ph.D candidate will work closely with the relevant members in the group along the progression of the project.

Supplementary information

Note that the approved Green Light form specifies CSC and is signed by the head of department. The same document is therefore used as approval from head of dept and Green Light.

Key words

Vascular biology, single-cell RNA sequencing, endothelial cells, pericytes

#8 Modelling of periodontal infection in a dynamic perfusion bioreactor

Type of recruitment

Visiting doctoral student, 12 months
Visiting researcher, 12 months

Project title

Modelling of periodontal infection in a dynamic perfusion bioreactor

Supervisor

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Qualifications of applicant

The visiting PhD student/visiting researcher must hold at least a bachelor's degree in dental or biological/natural sciences, preferably research experience related to the study of oral/periodontal diseases. The successful candidate should demonstrate competence and independence in performing laboratory work including expertise in experimental disease models, and be highly motivated and exhibit strong organizational, writing, and communication skills. The applicant should also have excellent communication and writing skills in English with certificates such as TOEFL, GRE, IELTS or equivalent

Relevant skills: experimental models, histochemistry, immunofluorescent staining, micro-CT analysis, cell culturing techniques, analysis of differential gene expression (e.g. RT-qPCR).

Background

Periodontitis is a biofilm-driven inflammatory oral disease that presents as the sixth-most prevalent chronic disease worldwide affecting almost 11.5 % of the global population, including Sweden. It does not only severely deteriorate peopleâ€™s quality of life by impairing the dentition but also adversely affects systemic health. Despite extensive use of experimental animals to understand the underlying mechanisms of periodontitis, several crucial considerations are raised concerning their suitability and reflection of the â€œreal-lifeâ€ situation, especially since not all aspects of human periodontitis can be predictably reproduced in animal models.

Research project description

The specific aims are a) to develop a physiologically-relevant periodontal tissue model within a dynamic perfusion bioreactor environment b) to establish a high-quality biomimetic biofilm-infection model representing the microniche where periodontitis initiated and c) to characterize the metaproteomic/proteomics profile of the interplay between biofilm and the tissue. It is anticipated that the development of this laboratory model for periodontal disease can be exploited for elucidating the mechanisms of the disease, and for developing novel therapies. Moreover, rather than analyzing the expression of single candidate genes or proteins in the system, the project will employ high-throughput technologies, such as quantitative proteomics. This approach will allow for the global screening of all the cellular and molecular events taking place in one single experiment, facilitating the identification and characterization of mechanisms that govern oral biofilm-related infectious processes.

Research group

Prof BostanciÂ´s research group focuses on in vitro and in vivo analysis of host-pathogen interactions in the context of periodontal diseases. This research line involves a range of complementary disciplines and approaches, including clinical periodontology, immunology, microbiology, bioengineering, proteomics, metaproteomics and systems biology. The group aims to better understand periodontal homeostasis and the underlying mechanisms of inflammatory periodontal pathogenesis. The ultimate goal is to improve the quality of periodontal care delivered through early and accurate diagnosis, and the development of innovative targeted therapeutic approaches. Prof BostanciÂ´s research group is located at the Department of Dental Medicine and ANA Futura Laboratories at Karolinska Institutet.

Supplementary information

Post-Doc: Kai Bao, PhD Expertise: Experimental disease models, tissue bioengineering, cell culturing, molecular biology, oral microbiology, multiomics, oral immunology, bioinformatics

Post-Doc: Angelika Silbereisen, PhD Expertise: Immunology, microbiology, immune assays, multiplex, assay development, saliva omics, proteomics

Key words

Tissue engineering, oral health, dental, biofilm, bioreactor, proteomics, oral microbiome, periodontal disease, oral infection, oral inflammation, saliva, oral-systemic link

#9 Hematopoiesis in tumors: A proof-of-principle study

Type of recruitment
Doctoral student, 4 years

Project title
Hematopoiesis in tumors: A proof-of-principle study

Supervisor
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Qualifications of applicant
We hope to recruit potential student who graduated from top universities by worldwide ranking. Applicants should have Master degree with basic lab training experience, fluent English speaking and writing. Also, applicants should have highly enthusiasm in tumor research. We expect he or she should have good team spirit in work as well.

Background
Malignant cells live in a sophisticated environment where multiple host cells (collectively called tumor stroma) relentlessly communicate with each other. In the tumor microenvironment (TME), cancer cells often instruct stromal cells including cancer-associated fibroblasts (CAFs), tumor-associated macrophages (TAMs), vascular cells, adipocytes, and even immune cells for supporting their growth and spreading. In most solid cancers, the stroma component dominates the entire tumor tissue. We are beginning to understand the critical roles of tumor stromal cells in facilitating tumor growth, metastasis, and alteration of drug responses. Our very recent surprising findings from the genome-wide expression profiling show that perivascular cells isolated from tumor tissues exhibit hematopoietic features similar to erythroblasts. Moreover, PDGF-stimulated fibroblasts in tumor tissues express high levels of erythropoietin (EPO). These unprecedented findings suggest that tumors are able to make their own blood cells. In support this notion, genetic tracing of NG2+ pericytes discovered that a substantial number of pericytes differentiate into erythroblasts in tumor tissues. We are now planning to do in-depth mechanistic investigation on pericyte´s capacity of differentiation into hematopoietic cells.

Research project description

We employ multidisciplinary experimental approaches to study tumor hematopoiesis and to provide proof-of-principle experimental evidence to support our hypothesis and new concept. Various in vitro and in vivo experimental models are implemented trace progenitor cell differentiation toward hematopoietic lineages. To provide conclusive and definite evidence, we will perform single cell sequencing analysis to reveal the identity of differentiated cells. Finally, various assays will be performed to investigate functions of tumor-derived hematopoietic cells.

Aim 1. To define the hematopoietic progenitor identity in the tumor microenvironment.

Our preliminary findings show that perivascular cells reside in the vessel wall possess hematopoietic stem cell features and can differentiate into erythroblast-like cells. These findings are completely unexpected and surprising, and suggest that tumors are able to produce their own red blood cells. If so, perivascular cells support tumor growth through a completely new mechanism by improving oxygen perfusion. To ensure pericyte differentiation toward hematopoietic lineages, tumor tissues must provide signaling molecules. Indeed, in our animal tumor models we have found that PDGFs in TME target the stromal fibroblasts (cancer-associated fibroblasts, CAFs) to induce EPO production. These data demonstrate that tumors provide both hematopoietic progenitor cells and differentiation factors.

Aim 2. To study molecular signaling pathways that drive vascular progenitor cell differentiation

To ensure differentiation of NG2+ cells into various hematopoietic lineages, various factors and signaling should coexist in the tumor microenvironment. Our preliminary results show an example of the PDGF-PDGFR system in governing perivascular cell differentiation. However, there should be more factors that are involved in driving progenitor cell differentiation into different lineages. For differentiation of perivascular cells into hematopoietic cells, perivascular cells have to be detached from the tumor vasculature. We previously showed that high expression of PDGF-B in tumors promotes detachment of pericytes from the tumor vasculature. In addition to PDGFs, other signaling pathways such as the angiopoietin 2-tie2 signaling and the VEGF-VEGFR1 system also significantly ablates pericytes from the tumor vessels. The VEGF-B and PlGF are also reported to disassociate pericytes from tumor vessels. We plan to test these non-PDGFs in our in vivo experimental settings. For this purpose, we have generated various tumor cell lines that express a specific factor, which will allow us to study their roles in promoting tumor hematopoiesis using the experimental settings described in Aim 1.

Research group

Our research program focuses on studying the fundamental mechanisms of angiogenesis, the key process of blood vessel formation, in various diseases. Our aim is to understand molecular and functional mechanisms of angiogenesis in the onset and progression of most common and lethal human diseases such as cancer, metabolic disease, and cardiovascular disease.

Through these mechanistic studies, we propose new concepts and paradigms that are beneficial for diagnosis, treatment, and prevention of these and other human diseases. The ultimate goal of our research is to develop novel therapeutics for treatment of angiogenesis-dependent diseases.

Our group now have senior researchers, PhD student and visiting researchers.

Supplementary information

Key words

tumor; tumor microenvironment; hematopoiesis

#10 Targeting NADPH oxidase- and mitochondria-induced oxidative stress in cardio-metabolic disease and associated renal complications

Type of recruitment

Postdoc, 24 months

Project title

Targeting NADPH oxidase- and mitochondria-induced oxidative stress in cardio-metabolic disease and associated renal complications

Supervisor

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Qualifications of applicant

Previous experience using small animal models and standard PCR and Western Blot techniques is mandatory. Assessment of renal and cardiovascular functions in vivo and ex vivo studies of vascular function will be an asset for this project. Previous experience/knowledge about mitochondrial respirometry, redox signaling, oxidative stress, inflammation, histology, immunohistochemistry is also desirable. Proficiency in the English language, documented by an internationally recognized test.

Background

Cardiovascular disease and type 2 diabetes, often associated with chronic kidney disease, are major health problems worldwide. Underlying pathophysiological mechanisms are still not clear but involve oxidative stress and compromised nitric oxide (NO) bioactivity. Oxidative stress involves increased production or decreased scavenging of reactive oxygen species (ROS) produced by various isoforms of NADPH oxidases (NOX) and mitochondria. The small signaling molecule NO, enzymatically produced by the NO synthase (NOS) system, importantly contributes to regulation of cardiovascular, metabolic and renal functions. However, NOS function is often reduced during aging and in disease states associated with hypoxia and oxidative stress. In addition, oxygen radicals readily react with NO thereby severely limiting its bioactivity. We propose that novel strategies that reduce oxidative stress and restore NO bioactivity may have therapeutic value in the triad of cardio-metabolic and renal disorders.

Research project description

Inorganic nitrate (NO3-) and nitrite (NO2-) have long been considered inert end products of NO metabolism. However, we and other groups have shown that these anions, which are found in high levels in green leafy vegetables, via serial reduction steps can undergo bioconversion to form NO in reactions entirely independent of NOS. As recently reviewed, we and others have shown that dietary supplementation with nitrate, to boost the NO3--NO2--NO pathway, in various disease models can lower blood pressure and improve endothelial function,1, 2 prevent or even reverse features of metabolic syndrome,3 and dampen ischemia-reperfusion associated injuries of the kidney.4 The planned project, using a translational approach, aims to further investigate the favorable effects and the underlying mechanisms following boosting of the NO3--NO2--NO pathway. In collaboration with the Industry, we are also investigating the potential therapeutic value of novel and selective NOX2 and NOX4 inhibitors in our models.

The postdoc will have access to a broad and comprehensive research platform, and experience a translational experimental approach. In vivo disease models (e.g. wildtype and transgenic mice fed with special diets high in both fat and salt), ex vivo vessel characterization (e.g. myography) and in vitro cell culture studies (e.g. endothelial cells) as well as biochemical experiments (e.g. ROS and NO analysis), are combined with studies in patients with cardio-metabolic and renal disease (e.g. analysis of ROS and NO markers in plasma and urine following 4 weeks intervention with inorganic nitrate or placebo). The in vivo monitoring techniques in mice involve blood pressure recording (tail-cuff or telemetry), assessment of metabolic function (glucose and insulin tolerance tests, fat and lean mass quantification by dual-emission X-ray absorptiometry), and renal function studies (14C-PAH and 3H-inulin clearance) at baseline and following induction of the disease. Tissue samples are collected, processed and used for various analyses to quantify disease status and NOX and mitochondrial ROS production. The ethics committee has approved the clinical intervention study with nitrate supplementation in patients with cardio-metabolic disease. Here, the postdoc will be involved in processing and analysis of the tissue samples regarding redox status.

This project entails novel dietary as well as pharmaceutical means of maintaining and increasing proper NO homeostasis. We hypothesize that these novel strategies, i.e. stimulating the NO3--NO2--NO pathway or inhibiting specific NOX isoforms, can correct redox signaling by modulating ROS and NO generation, and hence halt the development and progression of disease.

1. Carlstrom et al. Acta Physiol (Oxf). 2018;224:e13080.

2. Lundberg et al. Nat Rev Drug Discov. 2015;14:623-41.

3. Lundberg et al. Cell Metab. 2018;28:9-22.

4. Carlstrom M et al. Journal of internal medicine. 2019;285:2-18.

Research group

The research group consists of a mixture of postdocs, PhD students, biomedical scientists and associated or visiting researchers, who all interact and work closely together. For more details regarding our research projects, publications and constellation of the research group, please visit:

https://ki.se/en/fyfa/mattias-carlstrom-group

https://staff.ki.se/people/jonlun

Supplementary information

Key words

Nitrate, nitrite, nitric oxide, oxidative stress, cardiovascular, kidney, inflammation, diet, metabolism

#11 Dissecting the mechanisms behind the inadequate hypoxia signalling in diabetes

Type of recruitment

Visiting doctoral student, 12 months
Postdoc, 24 months
Visiting researcher, 12 months

Project title

Dissecting the mechanisms behind the inadequate hypoxia signalling in diabetes

Supervisor

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Qualifications of applicant

The applicant must be talented, well-organized, highly motivated and enthusiastic for science, have good communication skills and the ability to interact in an international and dynamic team. The applicant should have innovative thinking and be eager to solve problems. A documented practical experience in animal studies, cell culture, molecular biology and biochemistry is meritorious. Good knowledge in written and spoken English is a requirement.

Background

Diabetes is reaching epidemic proportions and is predicted to affect 300 million people worldwide by 2025. Chronic complications of diabetes represent the main concern for modern diabetes therapy, and it has become a priority to further characterise the pathophysiological mechanisms of these complications to ensure the development of novel rational therapeutic strategies.

Although the prolonged exposure of tissues to hyperglycaemia is the primary causative factor for chronic diabetes complications, it has recently become increasingly evident that hypoxia also plays an important role in all diabetes complications. Compelling evidence has accumulated over the last decade indicating that the cellular reaction to hypoxia is impaired in diabetes, and is a central pathogenic mechanism for diabetes complications. It is represented by a complex repression of hypoxia-inducible factor (HIF), which is the main regulator of the adaptive response to hypoxia. The exact mechanisms by which hyperglycaemia has a repressing effect on HIF are still not completely unravelled.

Research project description

The project proposes to investigate the pathways that are relevant for this repression in order to identify new potential therapeutic targets for complications of diabetes. The work will involve investigation in vitro but also confirmation in vivo in animal models for diabetes complications. Unique patient material that can generate hypothesis to be confirmed experimentally is available. If successful the work will provide the chance to tailor new therapy for complications of diabetes.

Research group

Growth and Metabolism

Supplementary information

Key words

#12 Management of ADHD and co-occurring cardiometabolic diseases

Type of recruitment
Doctoral student, 4 years

Project title
Management of ADHD and co-occurring cardiometabolic diseases

Supervisor
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Qualifications of applicant
We look for a highly motivated student with background in epidemiology, biostatistics, public health, psychiatry or other relevant fields. Experience with statistical software (e.g., SAS, STATA, or R) or programming languages is preferred. The successful candidate needs to have the ability to both work independently and work in a research team. For general entry requirements and English language requirements for doctoral education at KI, please see:

https://education.ki.se/assessing-equivalent-knowledge-for-general-eligibility-for-doctoral-education

https://education.ki.se/english-language-requirements-for-doctoral-education

Background
Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder that often persist into adulthood. Emerging evidence suggests substantial comorbidity and shared genetics between adult ADHD and cardiometabolic diseases i.e., obesity, type-2 diabetes and cardiovascular diseases (CVD). In Sweden and many other countries, prescriptions of ADHD medications have increased dramatically during the last decades. Such increases have been heavily debated in part due to the limited knowledge about potential cardiometabolic risks associated with ADHD medications, especially in adults. There is a critical evidence gap regarding the safety of ADHD medications in patients with co-occurring CVD, as well as the effects of ADHD medications on severity, management and prognosis of chronic cardiometabolic diseases. Moreover, patients with ADHD and these co-occurring conditions are typically in need of continuous pharmacological treatment

for several indications, which may lead to problems related to polypharmacy and drug-drug interactions, but the evidence for drugâ€“drug interactions in relation to ADHD medications from real-world practice is scarce.

Research project description

The overall aim of the doctoral project is to provide real-world evidence for the management of patients with ADHD and co-occurring cardiometabolic diseases. Data are available through linkage of national registers in Sweden, which provide longitudinal information on disease diagnosis, drug prescription, as well as medical and functional outcomes. This project will study the effectiveness, quality and safety of ADHD medications, as well as combined pharmacotherapy, in individuals with ADHD and co-occurring cardiometabolic diseases. In the project, the student will apply advanced pharmacoepidemiology methods and machine learning techniques for analyzing real-world data. Under supervision, the student will be responsible for literature review, data analysis, result interpretation, scientific article writing and data presentation.

Research group

Our research group is interested in understanding the causes and consequences of psychiatric disorders, as well as the risks and benefits associated with pharmacological treatments for these disorders, using large-scale population data. Our works have been published in leading scientific journals in general medicine, psychiatry and epidemiology. Together with Professor Henrik Larssonâ€™s group, we have an interdisciplinary research team from various backgrounds, including epidemiology, biostatistics, psychiatry and psychology. We also have close collaborations with a number of international leading researchers in the field.

Supplementary information

Key words

epidemiology, ADHD, cardiometabolic diseases, real-world data

#13 Mechanistic studies of amyloid aggregation associated with human diseases, molecular chaperone mediated inhibition and spider silk formation

Type of recruitment

Visiting doctoral student, 12 months
Postdoc, 24 months
Visiting researcher, 12 months

Project title

Mechanistic studies of amyloid aggregation associated with human diseases, molecular chaperone mediated inhibition and spider silk formation

Supervisor

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Department of Biosciences and Nutrition

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Home page:

Qualifications of applicant

The applicant should have a background in the subjects of biochemistry, molecular biology, biotechnology or equivalent. Experience in the biochemistry of intein, amyloid and/or silk forming proteins, and protein chaperones, as well as characterization of proteins by spectroscopic methods and microscopy are meritorious. Good ability to communicate in English is a prerequisite. Scientific expertise will be most important when assessing applicants.

Background

Amyloids are protein aggregates characterised by long unbranched fibrils of 7–13 nm in diameter and cross β-sheet structure. Pathogenic amyloid is linked to about 40 human diseases, including type-2 diabetes and the neurodegenerative disorders Parkinson disease and Alzheimer's disease (AD), whereas non-pathological amyloid with well-defined physiological roles has been identified in various organisms, including human and bacteria. Spider silk shares amyloid-like properties and is one of the toughest biomaterials that exist, making it a fascinating target for biomimicry. Spider silks are spun from proteins (spidroins) that undergo a rapid transformation from highly concentrated soluble dope with helical and disordered conformations to β-strand-rich fibres. During spidroin self-assembly, the repetitive regions are converted into β-sheet crystals connected by disordered linkers, and this process is regulated by globular N and C-terminal domains. The C-terminal

domain and also the repetitive regions have been shown to form amyloid; however, the importance of amyloid-like formation during the fast spider silk assembly process, and the underlying mechanisms are still poorly understood.

Molecular chaperones are ubiquitously expressed and responsible for the maintenance of protein homeostasis. Surveillance by human molecular chaperones may decline during aging, resulting in increased cellular stress and eventually leading to neurodegenerative diseases and other severe disorder.

Research project description

The BRICHOS domain is small (~100 amino acid residues), has chaperone-like properties, and has been found in several human precursor proteins, initially in Bri2, Chondromodulin-1 and prosurfactant protein C (proSP-C). BRICHOS is a recently established multi-talented chaperone, preventing fibrillar amyloid aggregation and toxicity as well as non-fibrillar protein aggregation, thus holding great potential for therapeutic applications. Understanding the mechanisms behind these phenomena have important impact on the possibilities to treat different protein misfolding diseases, but is largely missing due to lack of data at the atomic level. Bri2 BRICHOS multiple activities can be linked to distinct assembly states, and thus modulating the equilibria to specifically augment the anti-amyloid neurotoxic capacity as well as potentiate the anti-amyloid neurotoxic effects of endogenous Bri2 BRICHOS is a completely novel concept in the fight against AD and other amyloid disease. The first part of this project will focus on the molecular mechanisms of the dementia relevant chaperone domain Bri2 BRICHOS against self-assembly of proteins and peptides, e.g. amyloid-β peptide (Aβ42) and Tau associated with AD and islet amyloid polypeptide (IAPP) associated with type 2 diabetes, and the augmentation of chaperone activity for future clinical applications.

The second part of the project will focus on the amyloid-like characteristics of spider silk assembly. In particular, we are interested to study a specific motif present in certain repetitive regions in its soluble and fibrillar state, and unravel the importance of this amyloid structure during the fast spider silk assembly process.

In both projects, intein-mediated protein trans-splicing will be used. Intein is an internal protein segment that can catalyze a protein splicing reaction to self-excise from a precursor protein and to ligate the flanking sequences (N- and C-exteins) with a peptide bond to form a mature host protein (spliced protein). This technique combined with our new NT* solubility tag system is a novel strategy to understand the pathogenic mechanism of human amyloidogenic peptides and spider silk formation. Methods for this proposed project include a broad set of techniques, including biochemical and biophysical tools, electrophysiological measurements and animal models.

Some of our previous results have been published in Nature Communications, PLoS Biology, eLife, Communications Biology, Journal of Physiology, Journal of Biological Chemistry, ChemBioChem, Biochemical Journal, FEBS Journal, and Scientific Reports.

Research group

The research group has a broad and multinational (Sweden, China, Germany, Spain and India) profile, and currently consists of one professor, two assistant professors, two senior researchers, three postdocs, three PhD students and one technician.

Supplementary information

The potential candidate will be assigned with at least two supervisors, one main supervisor and one co-supervisor.

Key words

Molecular chaperone; Amyloid; Alzheimer’s disease; Spider silk formation; Intein

#14 Multi-Omics integrative analysis to understand chronic inflammatory lung diseases

Type of recruitment
Postdoc, 24 months
Visiting researcher, 12 months

Project title
Multi-Omics integrative analysis to understand chronic inflammatory lung diseases

Supervisor
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Qualifications of applicant
We have an opening for 1-2 postdoc/visiting researchers wishing to join multidisciplinary projects in systems medicine of chronic inflammatory lung diseases (primarily COPD and asthma). The successful candidate will be expected to perform the bioinformatics analysis work of high throughput data from a range of omics-based studies. The individual will be responsible for requirement analysis, programming, testing, and documentation.

Entry Requirement

- MS or Ph.D. in Bioinformatics, Computational Biology, Computer Science, or a related field.
- Good experience in processing, managing and integrating biological datasets.
- Proficiency with R and Bioconductor packages, one or more programming languages (Python, Perl, etc.), and databases (MongoDB, MYSQL, etc.).

Preferred

- Extensive experience with bioinformatics tools in omics analysis.
- Good command of statistics and machine learning.
- Experience in R package, R shiny app, or web-based visualization tools development.

Background

Chronic obstructive pulmonary disease (COPD) and asthma are the major pulmonary diseases with growing morbidity and mortality. Obstructive lung disease is a global health problem of pandemic proportions, with COPD alone affecting >10% of the population. Nearly 400 million people across all age groups currently live with asthma globally. COPD and asthma are heterogeneous, complex, age- and gender-related diseases, making it challenging to identify illness etiology and develop reliable diagnostic and treatment strategies. Well-defined subgroups of COPD and asthma that explain the different etiologies need to be defined to satisfy the need for effective biomarkers identification, diagnosis, and treatment.

The development of systemic computational methods and access to large-scale multi-omic datasets has provided the opportunity to study systematic differences in COPD and asthma's complex etiology. Multi-omics integration and computational systems medicine approaches have been developed and applied in the subgrouping of complex, heterogeneous diseases. Specifically, we have shown that multi-omics integration analysis improves the power to define subgroups with a small sample size in COPD (PMID: 29545283). The massive accumulation of omics data provides increased power to identification network-based modular biomarkers. These pathways or modules could be used to predict disease or classify subgroups with both statistical robustness and explainable biological meanings.

Research project description

The mechanism of COPD or asthma is not only controlled by independent groups of genes/proteins/metabolites that can be identified by traditional univariate statistics, but also by their interactions, making it important to develop system-level understanding of the disease. One of the greatest strengths of the systemic medicine strategy proposed in this project, in contrast to traditional limited research methods, is the possibility of objective screening of new biomarkers and mechanisms of the disease by integrating many molecular levels of omic data from different tissues. By combining rigorous, clinical phenotyping, and longitudinal data collection of multi-omics data with state-of-the-art omics methodology, biostatistics, and bioinformatics tools, this study represents a paradigm shift in the study of COPD and asthma.

Our main aim is to perform multi-omics data integrative subgrouping and biomarker identification of asthma and COPD in the U-BIOPRED paediatric and adult cohorts (ClinicalTrials.gov NCT01976767 and NCT01982162) and our in-house Karolinska COSMIC cohort (ClinicalTrials.gov NCT02627872. U-BIOPRED is a unique EU consortium dedicated to identifying distinct molecular subgroups of asthma based on integrated analysis of seven anatomical compartments' multi-omics data (19 data blocks of 10 omics platforms), coined "molecular handprint". The Karolinska COSMIC cohort is designed to investigate gender differences in smoking-

induced COPD (10 omics data blocks). Our recently developed systems medicine framework will be applied in both cohorts to identify molecularly distinct subgroups, in order to help stratify these heterogeneous populations into molecularly distinct entities. Characteristics in clinical parameters as well as alterations in multi-omics data (mRNA, proteomes, metabolomes, and lipid mediators) from multiple anatomical locations will be identified for each subgroup using custom bioinformatics and biostatistics methods, with emphasis on age and gender-driven subgroups.

Expected results include improved understanding of systemic COPD and asthma in different age and gender groups, respectively. This can also lead to improved techniques for early diagnosis, subgrouping, and phenotyping of COPD and asthma, as well as new pharmaceutical target molecules for the treatment, with the potential to be developed for clinical application. Given that no effective molecular predictors are currently available for the growing COPD and uncontrolled asthma patient group, the long-term consequences of the clinical and molecular subgroups proposed here have a potentially enormous impact on both quality of care and quality of life for the individual. The stratification of the large spectrum of COPD and asthma phenotypes represents an essential step to facilitate the development of new diagnostic tools and pharmaceutical targets, eventually reducing healthcare costs, improving quality of life, and saving lives.

Research group

The post-doctoral/visiting researcher will be part of the Pulmonomics research group (www.pulmonomics.net) at the Respiratory Medicine Unit, Center for Molecular Medicine and Department of Medicine, Solna. Our research interests can be broadly defined as developing a respiratory systems medicine framework for molecular sub-phenotyping of chronic inflammatory diseases of the lung. We focus equal efforts on translational studies of the response to environmental exposures in patient cohorts and innovation & methodology development in the fields of proteomics, multivariate modeling, and data integration.

Both the U-BIOPRED and Karolinska COSMIC projects included multiple national and international collaborators. This project focuses on the large-scale computational systems biology and integration segments, which represents the final stages of these decade-long projects involving interdisciplinary teams of clinicians, experimentalists, bioinformaticians, and data scientists.

Supplementary information

Key words

bioinformatics; multi-omics integration; asthma; COPD; chronic inflammatory lung diseases; subgrouping; biomarkers; programming; statistics; machine learning

#15 Understanding the role of CD4 T cells in cancer immunity

Type of recruitment
Postdoc, 24 months

Project title
Understanding the role of CD4 T cells in cancer immunity

Supervisor
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Qualifications of applicant
The candidate should have received their PhD in the field of immunology and/or cancer biology. Experience with single cell RNA-Sequencing (wet lab and computational), animal models of disease, cancer, flow cytometry and general lab techniques including cell culture, qPCR and western blotting will be regarded highly. Specialised understanding of T cells is also favourable.

Background
CD4 T cells recognise peptide antigens presented in the context of MHC-II molecules and are known to secrete a range of cytokines. These cytokines are known to promote the health of tissues including the gut, lungs, skin and adipose tissue. However, in some instances, CD4 T cells are implicated in pathogenic diseases including asthma, atopic dermatitis and inflammatory bowel disease. CD4 T cells are also appreciated to play a role in regulating the growth of cancers, but their precise role is more enigmatic.

Research project description
In this project, we aim to understand how CD4 T cells promote the health of mucosal and non-mucosal tissues. We will investigate ‘states’ of CD4 T cells in health and disease, focusing particularly on the role of CD4 T cells in cancer. While the bulk of studies on immune therapy of cancer have focused on promoting cytotoxic CD8 T cell function, CD4 T cells are increasingly appreciated to play an important role in cancer immunity and in responsiveness of tumors to immune therapies. Tumors are known to acquire mutations that lead to the emergence of ‘neoantigens’ with CD4 T cell-stimulatory capacity. However, CD4 T cells may also influence tumor immunity in antigen-independent manners.

This project will focus on characterising CD4 T cells in diverse clinical cancers and pre-clinical models of cancer using techniques including single cell RNA-Sequencing, mouse models, flow cytometry, etc.. Mechanistic studies to determine how CD4 T cells regulate tumor immune responses will be undertaken in gene-targeted mouse models.
In all, we expect the project to shed new light on the role that CD4 T cells play in cancer immune responses.

Research group

The group is currently comprised of one PhD student (Junjie Ma, CSC), a postdoctoral researcher (Julian Stark) and the group leader (Coquet). A new postdoctoral researcher will soon begin and a Masters student will also join the group in January 2021. We expect to have a team of 4-6 people over the next few years.

Supplementary information

Key words

CD4 T cells, T helper, cancer, single cell RNA-Sequencing, cytokines

#16 In vitro activation of human ovarian follicles

Type of recruitment
Postdoc, 18 months

Project title
In vitro activation of human ovarian follicles

Supervisor
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Qualifications of applicant
Successful candidate has good knowledge on female reproductive biology, including the physiology of the ovary. In addition, experience from research projects involving basic cell culture and molecular biology techniques is a requirement. A suitable background education would be for example a medical doctor or a M.Sc in (reproductive) biology. Our team is international and cross-disciplinary. Therefore good communication skills in English (both written and oral) are a necessity.

Additional merits for the candidate are experience in stem cell and/or primary cell culture and cell isolation techniques, as well as experience in handling clinical patient samples.

Background
Primary ovarian insufficiency (POI) is a condition where ovarian function seizes prematurely with early amenorrhea and infertility as a consequence before the age of 40. The incidence of POI is about 1/1000 in women aged 25-30, and as high as 1/100 in women aged 35-40. Currently fertility treatments for POI patients are extremely limited. Without assisted reproductive technology, the natural pregnancy rate is only 3.5%-4.4%. Many POI patients face egg donation as the only option to achieve pregnancy.
Activation of residual dormant follicles in ovarian tissue by in vitro exposure to an activator cocktail prior to transplantation of the tissue back to the patient has been developed as a novel treatment approach for POI patients. Although some pregnancies have been achieved following the protocol, it has proven to be difficult to repeat and apply to all patients. There are knowledge gaps relating to the exact mechanisms of the in vitro activation protocol and the normality of the in vitro activated ovarian tissue, which limits the understanding of safety and applicability. The answers to these questions could lay the foundation for further clinical development of the protocol.

Research project description

The objective of this study is to improve our understanding of molecular mechanisms underpinning the growth activation of human ovarian primordial follicles, using a 3D culture model of isolated follicles and a xeno-free ovarian cortical tissue culture system developed in the group. We will use these systems to compare the growth activation of follicles in the presence and absence of the activation cocktail. Molecular mechanisms will be studied using transcriptomics, RNAscope and immunostainings, and the findings will be connected to histomorphological analyses of the tissue samples as well as patient characteristics.

The applicant is expected to carry out primary tissue and cell culture studies using reported in vitro activation technologies (PTEN inhibitor vs “drug-free” in vitro activation) to examine the effects on follicle growth, health, and gene expression. Our particular interest is to compare the in vitro treated tissue and follicles to untreated ovarian samples to understand potential deviations from normal growth pattern. All materials and methods required for this project are set up in the laboratory, including a biobank containing >200 human ovarian tissue samples.

We expect that the results of the proposed study will shed light on our understanding of the normality of in vitro activated ovarian follicles and the molecular patterns underpinning their growth. Collectively, the project will pave the way to further development of treatment strategies for POI patients.

Research group

Damdimopoulou lab consists of four PhD students, one postdoc and one laboratory engineer (October 2020). The work of the group, entitled “Chemicals and Female Fertility”, revolves around three main topics:

I. delineation of cellular and molecular mechanisms that control human ovarian function and follicle growth from birth to menopause

II. development of advanced culture systems for follicle growth in vitro

III. investigation of the mechanisms by which chemical exposures affect ovarian function and follicle growth.

We use epidemiological cohort studies, clinical patient samples, in vitro culture systems, molecular biology methods and single-cell technologies to address these topics.

Supplementary information

Key words

Female fertility, Primary ovarian insufficiency, Reproductive medicine, Human ovary, Tissue culture, Primary cell culture, In vitro activation of follicles, Transcriptomics

#17 Lineage and fata-map reconstruction of germ cells and their role in epigenetic inheritance of disease

Type of recruitment
Doctoral student, 4 years
Postdoc, 24 months

Project title
Lineage and fata-map reconstruction of germ cells and their role in epigenetic inheritance of disease

Supervisor
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Qualifications of applicant
• _Doctoral student (48 months)
• _Postdoc (24 months)
We are recruiting a doctoral student for a period of up to 4 years or a postdoc for 2 years. It is important that the applicant be able to communicate well in English, be highly motivated, and be able to work well in an international environment. Good knowledge of written and spoken Englishis a requirement.The applicant is to have completed a master's degree for the doctoral student position or a doctoral degree for the postdoc position, specializing in medical biology. It is important that theapplicant have a strong interest or documented work experience in developmental biology and genetic and epigenetic gene regulation. Preferably, the applicant should also have experience working with mice, cell culture, molecular biology techniques. Experience with single-cell RNA Sequencing and associated analysis is a strong merit.

Background
Germ cells are often considered immortal as they act as the enduring link and sole messenger to relay genetic and epigenetic information across generations. Malfunction of germ cells has the greatest potential to affect animal reproduction and impair health outcomes across several generations known as epigenetic inheritance of disease. Therefore, a tightly regulated genetic and epigenetic program is essential for functional germ cells. Compared with somatic cells, germ cell development exhibits extraordinary features. Firstly, primordium germ cells

(PGCs) are specified far from their final destination (i.e. gonads) and matured during long migration. Secondly, germ cells have to accomplish several important tasks on time including regain of pluripotency and erasure of epigenetic memory. Several questions arise during this critical developmental period. What is the molecular mechanism to protect genome integrity during epigenetic remodeling? How stray germ cells escape surveillance and initiate tumorigenesis in later life? How germ cells respond to environmental stimuli and pass down adverse effects? We plan to address these questions using the molecular barcoding technique with the state-of-the-art single-cell omics tools, which will yield valuable insights into germ cell genesis in health and disease. Such knowledge will also allow us to further compare the fate maps across germ cell tumors and documented disease models of epigenetic inheritance.

Research project description

To reconstruct the germ cell fate map, we will use barcoded lentivirus particles to target developing premigratory germ cells. We will design a lentivirus vector engineered with a germ cell-specific enhancer (e.g. Oct4dPE) tagged with various barcodes and GFP reporters. Ideally, we want to target each premigratory germ cells with a unique barcode. We will inject lentivirus with various titrationat E6.5 and collect premigratory germ cells at E8 by FACS sorting and validate the transfection efficiency by decoding the barcodes with single-cell RNA-sequencing. After optimization, we will analyze germ cells from gonads at later timepoints to construct lineage trees based on the barcodes and investigate if there exist any big and small clones together with the unique molecular signature. This novel approach will for the first time address the clonal proliferation and structure in the gonad during germ cell genesis.

In both human cohorts and animal models, parental health condition and environmental exposure have been shown to transgenerationally (F2 generation and beyond) affect offspring phenotypes and susceptibility for disease development later in life, as termed as “fetal programming”. In collaboration and by using the mouse model, we have found strong evidence that reproductive and metabolic phenotypes of polycystic ovarian syndrome (PCOS) mother can be transmitted beyond F1 generation up to F3 offspring. Such phenotypic transmission is accompanied by developmental programming and germ cell moderation (Nature Medicine, 2019 Dec). Our followup work aims to distinguish the transgenerational effects by the germline moderation from the maternal uterine environment and identify the molecular links across the generation. We are in the process of establishing new PCOS mouse models by IVF and embryo transfer in surrogacy mothers. We start an extensive phenotypic and molecular analysis, aiming to identify the molecular underpinning involved in germline moderation with future physiological defects.

Research group

The Deng lab is focusing on understanding genetic and epigenetic regulation in the germline cycle, linking these processes to tumor initiation and epigenetic inheritance of disease. The lab has recently received the Wallenberg Fellow grant

for the project described here and will therefore be able to provide sufficient resources for the student to carry out the proposed project. Currently, the lab consists of two registered Ph.D. students, two postdoctoral fellows, and one master project student. We are situated in a new research building, Biomedicum B5. We actively collaborate with other research groups for bioinformatical expertise or technological knowledge exchange. The Deng lab is part of several seminar series where the student will learn about ongoing fundamental biological research at Karolinska Institutet and will have the opportunity to present their work locally and internationally.

Supplementary information

Key words

Germ cells, lineage tracing, cancer, Crispr/Cas9, DNA barcoding, single-cell sequencing, tissue

culture/organoid

#18 Prognostic education of non-malignant cells in the tumor microenvironment

Type of recruitment
Doctoral student, 4 years

Project title
Prognostic education of non-malignant cells in the tumor microenvironment

Supervisor
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Qualifications of applicant
This PhD project is well suited for a student with medical, biology, or bioinformatics background. The criteria for being admitted to PhD studies at Karolinska Institutet must be fulfilled. The PhD candidate must be ambitious, structured and willing to learn new techniques and construct new knowledge. A willingness to work together with colleagues with different backgrounds and expertise is important. Personality and skills that match and complement the rest of the sarcoma TME team will be considered during the interview process.

A basic understanding for research design and scientific communication is essential for success of the project. English is the every-day language in the laboratory. Prior laboratory experience is considered a merit, but is not mandatory. An interest in either medical pathology or bioinformatics is beneficial.

Background
Non-malignant cells of the tumor microenvironment control tumor growth, metastasis and response to treatment. These processes are well studied in tumors derived from epithelial cells, but not yet described in the various subtypes of adult and pediatric sarcoma.

The sarcoma tumor microenvironment team with collaborators perform explorative studies to map molecular and cellular communication between different cell types in sarcoma. Our model systems indicate that normal cells in the body suppress early sarcoma growth, but lose this ability during tumor progression. With time, they may instead act tumor promoting.

So far, we have for example demonstrated an association between stromal PDGFRB expression with the most aggressive subtype and metastasis in pediatric rhabdomyosarcoma patients (Ehnman et al., Cancer Research, 2013). Recently, we demonstrated a prognostic role of CD20+ B cells in adult soft tissue sarcoma (Tsagozis et al. and Ehnman, Cancer Immunol, Immunother, 2019). This latter finding was confirmed in independent sarcoma cohorts and linked to response to immunotherapy (Petitprez et al., Nature, 2020).

Altogether, our research aims to characterize cellular crosstalk and explore relevant molecular mechanisms involved in sarcoma progression. We hope to identify biomarkers and molecular targets that could guide the development of personalized medicine with principally different modes of action, that is, targeting of the communication with non-malignant cells.

Research project description

Aim

The overall aim with the PhD project is to further characterize our findings suggesting that malignant cells in sarcoma make use of, and reprogram, normal cells in the body to participate in tumor progression. Specific aims will focus on (1) therapeutic targets, and (2) novel biomarkers that can give information about patient survival (prognostic marker) or response to therapy (predictive marker).

Study design overview

The study design is particularly beneficial for a PhD candidate who wish to learn a wide range of molecular methods and how to apply them in the tumor setting. Importantly, the questions to be addressed are likely to be relevant in multiple tumor types, not only sarcoma. This also implies that the PhD project is well suited to act as a bridge to further molecular oncology studies for a PhD candidate with the ambition to pursue a translational research career.

Work packages

Experimental approaches will be outlined in detail together with the PhD candidate, particularly considering the applicant´s own interest and expertise. The intention is to cover several essential aspects of sarcoma biology, which are surprisingly largely unexplored in the existing literature. Patient samples have already been collected and are ready for analysis.

The first work package characterizes unpublished molecular findings from mouse model systems, which consistently demonstrate that non-malignant stromal cells display a tumor-inhibitory phenotype that is lost upon reprogramming by sarcoma cells. A preliminary manuscript exists, but additional bioinformatics analyses on an international validation cohort remain.

The second work package, focusing on antigen-presenting immune cells in an immunosuppressive tumor microenvironment, explores consistent survival associations of a specific combination of antigen presenting cells and T cells in independent sarcoma cohorts. A preliminary manuscript exists, but the findings will be validated by IF multiplexing and digital image analysis.

The third and fourth work package will expand observations made in the first and second work packages, but with a focus on cell culture model systems, angiogenesis and malignant transformation of non-malignant stromal cells in the tumor microenvironment.

Expectations and intended learning outcomes
Laboratory techniques that the student is expected to master after four years of study include 2D/3D cell culture in co-culture formats, qPCR, immunoblotting, IHC/IF multiplexing, microscopy and digital image quantification. Practical laboratory work will be complemented with bioinformatics and statistics.

The proposed studies are well connected, but at the same time, contain principally different methods. The modern and technically advanced research environment at BioClinicum provides an excellent basis for such a PhD project. Collaborations are essential for successful project progress and networking is encouraged as part of the education.

Research group

The sarcoma tumor microenvironment team consists of Monika Ehnman (team leader), one CSC PhD student, one postdoc, and one bachelor student. Group meetings, journal clubs, and other social activities are held together with the Prof Arne Östman research group or within Task Force sarcoma, which is a KI-sponsored network of researchers and clinicians working together with sarcoma. The majority of ongoing projects is in collaboration with sarcoma clinicians at the Karolinska University Hospital (pathologists, surgeons, oncologists).

Monika Ehnman is an Assistant Professor working as a full-time researcher at BioClinicum. The research activities are located in a modern, open space laboratory together with the Prof Olle Larsson/Felix Haglund research group working with sarcoma pathology and sequencing. Laboratory space and equipment are also shared with the Prof Lars Holmgren research group working with vascular biology in vitro and in vivo.

Supplementary information

Research environment and supervision

The sarcoma tumor microenvironment team offers a scientifically high standard research environment with the ability to interact with the rest of the research community at Karolinska Institutet and the Karolinska University Hospital. Local, national and international conferences are attended on a regular basis.

The PhD candidate will be supervised by Monika Ehnman (main supervisor) and at least two additional cosupervisors (professors) with complementary expertise considering project design and the PhD candidate´s knowledge and interest. Supervision will be well balanced between, on one hand, the development of the PhD candidates own ideas, on the other hand, the original project idea with valuable input from colleagues and international collaborators. The right candidate will be given the opportunity to grow both at the professional as well as the personal level.

Key words

cancer, sarcoma, tumor microenvironment, prognostic factors, cancer therapy, stroma, angiogenesis, metastasis, tumor, microscopy, xenografts, cell culture, mesenchymal cells, immunology, pathology, rhabdomyosarcoma

#19 Capturing and modeling epigenome dynamics

Type of recruitment
Postdoc, 24 months
Visiting researcher, 12 months

Project title
Capturing and modeling epigenome dynamics

Supervisor
Simon Elsässer, Senior Researcher or maybe better Principle Investigator
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Qualifications of applicant
Required skills of the successful candidate are:

- firm knowledge in R, Unix/Linux, Perl, Python
- robust mathematical and statistical background knowledge
- extensive experience in the analysis of next-generation sequencing data
- experience in pipeline development and data management
- knowledge of relevant biological areas (chromatin and gene expression, genetics and epigenetics)
- experience in MatLab, Mathematica or related programming languages is an advantage
- excellent knowledge in biostatistics
- experience in data genomics data mining and visualization
- Excellent understanding of biological concepts and/or willingness to learn. Experience in working with wet lab scientists
- proficiency in written and spoken EnglishNote: It is an option for the applicant to incorporate hands-on wet lab work into the research project if robust molecular biology, tissue culture and biochemistry skills exist in addition to the required skills above.It is a merit if the applicant can document the following:
- Excellent organizational, communication and social skills
- Excellent presentation skills

Background
Chromatin integrates a multitude of signals to control gene expression, some of which have the propensity to be maintained through replication and cell division. In my laboratory, we are developing quantitative methods to study the molecular circuits that underlie epigenetic gene regulation and inheritance. Our focus on epigenetic processes is in stemness features and lineage commitment of

pluripotent stem cells. We are using mouse and human cell embryonic and induced pluripotent stem cells in ex vivo culture as highly tractable model systems for early human and mouse embryogenesis. We are mapping multidimensional epigenomics data onto defined differentiation trajectories to, for example, understand the maintenance of pluripotency transcription factor circuits, and the exit thereof. We are particularly interested in Polycomb group proteins, which are evolutionarily conserved master regulators of cell identity and differentiation and have long been a paradigm for epigenetic gene regulation. Based on our emerging quantitative data from mouse (Kumar and Elsässer, 2019) and human ES cells (unpublished work), we believe that we can gain new insights into mechanistic action of PcG proteins in early embryonic developments.

Research project description

For our growing interdisciplinary and multi-national team, we are recruiting a Bioinformatician dedicated to epigenomics next-generation sequencing (NGS) analysis, data mining and visualization, computational modeling. Overall aim of the postdoctoral project will be to analyze data and develop software to integrate our multidimensional quantitative data, including user-friendly primary analysis pipelines, genome-wide data analysis and flexible visualization. Higher-level analysis may include developing novel strategies to infer function or mechanism using machine learning or modeling. For example, mathematical models that describe dynamic chromatin states will be developed and tested on the datasets. Using such models, we can derive quantitative descriptions of pluripotency networks and differentiation trajectories.

Our method for determining chromatin dynamics relies on multiplexing a series of measurements over time, which then can be quantitatively compared. Typically, a protein is pulse-labeled in the cells and optionally chased, making parameters like on- and off-rates, steady state flux - in theory - accessible from the collected genome-wide data. Practically, the signal at a given time point is a combination of these parameters and thus it is necessary to use either a deterministic or stochastic approach to deduce the clean parameters. Here, we envision that the postdoc will build a model of the process in silico that can be fitted to the experimental data to yield rate constants. Also here, an important subaim will be the development of user-friendly tools to streamline processing kinetics from the primary data and output various useful visualizations that can be used in publications.

To correlate quantitative chromatin profiles with functional outcome, we use a number of additional genome-wide techniques such as nascent transcriptomics (NET-Seq or TT-Seq). We also make use of the wealth of existing genomics dataset in the literature. Here, we are aiming to implement automated pipelines to process datasets and make correlations between datasets using simple metrics or more advanced machine learning algorithms. A new frontier in genomics represents epigenomic profiling at the single-cell resolution. Studying single cells instead of bulk gives important insights into cell-to-cell variability and functional differentiation in a population. Yet single cell data will always have the limitation of

only scarcely sampling the epigenomic landscape. We are thus aiming to infer quantitative features in single cells by combining single-cell and quantitative bulk data in new ways.

Research group

The Elsässer lab is located at the modern Science for Life Laboratory (SciLifeLab) in Stockholm, Sweden. The collaborative institute and national infrastructure hub provides a world-class environment and concentration of bioinformatics expertise. We are part of the Department of Medical Biochemistry at Karolinska Institutet. The Elsässer lab is also part of the Ming Wai Lau Center (MWLC) for Repairative Medicine which includes a biofinformatics core in Hong Kong. MWLC bioinformatics core has strong expertise in single cell methods.

The current group consists of five postdocs and 6 PhD students, including on computational biologist and a bioinformatics PhD student. The postdoc will be part of a strong bioinformatics team and work together with experimentalists in the lab on individual datasets and in parallel will develop universal software packages that facilitate primary and advanced data analysis. The postdoc will also interact with bioinformaticians at the MWLC.

Supplementary information

Key words

Epigenetics, Epigenomics, ChIP-Seq, ATAC-Seq, MINUTE-ChIP, single cell, mathematical modeling, systems biology, proteomics, stem cells, cancer

#20 Immunoprofiling of juvenile idiopathic arthritis

Type of recruitment
Doctoral student, 4 years

Project title
Immunoprofiling of juvenile idiopathic arthritis

Supervisor
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Qualifications of applicant
We are looking for a doctoral student with a background in biomedicine/medicine with knowledge of immunology. Education within biostatistics and experience of working with larger data sets are advantageous, as is experience of laboratory work such as cell culture, immunohistochemistry, FACS, western blotting and PCR.

The applicant should be highly motivated to undertake a doctoral education, be self-driven and able to take responsibility for his/her project while at the same time be open for collaborations. Excellent interpersonal and communication skills in spoken and written English are necessary.

Background
Juvenile idiopathic arthritis (JIA) is an umbrella term for 7 clinically defined subtypes of chronic arthritis each with a disease onset before the age of 16. All subtypes encompass inflammation, joint destruction and pain; however, these disease hallmarks can appear independent of each other. It needs to be clarified which immune mechanisms drives each hallmark and whether the subtype division primarily based on clinical features is appropriate to ensure optimal treatment of the patients. The immune profile of each subtype is not clearly defined, which immune reactions that are shared and which that are specific for a certain subtype. Our longstanding research has defined the alarmin HMGB1 as a pathogenic mediator of arthritis and a potential drug target. Good predictive and diagnostic biomarkers still need to be defined for JIA and there is a need for better therapeutic options. In an expanding research field, the impact on peripheral inflammation on cognitive deficits is becoming increasingly clear. However, this is not at all well exploited in arthritis.

Plasma, urine and synovial fluid samples from JIA patients are retrieved from the sample collection JABBA established and housed within the research group. JABBA contains more than 6000 samples from 500 JIA patients collected in an ongoing collection since 2009. Clinical data is registered and accessible in the national pediatric rheumatology quality register (barnreumaregistret) with more than 95% coverage.

Research project description

The purpose of this doctoral project is to reveal the immunological mechanisms mediating juvenile idiopathic arthritis (JIA) and their correlations to the clinical disease hallmarks inflammation, joint destruction and pain. This forms the basis for development of both prognostic and diagnostic biomarkers and for new therapy. In addition, we aim to explore whether chronic inflammatory arthritis induces neuroinflammation resulting in cognitive deficits. Specific projects are:

1) Proteomics analysis of JIA samples

We will use the synovial fluid samples and plasma samples we have collected in JABBA for immunoprofiling by Proximity Extension Assay (www.olink.com) methodology. The study set up will allow both a cross-sectional analysis and a longitudinal study as we have repeated synovial fluid samplings from patients spanning from early time points to up to 6 years after diagnosis. Pathway analysis will be performed by Ingenuity. Strict stratifications of groups will be performed bidirectionally using clinical parameters available through the quality register and based on molecular phenotypes revealed by the pathway analysis. This study will be unique in its longitudinal approach and the availability of data regarding inflammatory activity, destruction and pain in the quality register.

2) New targets for therapy

We will investigate biomarkers strongly associated with a specific subtype of JIA or a specific clinical feature revealed by the immunoprofiling studies, above as potential targets of therapy. This will be performed by cellular studies (effect of biomarker protein on activation of immune cells and synovial fibroblasts, chondrocytes and osteoclasts) as well as using the experimental arthritis models available within the research group. Using arthritis models we will test the contribution of the defined biomarker proteins to arthritis-associated features by either injection of protein (can it induce a certain feature) or inhibition of the protein by antibodies/inhibitors (can a certain feature be suppressed).

3) Association of arthritis with cognitive deficits

We will assess if and how chronic arthritis induces neuroinflammation, focusing on the hippocampal area, by inducing collagen-induced arthritis in mice and retrieving

brains and plasma after established clinical disease. Brain sections will be staining for inflammatory markers, including HMGB1, and neuroinflammation assessed. In a second step, markers for neurodegeneration such as S100B and neurofilament, can be measured in plasma. If clear signs of neuroinflammation is evident, cognitive testing will be performed.

4) The role of HMGB1 in arthritis

Our longstanding research demonstrates the alarmin HMGB1 to be a pathogenic factor in arthritis. We are continuously exploring its functions on inflammation, bone- and cartilage destruction and pain by molecular and cellular approaches. How it is regulated and how it can be targeted by therapy.

Research group

Helena Erlandsson Harris - Professor, PI

Cecilia Aulin - Civil engineer, PhD, senior researcher

Erik Sundberg - pediatric rheumatologist, PhD

Manoj Neog - PhD, Post-doc

Henna Salo - MSci biomedicine, doctoral student

Raya Saleh - MSci biomedicine, doctoral student

Rebecka Heinbäck - MSci biomedicine, doctoral student

Heshuang Qu - MSci biomedicine, doctoral student

Karina Mördrup - research nurse

Supplementary information

The Erlandsson Harris group is a part of the rheumatology unit which encompasses close to 100 researchers. The laboratory is located at the center for molecular medicine, a research center with a focus on chronic inflammatory diseases, at the KI-Karolinska hospital area in Solna. Within the group, we are working closely together on our projects and we also collaborate with other groups within and outside our unit and KI.

The project described above will include analysis of large data sets (from proteomics studies) and work with clinical quality registers. Additionally, classical cell biology and cellular immunology wet lab techniques will be employed.

Key words

arthritis, proteome, immunoprofiling, inflammation, HMGB1, inflammatory disease

#21 Neuroimaging studies in Dementia

Type of recruitment
Postdoc, 24 months

Project title
Neuroimaging studies in Dementia

Supervisor
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Qualifications of applicant
We are looking for a postdoctoral fellow in the field of Medical Sciences (Medicine, ideally Neurology, Radiology, Psychiatry or Geriatrics; Psychology; Neuropsychology; or Biology) or Engineering (Medical Engineering; Physics; Statistics and/or Data Mining). We are primarily looking for a fellow who can join our lab for 24 months, but shorter time periods may also be considered depending on student´s interest or possibilities (e.g. between 10 months and 24 months).

Previous experience with Neuroimaging is not mandatory but is highly appreciated.

Previous experience with Dementia Research is not mandatory but is highly appreciated.

Background
Dementia is a world-wide problem for health systems, patients, families and society. There is currently no treatment to stop or cure the disease. Among different dementia types, Alzheimer's disease (AD), dementia with Lewy bodies (DLB) and vascular dementia (VD) are the most common types.

Despite the clear clinical separation between DLB, AD and VD, there is a substantial neuropathological overlap among these disorders. More than 50% of the patients with DLB show AD pathology (amyloid-β and tau neurofibrillary tangles) and cerebrovascular pathology at autopsy, in addition to Lewy body pathology. However, little is known about how these pathologies build up during life, whether they influence each other, and how they promote disease progression and clinical phenotype in DLB.

The postdoc fellow will be part of an unique and world-leading project using the most advanced neuroimaging techniques. The goal is to elucidate the association between different brain pathologies, in vivo, and to investigate how they lead to brain atrophy and influence clinical phenotype in DLB.

Research project description

The postdoc fellow will use cutting-edge neuroimaging techniques to unveil the role of cerebrovascular pathology in DLB. The fellow will also use state-of-the-art PET and MRI biomarkers to investigate the association between cerebrovascular and AD pathologies with neurodegeneration and clinical phenotype in DLB.

A strength is the large data available, including around 5,650 individuals from eight international cohorts (patients with DLB, and patients with AD dementia and healthy controls for comparison). I addition, 120 new patients and controls will be collected at Karolinska University Hospital. This smaller dataset will be relevant to target the most specific questions.

Another strength of this project is the opportunity to participate in a global collaboration between 40 centers in Europe and USA. The postdoc fellow will be connected to an extremely strong scientific network, will be able to use powerful clusters and infrastructure for image analysis, and will be in contact with world experts in the field of neuroimaging and dementia.

Preliminary results: Our preliminary results show an association between cerebrovascular disease,

neurodegeneration and cognitive performance in healthy individuals. Further, increased cerebrovascular disease is associated with atrophy in posterior brain areas and clinical phenotype in DLB. These results were presented in the last AAIC conference in Amsterdam 2020.

Significance of the postdoc project: We expect to elucidate pathogenesis in DLB, eventually helping to improve diagnosis of the disease.

Research group

The group of Dr. Ferreira currently includes two PhD students and two Postdocs, and is part of the larger Imaging Research Group of Karolinska Institutet, one of the

most important Imaging labs in Europe (https://ki.se/en/nvs/imaging-research?_ga=2.122298316.617968212.1603054833-2058560825.1602576725).

The group of Dr. Ferreira has long tradition in investigating neuroimaging and cognition in normal aging and neurodegenerative disorders such as Alzheimer's disease and dementia with Lewy bodies.

The group is in the frontline of biological subtypes of Alzheimer's disease (https://pubmed.ncbi.nlm.nih.gov/32047067/) and recently, also in biomarkers of dementia with Lewy bodies (https://pubmed.ncbi.nlm.nih.gov/32989106/).

Supplementary information

Key words

Dementia; Neuroimaging; Biomarkers; Cognition; Alzheimer's disease; dementia with Lewy bodies; Cerebrovascular disease; Magnetic Resonance Imaging; Positron Emission Tomography

#22 Deep learning based analysis of behavior in mouse models of disease

Type of recruitment
Doctoral student, 4 years

Project title
Deep learning based analysis of behavior in mouse models of disease

Supervisor
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Qualifications of applicant
Expertise in coding and programming is essential to carry out the advanced analyses at the basis of this project. The CSC scholar will work at the interface between "wet" science and software development. Preferentially, he/she should have a background on computer science and good knowledge of coding platforms (e.g., R, Python, Matlab) with an interest in the applicability of artificial intelligence approaches to biological questions.

Background
Parkinson's disease (PD) treatment relies in large part on dopamine replacement therapies based on L-DOPA and dopamine receptor agonists (e.g. pramipexole). These drugs attenuate the motor symptoms of PD, but they also cause the emergence of severe complications. For instance, administration of L-DOPA leads to the development of dystonic and choreic involuntary movements, generally referred to as L-DOPA-induced dyskinesia (LID), which significantly reduce the beneficial effect of this drug. In addition, administration of dopamine D2/D3 preferential agonists, including pramipexole and ropinirole, leads to compulsive repetitive behaviors (punding) disruptive of the patient's quality of life. To study the mechanisms at the basis of these ailments it is necessary to optimize appropriate animal models. The supervisor laboratory has worked at the validation of a mouse model of PD reproducing LID and plan to extend these analyses to the assessment of stereotyped, repetitive behaviors caused by administration of pramipexole. The analysis of these pathological manifestation typically requires visual inspection and scoring of behaving mice, which are time consuming and often prone to subjective bias. Against this background, the development of machine learning based methodology to improve and accelerate behavioral analysis would be a major breakthrough.

Research project description

The project is based on behavioral analyses performed in a mouse model of PD (from now on referred to as PD mouse). Specifically, we will inject mice with the toxin 6-hydroxydopamine (6-OHDA), which reproduces the loss of dopamine innervation to the basal ganglia typically observed in PD patients.

In Specific Aim 1, we will focus on the analysis of abnormal involuntary movements (AIMs) generated by administration of L-DOPA to the PD mouse. AIMs have been validated as a surrogate marker of LID observed in PD patients and consists of (1) dystonic turning of the upper body, (2) forelimb fluttering and (3) orofacial dyskinesia. Mice will be injected with 6-OHDA in the dopaminergic medial forebrain bundle. After recovery the animals will be treated with daily injections of L-DOPA for 9 days and AIMs will be recorded immediately following the last administration. The student will first familiarize with the techniques to generate the PD mouse model and with the specific behaviors (i.e. AIMs) to be examined. The student will then proceed to optimize the analysis using open source-based analysis software.

In Specific Aim 2, the student will study the repetitive movements generated in the PD mouse by administration of pramipexole, which is a common anti-parkinsonian medication. We will focus on the analysis of grooming, which in mice consists of a series of stereotyped movements executed along the rostro-caudal axis of the body. Grooming is considered a potential behavioral marker of obsessive compulsive disorders, such as those often observed in PD patients under pramipexole treatment. Enhanced grooming as well as interruption of its regular cycle will be examined in PD mice treated with pramipexole using the same deep-learning approach employed in Specific Aim 1.

Altogether these experiments will provide a basis for reliable and rapid analysis of pathological behaviors in an animal model of disease, thereby paving the way to the evaluation of pharmacological and genetic interventions which may represent potential therapeutic approaches to the management of PD, and help to clarify the mechanisms at the basis of this disorder.

All necessary instrumentation and advanced expertise will be available thanks to a collaborative interaction between the laboratory of the supervisor at KI and colleagues at the Royal Institute of Technology.

Research group

Gilberto Fisone, Professor, PI

Daniel Medeiros, Postdoctoral fellow

Laura Boi, Postdoctoral fellow

Clarissa PisanÃ², Postdoctoral fellow

Carina Plewnia, PhD student

Supplementary information

Key words

Parkinson's disease, machine learning, computer science, L-DOPA-induced dyskinesia, obessive compulsive disorders, behavior, mouse

#23 Immunogenicity of biopharmaceuticals

Type of recruitment
Doctoral student, 4 years

Project title
Immunogenicity of biopharmaceuticals

Supervisor
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Qualifications of applicant
We are looking for someone with documented knowledge in immunology and preferentially also with lab experiences and skills in several of the basic immunological methods.

Background
Development of new biopharmaceutical products (BPs) offer increasingly new opportunities to treat chronic inflammatory diseases like multiple sclerosis (MS), rheumatoid arthritis (RA), inflammatory bowel disease (IBD) and systemic lupus erythematosus (SLE). BPs are defined as drugs that are produced by living organisms through recombinant DNA and as proteins they are potentially immunogenic. The immune system reacts against these repetitively administered BPs, even those that are humanized, and a significant proportion of the treated patients develop anti-drug antibodies (ADA). In patients with high titres of ADA, the drug will fail to reach their intended target and the patients become in essence untreated. These patients would benefit from being identified in the clinical routine and as soon as possible switch to another drug to avoid disease break through and unnecessary and often irreversible loss of function. Moreover, induction of ADA works as a good vaccination and there is a risk that patients returning to a treatment that they previously been immunized against might get a severe and unpleasant booster reaction.

Research project description
For this PhD position there are four major projects:

1. The first is to extend already existing methods to other diseases, where the same treatments are used; to adapt the assays to new biosimilars; and to introduce tests for immune complexes when needed. In collaboration with clinicians and access to clinical samples and clinical data from registries, we will be able to determine

optimal drug levels, values for recommendations of when ADA tests should be done and to set clinically relevant threshold values where we can recommend when the patients should be switched to a less immunogenic drug.

2. The second is to investigate to what extent the formation of immune complexes between the drug and ADA will influence the test results and what clinical relevance these have. We have published data on rituximab treated MS patients experiencing serum sickness 10 days after infusion, who were all anti-rituximab ADA positive (Holmøy, 2019). Similar results were found for a rituximab treated vasculitis patients recently. Thus, methods that are drug tolerant are needed to be able to measure ADA at these clinically relevant time points and we should be able to provide them for several additional BPs.

3. The third is to establish the predicted effect of monitoring the drug level is that it will lead to a timelier and informed treatment decision adapted to individual variations, where some patients have low drug level due to rapid clearance and would benefit from dose escalation and some have high titer ADA and thus would benefit from switching to a less immunogenic drug.

4. The forth project aims is to investigate if ADA immunity works like vaccinations and thus if a re-dose of the same biologics that the patients previously have been ADA positive for might elicit a strong booster of the response with yet unknown clinical complications. We need more evidences for this potentially detrimental effect and thus investigation of the cellular immunity is warranted. This can now be done with Elispot tests from MabTech for infliximab, adalimumab and natalizumab B and T cells. We will especially look for patients that previously were ADA positive, but now have undetectable levels of ADA as compared to them that are still ADA positive.

Research group

We are currently one post doc, one PhD student and one BMA working in the group. In addition we try to have at least one master student and a few affiliated member that contribute part time. The CMM building houses several research groups working with chronic autoimmune diseases and so many of the methods and scientific questions of interest are shared with many of the other groups here. I think you will find this environment inspiring!

Supplementary information

Key words

anti-drug antibodies (ADA), memory B cell, memory T cell, biological drugs, serology assays, ECL/MSD

#24 Exploring lymph nodes as an interface between cancer and the immune system

Type of recruitment
Doctoral student, 4 years

Project title
Exploring lymph nodes as an interface between cancer and the immune system

Supervisor
Jonas Fuxe, Associate Professor
Department of Laboratory Medicine

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Qualifications of applicant
• A master's degree in a relevant area, such as biomedicine or veterinary medicine
• Theoretical background in cell biology, molecular biology, tumor biology and immunology
• Interest and preferably experience in performing animal studies
• Experience in using standard cell and molecular biology techniques including cell culture, western blot, PCR, immunofluorescence analysis and plasmid transduction.
• Excellent abilities in English speaking and writing

Background
Metastatic spread of cancer cells to vital organs is the major cause of death in cancer. Understanding metastasis has remained an elusive task and consequently, there is a lack of treatments that target metastasis. An accumulating amount of data show that the immune system plays an important role in dictating the metastatic behavior of tumors. Others and we have found that inflammatory cytokines overexpressed in tumor tissues can trigger re-activation of epithelial-mesenchymal transition (EMT). Cancer cells undergoing EMT lose epithelial characteristics and gain migratory and metastatic properties. Tumor cells with various degrees of mesenchymal characteristics have been identified in the circulation and at metastatic sites.

Solid tumors frequently spread via the lymphatic system. Accordingly, enlarged lymph nodes (LNs) represent an early sign of metastatic spread, and is used for cancer staging and for decisions on treatment strategies. LNs are peripheral immunological organs containing various subsets of immune cells including B and T lymphocytes, and macrophages. LNs act as traffic joints where cells drained from peripheral tissues interact with the immune system. However, it is not clear how

tumor cells gain access to lymphatic vessels and migrate to lymph nodes. In addition, little is known about the interaction between tumor cells and immune cells in LNs and how this affects the metastatic process.

Research project description

Recently, we found that breast cancer cells undergoing TGF-β1-induced EMT become activated for targeted migration through the lymphatic system similar to dendritic cells (DCs) during inflammation. In this research proposal, we will test the hypothesis that EMT affects tumor cell interaction and communication with resident immune cells in LNs and further spread to distant sites.

Specifically, we will;

1) Study how EMT affects tumor cell dissemination to LNs and distant sites

In collaboration with Professor Mikael Karlsson at KI, we have established a mouse footpad model and have shown TGF-β1-induced EMT promotes targeted migration of breast cancer cells through lymphatic vessels. Using this model system, we will explore EMT properties of breast cancer cells and identify candidate genes involved in the migration of EMT cells to LNs. Preliminary data show that tumor cells undergoing TGF-β1-induced EMT upregulate genes known to be expressed in DCs and important for their trafficking to LNs. The most interesting ones will be knocked down using CRISPRcas9 or shRNA and evaluated for their involvement in lymph metastasis.

2) Study how EMT affects tumor cell dissemination to LNs and distant sites

We will also investigate how infiltration of EMT cells will affect the organization, polarization and function of resident immune cells in LNs. Based on our knowledge about the interaction between breast cancer cells and immune cells in the primary tumor, we expect that the presence of metastatic breast cancer cells in the lymph nodes will have a considerable effect on the organization and function of resident immune cells in LNs. We will examine the kinetics of how immune cell populations expand and/or reorganize as breast cancer cells infiltrate the lymph nodes. FACS sorting will be used to isolate different cellular components of LNs and changes in gene expression will be analyzed by RNA seq analysis at the BEA core facility at KI.

3) Explore the expression of EMT markers in LNs from cancer patients

In collaboration with Professor Malin Sund at Umeå University, we will pursue studies to explore novel EMT markers in LNs from breast cancer patients. We will study whether the DC candidate genes correlate with LN metastasis. We hypothesize that the spread of cancer cells to lymph nodes might be overlooked by existing staining protocols used in the clinic, which rely on the usage of epithelial markers to detect tumor cells. Detection of EMT cells in lymph nodes could change clinical protocols for evaluation of lymph node metastasis and affect treatment strategies.

Significance

The studies outlined in this program are expected to provide novel insights into how tumor cells migrate to and interact with immune cells in LNs to distant sites by interacting with different types of endothelial cells. The implications of these findings could be vast as they may lead to the discovery of new targets for anti-cancer therapy.

Research group

Assoc. professor Jonas Fuxe has high competence in studies on tumor cell dissemination to LNs. He has published high impact papers and organized advanced courses and a Nobel Conference on the topic. He has been main supervisor for 5 PhD students, 6 postdocs and master's students from different countries. Fuxe will be the main supervisor and will supervise the student on a weekly basis. Group meetings and journal clubs will be held once a week.

Professor Mikael Karlsson will be co-supervisor and he has high expertise in onco-immunology. The collaboration between Fuxe and Karlsson has been ongoing for several years and has resulted in published articles, review papers, and book chapters.

Two postdocs, Malgorzata Parniewska in Fuxe's group and Marit Melssen in Karlsson's group, are involved of this collaborative project and will supervise the PhD candidate on a daily basis. In addition, collaborative meetings with Fuxe & Karlsson groups will be held every second month.

Supplementary information

The PhD student will perform the studies in a dynamic and international research environment at the Department of Laboratory Medicine and Division of Pathology at ANA Futura at Karolinska Institutet. The teams within the Department perform research in related topics including cancer and inflammation and share equipment,

reagents, technical and methodological knowhow. The laboratories are at highest standards and fully equipped with all necessary equipment for molecular biology, biochemistry and cell culture techniques. In addition, advanced common facilities for Histology, Microscopy (confocal, regular fluorescence and brightfield), imaging analysis, flow cytometry and mass spectrophotometry are present in ANA Futura. Within the clinical pathology lab, special rooms for handling blood- and tissue samples, and for treatment of cells with cytotoxic drugs are up and running. A multiplex staining facility with a VECTRA 3 SYSTEM (PERKIN ELMER) with tissue segmentation, co-localization and phenotyping has also been established. Departmental seminar series are organized every second Thursday, where PhD students and postdocs present their projects. Once or twice per year, the student will present his/her research. This provides the student with excellent opportunities to interact with other students/postdocs, get familiar with their projects and methods as well as give and get feedback.

Key words

Cancer; Metastasis; Lymph nodes; Immune system; Epithelial-Mesenchymal Transition

#25 Exploring the role of the coxsackie- and adenovirus receptor in cancer metabolism

Type of recruitment
Postdoc, 24 months

Project title
Exploring the role of the coxsackie- and adenovirus receptor in cancer metabolism

Supervisor
Jonas Fuxe, Associate Professor
Department of Laboratory Medicine

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Qualifications of applicant
• A PhD in a relevant area, such as biomedicine or veterinary medicine
• Theoretical background in cell biology, molecular biology, tumor biology and immunology
• Interest and preferably experience in performing animal studies
• Experience in using standard cell and molecular biology techniques including cell culture, western blot, PCR, immunofluorescence analysis and plasmid transduction.
• Excellent abilities in English speaking and writing

Background
Metastatic spread of cancer cells to vital organs is the major cause of death in cancer. Understanding metastasis has remained an elusive task and consequently, there is a lack of treatments that target metastasis. Tumor cells change their metabolic state as they become more aggressive and metastatic. Recent data suggest that these metabolic changes are related to the induction of epithelial-mesenchymal transition (EMT), a latent developmental process, which can be reactivated in cancer tissues by inflammatory cytokines overexpressed in tumor tissues.

Recently, we identified the coxsackievirus and adenovirus receptor (CXADR) as a previously unrecognized negative regulator of the AKT signaling pathway. We found that CXADR forms a protein complex with the scaffold protein MAGI-1 and the AKT inhibitors PTEN and PHLPP2. Moreover, we found that CXADR controls the stability and function of PTEN and PHLPP2 as AKT inhibitors. Loss of CXADR, which is a characteristic feature during carcinoma progression, promoted hyperactivation of AKT and sensitized cells to undergo epithelial-mesenchymal transition (EMT) in response to the cytokine transforming growth factor beta 1 (TGF-□1). One arm of

the AKT pathway is known to control glucose metabolism but whether CXADR plays a role in regulating glucose metabolism has not been studied.

Research project description

Based on our recent identification of CXADR as a negative regulator of AKT and the important role of AKT in glucose homeostasis, we hypothesize that CXADR might play a role in regulating the metabolic arm of the AKT signaling pathway. Loss- and gain-of-function experiments and subsequent metabolomics analysis will be performed to study whether CXADR regulates AKT signaling and glucose metabolism in normal cells and cancer cells. Part of these studies will be performed in collaboration with the metabolic research facility at KI. We will also study the role of CXADR in mouse models of type 2 diabetes and cancer progression into a more malignant state.

Research group

Assoc. professor Jonas Fuxe has high competence in EMT research. He has published high impact papers and organized advanced courses and a Nobel Conference on the topic. He has been main supervisor for 5 PhD students, 6 postdocs and master's students from different countries. Fuxe will be the main supervisor and will supervise the postdoc on a weekly basis. Group meetings and journal clubs will be held once a week. A newly recruited PhD student, another postdoc and a master's student will also be part of the group.

Supplementary information

The postdoc will perform the studies in a dynamic and international research environment at the Department of Laboratory Medicine and Division of Pathology at ANA Futura at Karolinska Institutet. The teams within the Department perform research in related topics including cancer and inflammation and share equipment, reagents, technical and methodological knowhow. The laboratories are at highest standards and fully equipped with all necessary equipment for molecular biology, biochemistry and cell culture techniques. In addition, advanced common facilities for Histology, Microscopy (confocal, regular fluorescence and brightfield), imaging analysis, flow cytometry and mass spectrophotometry are present in ANA Futura. Within the clinical pathology lab, special rooms for handling blood- and tissue samples, and for treatment of cells with cytotoxic drugs are up and running. A multiplex staining facility with a VECTRA 3 SYSTEM (PERKIN ELMER) with tissue segmentation, co-localization and phenotyping has also been established. Departmental seminar series are organized every second Thursday, where PhD students and postdocs present their projects. This provides the student with opportunities to interact with students/postdocs.

Key words

Cancer; Metastasis; Glucose metabolism; Epithelial-Mesenchymal Transition

#26 AI-aided digital pathology of gastrointestinal cancer liver metastases

Type of recruitment
Postdoc, 18 months

Project title
AI-aided digital pathology of gastrointestinal cancer liver metastases

Supervisor
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Qualifications of applicant
Motivated and curiosity driven researcher with a background in machine learning, deep learning, or computer vision. Previous experience with python, or R, or C++ is required. Experience with human or animal pathology is a strong plus, but not an absolute requirement.

Background
Metastases are the main cause of death for cancer patients. In Sweden alone, more than 6000 individuals are diagnosed each year with gastrointestinal cancers, which most frequently metastasise to the liver.

Histopathological studies have revealed that histological features such as tumor regression after preoperative chemotherapy, as well as the pattern of cancer cell invasion into the surrounding tissue determine the clinical aggressiveness of liver metastases.

Specifically, tumours that co-opt the normal stroma and replace healthy parenchymal cells show highly aggressive behaviour. By contrast, tumours that fail at co-opting the existing stroma are associated with superior survival.

Scoring histological features and the pattern of invasion is laborious for pathologists and prone to error due to interobserver variation. Hence, despite their proven clinical usefulness, the patterns of tumor invasion are not used in clinical practice today.

Research project description

Overall aim: In this project, you will develop a novel intelligent system for automatic, precise, objective and reproducible recognition of various visual histological characteristics relevant for metastases relapse after operation. A special focus will be on refining and validating an already existing AI algorithm to score so-called "growth patterns" that reflect biologically distinct modes of tumour invasion into the liver parenchyma (e.g. see Fernández Moro et al BMJ Open Gastroenterology 2018).

By integrating appropriate multi-feature, multi-scale visual representation schemes

and hierarchical classification models in a specialised computer system, you will work towards a precise and objective morphological assessment of the risk for cancer relapse after operation based on histopathological slides of resected human liver metastases.

Practical workflow:

In a first step, whole slide scans from human liver metastases are preprocessed to account for variations in staining and scanning conditions. Then, a series of segmentation methods is tested including fuzzy c-means clustering, the Hidden Markov model, adaptive thresholding or seeded region growing. The result is a labelled and processed database of digital slide images. Next, multiple visual features at different scales will be extracted, including pixel level features such as colour, texture, and salient points, object level features such as shape and the geometry features, as well as high level structured topological features. Subsequently, feature selection methods such as minimum-redundancy maximum-relevance will be used to reduce the high dimensionality resulting from the use of multiple features. Then, a hierarchical fusion model for combining low-level features will be applied for visually representing the histology structures.

For hierarchical learning and classification, a hierarchical ensemble classification scheme will be used to incorporate the multi-scale feature representation. A heterogeneous collection of state-of-the-art classifiers will be considered, including Support Vector Machines (SVMs), Bayesian Networks, Decision Trees and Artificial Neural Networks (ANNs).

The developed technologies will be evaluated and trained using slide scans from patients with gastrointestinal liver metastases, acquired at Karolinska University

Hospital and annotated by experienced pathologists. These annotations represent the expert-annotated ground truth, based on which the models will be trained.

The resulting AI-based system will be used to generate automated annotations for almost 1000 patients operated at Karolinska during the last decade and they will be integrated in other projects of the lab that focus on molecular markers and radiological recognition of liver metastases pathology.

Research group

The project is a close collaboration between our lab at Karolinska Institutet Huddinge, the Pathology Department of Karolinska Hospital and the research group of Qianni Zhang, Queens Mary's University London (http://www.eecs.qmul.ac.uk/~qianniz/).

The host research group uses various wet lab techniques, mouse models and patient samples to investigate metastatic invasion. The core group consists of one postdoc, one Master student, and two affiliated PhD students.

The collaborating pathologists have decades of experience with gastrointestinal pathology.

The main practical collaborator providing in-depth expertise with AI-based techniques is Qianni Zhang, Queen Mary's University, London. Close collaboration with Qianni's group is expected and, if the situation regarding the novel coronavirus allows, research visits are planned throughout the postdoctoral period. Alternatively, interactions can be based on video meetings.

Supplementary information

Key words

AI, machine learning, colorectal cancer, pancreatic cancer, oncology, pathology, metastases

#27 Metabolic regulation of genome stability

Type of recruitment
Postdoc, 24 months

Project title
Metabolic regulation of genome stability

Supervisor
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Qualifications of applicant
We are looking for a postdoctoral researcher to drive an exciting research project investigating the novel relationship between metabolism and genomic instability in cancer.

The successful candidate should hold a PhD degree in biomedical, cell- or molecular biology. The applicant should have prior experience in molecular mechanisms of DNA repair and/or replication and relevant techniques. We are looking for a bright, ambitious and highly motivated researcher who can work well in a team, in a multidisciplinary and highly international and ethnically diverse laboratory.

The applicant should have good social and analytical skills and be able to organise and prioritise research within the project timetable. The applicant should have excellent written and oral communication skills and be fluent in English, written and spoken. Emphasis will be placed on personal suitability.

Background
Recent investigations have revealed an emerging role of metabolic enzymes and metabolites as regulators of DNA repair upon anti-cancer treatment in order to maintain the genome integrity of the cancer cell. Thus, uncovering new links between cancer metabolism and genome stability, which is the aim of our research, holds great promise in development of novel anti-cancer strategies. More specifically, we are characterizing the role of metabolism in genome stability and whether metabolic enzymes have functions in the cellular response to DNA damaging anti-cancer treatments (i.e. radiotherapy and chemotherapeutics).

Research project description
We recently discovered that the glycolytic enzyme PFKFB3 associated with cancer transformation functions outside of its conventional metabolic network as an

essential regulator of DNA repair and thereby genomic stability (Nature Communications, 2018). PFKFB3 regulates recruitment of key proteins in the homologous recombination DNA repair pathway and consequently cell survival upon DNA damaging ionizing radiation (IR; i.e radiotherapy). With the aim of inhibiting PFKFB3 in a clinical scenario and to develop a tool to study the enzymatic activity of the enzyme, we developed a selective and potent PFKFB3 inhibitor in collaboration with a biotech company.

This project aims to unravel how PFKFB3 and associated proteins contribute to DNA repair and replication, determine the underlying mechanisms and evaluate PFKFB3 inhibition in clinical ex vivo material towards the goal of developing novel anti-cancer strategies. The appointed person will use state of the art techniques and models such as patient derived ex vivo cultures, organoids, CRISPR/Cas9 knockouts, live cell metabolic measurements, confocal imaging and digital image processing to study DNA repair and replication on the single cell level and individual replication fork dynamics. The appointed person will be expected to plan, perform, analyse and interpret experimental results independently and within the team, present at scientific conferences and participate in national/international collaboration networks. The applicant is expected to be dedicated to full time experimental research and should maintain accurate and up to date research records.

The project not only aim at providing novel and ground-breaking biological insights but also to provide improved therapeutic options for cancer patients and techniques to study DNA repair and replication.

Research group

The position is placed in the research team headed by Ass Professor Nina Gustafsson situated at the Science for Life Laboratories, https://ki.se/en/onkpat/research-team-nina-gustafsson. The research group is a creative and dedicated team, with one senior postdoc and two PhD students, that performs translational cancer research with focus on metabolic regulation of the DNA damage response. We have several collaborations involving world-leading researchers and clinicians, providing excellent network opportunities.

We share laboratories with the research group headed by Professor Thomas Helleday and Deputy group leader Ulrika Warpman Berglund, which provides an excellent translational and scientific environment. The multidisciplinary research group includes PhD students, postdocs and senior scientists within biology, biochemistry, medicinal chemistry, and pharmacology, many with experience from the pharmaceutical industry.

Supplementary information

At the Department of Oncology-Pathology basic, translational and clinical research and educational activities related to cancer is carried out. Approximately 300

people from over 40 nations are currently working at the department. About 30 research groups with various cancer research profiles are involved and we have around 110 PhD students. The Department of Oncology-Pathology is responsible for undergraduate courses in Pathology, Oncology and Forensic Medicine for medical students, as well as for Tumor biology courses for biomedicine students and Pathology courses for opticians.

Key words

Cancer, DNA repair, replication, metabolism, genomic instability.

#28 Investigating breast cancer treatment resistance through bioinformatics

Type of recruitment
Doctoral student, 4 years

Project title
Investigating breast cancer treatment resistance through bioinformatics

Supervisor
Johan Hartman, MD, PhD, Associate Professor
Department of Oncology-Pathology

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Qualifications of applicant
Absolute requirements:

-A master degree on bioinformatics/biostatistics/computer science or equivalent.

-Previous experience in gene expression data (affymetrix microarray, RNA-seq, and/or scRNA-seq) analysis.

-Programming skills in statistical software environments, preferably in R.

-Excellent interpersonal communication skills (written and verbal English).

-Good data management and documentation skills.

Preferred requirements

-Experience in cancer related databases such as TCGA, COSMIC, dbSNP etc.

-Programming skills in other languages, eg. Python, C++ and/or Perl.

-Basic knowledge in tumor biology, especially breast cancer.

-Certain experience with genomic sequencing data (WGS/WES) handling and wet lab techniques (DNA/RNA extraction from FFPE materials and/or fresh tumor tissues).

Background

Breast cancer remains to be the most common malignancy for women worldwide. A few biomarkers are used to provide guidance for treatment decisions, namely estrogen receptor (ER), progesterone receptor (PR), human epidermal receptor 2 (HER2) and Ki67. ER expression confers strong indications for response to endocrine therapy, whereas patients with HER2-overexpressing tumors can be effectively treated with anti-HER2 therapy. However, such management of breast cancer patients is insufficient to distinguish resistant tumors.

Research project description

We have constructed several retrospective population-based breast cancer cohorts consisting of anti-HER2 or anti-endocrine therapy treated patients in Stockholm, Sweden. Gene expression assay will be performed, and the student will work on establishing analysis pipelines for generating PAM50 molecular subtypes, specific gene expression and molecular pathway activity. When available, DNA sequencing/analysis will also be performed, and the student will participate the analysis of tumor somatic mutation profile in relation to treatment resistance.

Research group

The Hartman research group is performing leading breast cancer research of highest scientific level. Our scientific aim is to identify therapy predictive parameters to personalize cancer care. The research group has access to a large number of clinical materials, as well as extensive ongoing collaborations with other KI/SciLifeLab research groups and facilities.

At present, the Hartman group consists of two PhD students, two postdoctoral researchers, one research coordinator, and several affiliated clinicians.

We work in close collaboration with data scientists, machine-learning scientists and bioinformaticians at KI and KTH.

Supplementary information

Key words

Bioinformatics, machine-learning, tumor biology, breast cancer, oncology, NGS, precision medicine.

#29 Personalized Medicine and Multimodal Imaging in Cancer

Type of recruitment

Visiting doctoral student, 12 months
Postdoc, 24 months
Visiting researcher, 12 months

Project title

Personalized Medicine and Multimodal Imaging in Cancer

Supervisor

Moustapha Hassan, Professor
Department of Laboratory Medicine

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Qualifications of applicant

Specific requirements are:

1) MS or PhD in the field of pharmacology/medicine and/or medical sciences;

2) Research experience in cell biology and animal models;

3) Excellent written and oral English skills;

4) Documented experience in writing and publishing scientific papers.

Other meritorious competences include:

1) Research skills: FACS; cytotoxicity assay; immunohistochemistry; chromatography and mass spectrometry; Fluorescence microscopy.

2) Research experience: pharmacokinetics/pharmacodynamics; preclinical in vivo imaging; animal models of leukemia, lymphoma, myeloma and GVHD.

Background

Stem cell transplantation (SCT) is the only curative treatment for many patients suffering hematologic-, solid- tumors, inborn errors or genetic disorders. Despite

decades of successful SCT, graft-versus-host-disease (GvHD) remains one of the most significant causes of morbidity and mortality in SCT patients. Furthermore, SCT is associated with late cardiovascular complications.

The research of our group “Experimental Cancer Medicine (ECM)” aims to enhance the clinical outcome including higher survival rate and better quality of life for cancer patients treated with chemotherapy and undergoing SCT via increased treatment efficacy and minimize or eliminate the adverse effects.

We have developed SCT model to study the underlying mechanisms of GVHD and arterial damage in order to evaluate prophylactic strategy. Recently, we have developed solid models of hematological malignancies in order to understand the mechanisms of graft-versus-leukemia (GVL) effect.

We have shown that genetic variations in patients highly affect the metabolic pathway and/or the bioactivation of several chemotherapeutic agents which in turn can explain the high variation observed in treatment efficacy and hence the clinical outcome of SCT.

We developed a number of nano-carriers to be loaded with chemotherapy, contrast agent and targeting moiety. The aim of the structured nano carriers is to function as an early diagnostic marker using multimodality and as a marker to follow up the treatment efficacy.

Research project description

We aim to recruit visiting PhD student, posdoc/researcher in the following research projects:

Personalized medicine prior to stem cell transplantation:

Although stem cell transplantation (SC T) is a curative treatment and sometimes is the only treament for many patients, the results are often far from satisfactory. After SCT, complications including liver- and lung- toxicity; infections, graft rejection, CNS- toxicity, secondary tumors and graft-versus-host disease (GVHD) deteriorate the quality of life of the patient and usually lead to morbidity, mortality, high economic costs for the society and less successful clinical results.

Recently, studies showed a higher incidence of cardiovascular complications in adults who received stem cell transplantation as young children and were treated with high doses of chemotherapy. Our aims in the present project are:

1. To elucidate the mechanisms underlying cardiotoxicity,

2. To develop and evaluate new prophylactic treatment and

3. To personalize the chemotherapy treatment prior to SC T based on the patient genotype.

Understanding the underlying mechanisms of cardiotoxicity in combination with personalized therapy based on the patient´s gene expression and relevant prophylactic treatment, will increase the treatment efficacy and certainly will minimize the risk of acute and late side-effects.

Molecular imaging and theranostics in cancer:

In the present project we aim to develop new contrast agents in combination with new molecular imaging strategies to offer tools for the need to address accurate early diagnosis and personalize medicine for cancer patients. We will design and validate multimodal imaging agent that can be applied for optical imaging, ultrasound imaging, photoacoustic imaging, MRI, CT and magnetic particle imaging. The goal is to combine the advantages of different imaging techniques, i.e. sensitivity of detection and resolution of the image. The integration of multimodal imaging technologies would therefore provide complementary and complete information for subsequent decision-making.

We will also further improve the specificity and sensitivity of the imaging agents by incorporating specific antibodies to target tumor and/or to function as tumor marker. Such multi-target imaging agent will facilitate an early diagnosis, stage the disease and predict relapse for cancer patients. We aim also to develop the nanoparticles to form theranostics agents by loading imaging contrasts in combination with chemotherapy. Such multifunctional NPs will allow us to perform early diagnosis, follow drug delivery into the tumor and to monitor the treatment efficacy and hence improve the clinical outcome for cancer patients.

Research group

Moustapha Hassan (MD, PhD) Professor of Transplant Research at Dept. of Lab Med (H7), KI. M. Hassan has many years of experience in stem cell transplantation/chemotherapy research. His research focuses on personalized medicine, nanomedicine/theranostics and transplantation related complications. He is the inventor of liposomal busulfan. He is in the key coordinator position in EU and Sweden in pharmacological guided personalized treatment of conditioning regimen in connection with bone marrow transplantation since 1990s.

Moustapha Hassan is currently Director of the Preclinical Laboratory at the Karolinska University Hospital–Huddinge, Sweden and Professor of Transplantation Research at the Karolinska Institutet, Sweden.

The research group is composed of 4 senior researchers and 3 PhD students. Currently, Hassan is the project leader of two HORIZON 2020 projects, one VR project, CIMED project and one Barncancerfonden project.

Supplementary information

The group is hosted at Biomolecular and Cellular Medicine (BCM), Department of Laboratory Medicine, Karolinska Institutet. BCM is perfectly equipped with all the basic equipment for cell biology, molecular biology, pharmacology and pharmacokinetics studies.

Four core facilities are available in BMC, including Vecura GMP Laboratory, Morphological Phenotype Analysis (MPA), Preclinical laboratory (PKL) Portal and Electron microscopy Unit. All the imaging experiments will be performed at Preclinical Imaging Facility which hosts IVIS Spectrum (optical imaging), Quantum FX (micro CT) and Vevo LAZR (micro ultrasound/photoacoustic), Nanoscan PET/MRI and a new MPI scanner from Magmatic Sights.

The research group include:

Dr. Ying Zhao (PhD), senior researcher in Hassan' group and facility manager of the Preclinical Imaging Facility at the Karolinska University Hospital. Her research focuses on molecular imaging, cellular and gene therapy, and nanomedicine.

Dr. Manuchehr Abedi Valugerdi, Senior researcher in Hassan' group, assoc. prof. His research field focus mainly on immunology of cancer, and the effect of chemotherapy on the immune system.

Dr. Sandra Oerther, researcher in Hassan' group, her research field focus mainly on pain related to cancer and chemotherapy. Her studies are investigating the effect of chemotherapy on peripheral neuropathy.

Assistant Prof. Ibrahim El Serafi, researcher in Hassan' group. His research field focus mainly on personalized treatment for patients undergoing stem cell transplantation. His studies the effect of chemotherapy on the immune system.

Key words

Personalized medicine, GVHD, multimodal imaging, Stem cell transplantation, theranostics, nanomedicine.

#30 Combining DNA repair inhibitors and immunomodulating drugs to improve anti-cancer treatment

Type of recruitment
Doctoral student, 4 years

Project title
Combining DNA repair inhibitors and immunomodulating drugs to improve anti-cancer treatment

Supervisor
Thomas Helleday, Professor
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Qualifications of applicant
Required qualification:

Master/bachelor in clinical oncology, medicine or other education relevant for this PhD project.

Other desirable qualifications:

Earlier research experience in relevant area and in writing scientific papers etc.

Leadership experiences, such as planning experiments, attracting awards and fellowships and presenting at scientific conferences/meetings.

Background
DNA damaging agents as well as immunocheckpoint inhibitors are mainstream and first-line treatment today and combining these have been identified to in certain cases to improve responses. We are developing inhibitors to the DNA damage response and repair (DDR) that are able to introduce DNA damage primarily in cancer cells using for instance the synthetic lethal concept. There is a good chance DNA damaging agents and DDR inhibitors potentially may increase immunogenicity through for instance the cGAS and STING pathway. The aim here is to identify how DDR inhibitors, primarily those developed in our own laboratory such as MTH1, MTHFD2, OGG1, NUDT5, etc may trigger cGAS, STING pathway and immune

responses in normal and cancer cells and in vitro and in vivo, ad identify potent combinations in vivo to improve anti-cancer treatments.

Research project description

1. Identify how different DDR inhibitors may trigger an immune response and detail the molecular mechanism of action in cancer and normal cells, e.g., cGAS and STING pathways.

2. Set up an in vivo model, preferably patient-derived xenograft, where combination treatment between immune oncology treatments (e.g., PD1, PDL1) and DDR inhibitors can be evaluated.

3. Investigate combinations of immune oncology and DDR inhibitors and detail the mechanism of action. Investigate safety profile of combination treatment.

4. Identify biomarkers that predict response to specific combination treatments and evaluate these biomarkers from cancer patients' biopsies obtained through other projects and where ethical permit allows analysis of indicated biomarkers.

Research group

The Helleday laboratory, located at Scilifelab Stockholm, focuses on understanding the basic processes of DNA repair and nucleotide metabolism, translating original findings into novel treatments of cancer inflammation and virus infections. The strategy has for a long time been to have a multidisciplinary translational research group where basic scientists work alongside medicinal chemists, pharmacologists, drug developers as well as clinical trials experts. Staff working in the Helleday laboratory are all involved in the process from the early target discovery discussions all the way to phase II trials in patients. Our philosophy is that the people in the team is the main asset and that the input from all expertise contributes to sharpening the projects to increase the likelihood of success in our ultimate goal: to battle human diseases and improve lives.

Supplementary information

Key words

DNA repair inhibitors, immunomodulating drugs, anti-cancer treatment

#31 Autoantibodies in rheumatoid arthritis with focus on cartilage proteins

Type of recruitment
Postdoc, 24 months
Visiting researcher, 12 months

Project title
Autoantibodies in rheumatoid arthritis with focus on cartilage proteins

Supervisor
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Qualifications of applicant
PhD or comparable exam. Knowledge in immunology, immunological/cell biology technology, biostatistics and animal experimental technology. Fluent English.

Background

Autoimmune diseases, such as rheumatoid arthritis (RA), develop in three distinct stages: priming, onset and chronicity (Ge and Holmdahl, Nature Reviews of Rheumatology 2019). Most likely, the same type of development stages occurs in different types of autoimmune diseases.

In most of these diseases, priming is characterized by activation of B cells to produce disease-specific IgG autoantibodies that may appear in the blood several years before clinical onset. In the case of RA these include antibodies directed towards modified immunoglobulin and citrullinated protein antigens (ACPA). However, how this priming stage becomes an inflammatory attack on the joints, leading to clinical onset, remains unknown.

We have isolated B cells and antibodies that crossreacts with joint cartilage and their specificity. For studies of RA we have identified relevant epitopes selected joint proteins and made a Luminex based multiplex test.

We have previously shown that the immune system is not completely tolerant of proteins associated with cartilage proteins, which induce arthritis in mice, and several of these proteins, as well as antibodies, have the potential to induce but also to regulate arthritis. We have identified epitopes on selected cartilage proteins that are recognized by autoreactive B cells and antibodies. Importantly these B cells and antibodies could have both regulatory but also pathogenic functions.

Research project description

In the project Luminex will be used to perform the diagnostic multiplex test on already established cohorts of RA as well as serum from individuals with emerging RA. Antibodies specific for these epitopes will be characterized both functionally and to be used as standard antibodies in the assay.

The results will be analysed by biostatistically both in our laboratory and together with cooperating clinicians.

In the next round of analysis we will identify new peptides, that comes from work in the animal models. We have established monoclonal antibodies specific for the relevant epitopes. The first goal will be characterized these regarding function and epitope specificity. Functional studies is done by injection of antibodies in the mouse and study effects on arthritis, bone erosion and pain. The antibodies should also be used to characterize the expression of the target protein in different tissues of the mouse (skin, lung, vessels, joints. For the studies we have available unique humanized mouse strains available in the laboratory (expressing DR*0401, DR*0405 associated with rheumatoid arthritis as well as arthritis in the mouse models) and analyse the peptides specific response both for B cells and T cells. These humanized mouse models are unique and not available elsewhere as they mimic the human disease including the production of antibodies to citrullinated proteins, including such antibodies crossreacting with cartilage.

To date, joint cartilage proteins have been proven to be involved in autoimmune diseases. Experimental investigations of these proteins have provided insights into the diverse roles of this class of constitutive proteins in autoimmune and inflammatory diseases like RA. Importantly, clinical relevance and therapeutic opportunities for pharmacological modulation of these proteins are largely unexplored. Much work lies ahead as these and other questions are addressed a route to harnessing the expanding base of knowledge about joint cartilage proteins for clinical benefit among patients with autoimmune diseases.

Research group

The Medical Inflammation Research (MIR) laboratory is located within the Karolinska Institute, in the Biomedicum building, with full access to core facilities, collaboration, research courses and seminars. The laboratory is fully equipped for the project and has 20 members from PhD students to professors. We have also tight collaboration with research groups in China and perform several projects (both analysis of human samples and animal experimental technologies).

Supplementary information

Key words

Immunology, Rheumatoid arthritis, Cartilage, Autoimmunity

#32 Oxidative regulation of autoreactive B cells

Type of recruitment
Visiting researcher, 12 months

Project title
Oxidative regulation of autoreactive B cells

Supervisor
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Qualifications of applicant
PhD or comparable exam. Knowledge in immunology, immunological/cell biology technology, biostatistics and animal experimental technology. Fluent English.

Background
The immune system is selected on endogenous self-structures. Both T cells and B cells are selected in central lymphoid organs (thymus and bone marrow) to respond to self, both self-antigens and costimulatory molecules and antigen receptors. This stimulation leads to rescuing of the developing lymphocytes but also different types of differentiation. It is well known that thymus produces both anergic effector T cells but also regulatory T cells but it is less clear whether similar cell types are produced in the bone marrow.

Our group has been interested in how cartilage antigens, such as type II collagen (CII) selects the immune system (see Raposo et al Nat Com 2018 and Ge et al Nat Rev Rheumatology 2019). We now have strong evidence that expression of CII in central lymphoid organs, both bone marrow and thymus, selects autoreactive lymphocytes with key regulatory properties. Interestingly the specificity of these lymphocytes are conserved between mouse and humans. The selecting MHC class II molecules differs but we have now established humanized MHC class II knockin mice which regulates the immune system in a physiological way and these mice can develop a disease mimicking rheumatoid arthritis (RA). In addition, the selection of the autoreactive lymphocytes are oxidative regulated. A major gene regulating autoimmune disease in both humans and mice is Ncf1, a critical component of the NOX2 complex. In the present project we will address the role of Ncf1 mediated redox regulati

Research project description

We will address the possibility that B cells are redoxregulated during their selection and how this will affect autoimmune disease development. The basis for this is that we (see Holmdahl et al Immunol Rev 2016) identified the Ncf1 gene to be the most important polymorphic gene regulating both animal models but also some major autoimmune diseases, including RA. Using mouse systems we have now strong evidence that B cells are regulated by Ncf1. We have made unique conditional mouse strains inducing the expression of Ncf1 allowing to study a dominant influence of the NOX2 complex that is a non-redundant source of induced peroxide. This mouse models will be studies using specific Cre leading to NOX2 functional expression in specific B cell types and their development will be followed using VDJ knock in CII reactive B cells. The B cells at different functional stages, determined by in vivo unique expression, will be studied on a single cell stage using high throughput RNA sequencing combined with proteomics and detailed immune functional assays.

Research group

The Medical Inflammation Research (MIR) laboratory is located within the Karolinska Institute, in the Biomedicum building, with full access to core facilities, collaboration, research courses and seminars. The laboratory is fully equipped for the project and has 20 members from PhD students to professors. We have also tight collaboration with research groups in China and perform several projects (both analysis of human samples and animal experimental technologies).

Supplementary information

Key words

Immunology, B cells, Ncf1, Peroxide, Rheumatoid arthritis, Cartilage, Autoimmunity.

#33 Plant based drugs against rheumatic disorders

Type of recruitment
Doctoral student, 4 years

Project title
Plant based drugs against rheumatic disorders

Supervisor
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Qualifications of applicant
The PhD candidate should have knowledge in biomedical research and interest in bioassays and in vivo experiments. Practical experience with molecular biology techniques, cell reporter assays and phenotypic screening assays is a merit. The applicant must have excellent communication and collaborative skills and be proficient in English.

Background
There are many possibilities to take advantage of plant based molecules for treatment and diagnosis of rheumatic disorders. For once we have characterized a molecule from sun flower (SFT1) which is a small cyclic peptide that can be used to stabilize autoantigenic epitopes in order to neutralize pathogenic autoantibodies, sorting and isolation of specific cells as well as tools for improved detection of autoantibodies. A quite different approach is to take advantage of the knowledge in traditional medicine and isolate bioactive compounds from plants and herbs with known anti-rheumatic properties. This approach was awarded the Noble Prize in medicine to Professor Tu Youyou in 2015 for her discovery of Artemisinin, an antimalarial drug. In this project, we will continue the work on SFT1 and study its role as a scaffold for blocking/neutralization of pathological autoantibodies against citrullinated proteins (ACPA). We will also explore anti-rheumatic molecules generated within the JRBCM project, an ongoing collaboration between Guangdong Provincial Hospital of Chinese Medicine, Karolinska Institutet and Uppsala University. Here we focus on three formulations which are used in Chinese traditional medicine, which have shown positive results in both animal models of arthritis as well as in clinical trials in man. The project is generating a compound library with known and unknown molecules and the further identification of compounds will be guided by human bioactivity assays.

Research project description

Rheumatoid arthritis (RA) is characterized by the presence of highly specific autoantibodies recognizing citrullinated proteins, so called ACPA. ACPA are detected in about 70% of RA patients and appear years before onset of clinical disease and their presence correlates with genetic (shared epitope) and environmental (smoking) risk factors. ACPA associate with an erosive disease course, suggesting a direct pathogenic involvement in disease initiation and progression. It has been demonstrated that ACPA can activate the classical and the alternative complement pathways in vitro, they predict the development of RA when present in undifferentiated arthritis and arthralgia, and induce production of TNF-alpha. In RA we have identified novel endogenously citrullinated peptides that are recognized by ACPA 1. We have purified large amounts of ACPA from RA patients sera 2 and shown induction of osteoclastogenesis and bone loss both in vitro and in vivo by vimentin-targeted ACPA 3. Moreover, there is evidence that ACPA is involved in pain induction in arthritic joints4. We have previously demonstrated that the small circular sunflower trypsin inhibitor 1 (SFTI-1) is a suitable scaffold for increasing the stability of autoantigenic peptides for use in diagnostic tests, neutralization of ACPA and isolation of specific cells 5-7. In the current project, the SFTI-1 frameworks will be used in combination with poly and monoclonal ACPA that induce inflammation in vivo.

The aims are:

1) Study ACPA induced pathology (pain, tendinitis) in vivo and test if neutralization using SFT-1 based molecules with stabilized citrullinated epitopes can prevent such effects.

2) Evaluate the use of SFT-1 stabilized epitopes for superiority over currently used immunological assays.

3) Further study the pathophysiological role of various poly and monoclonal ACPA in order to better understand their mechanisms of action.

4) Aims 1 and 3 include the use of in vivo models of arthritis as well as various cell based assays. As comparators, we will take advantage of the Chinese traditional medicine project, that generate compounds with potential anti-rheumatic properties. Here their effects will be investigated in the light of ACPA induced inflammation and their potentials to prevent ACPA mediated inflammation.

References:

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2 Ossipova, E. et al. Arthritis Research & Therapy 12;16(4):R167, (2014).

3 Harre, U. et al. J Clin Invest 122, 1791-1802, (2012).

4 Wigerblad, G. et al. Annals of the Rheumatic Diseases 75, 730-738, (2016).

5 Gunasekera, S. et al. ACS Chem Biol 13, 1525-1535, (2018).

6 Fernandes-Cerqueira, C. et al. Arthritis Research & Therapy 17, (2015).

7 Wang, Y. et al. Arthritis & Rheumatology 70, (2018).

Research group

Professor Per-Johan Jakobsson (PJJ) is senior scientist and since 2014 holds a combination professor position in translation inflammation research and rheumatology. For the outlined project, PJJ supervises three researchers: Helena Idborg (analytic chemists) and Karin Larsson (civil engineer) that focuses on systems biology and mass spectrometry based analyses of lipids in arthritis and cancer, respectively. Postdoc Bing Peng (analytic chemists) who works on mass spectrometry based lipidomics and proteomics related to artritis. PJJ currently also supervises three PhD students: Julia Steinmetz since 2017 and Jianyang since 2020, both working on prostaglandin research and inhibitors of mPGES-1 in rheumatic diseases with concomitant vasculopathies and arthritis, respectively. PhD student Charlotta Preger works on tRNA synthases in systemic autoimmune diseases since 2018. Associate professor, Marina Korotkova belong to the group of PJJ and focuses on arthritis research.

Supplementary information

Key words

Autoimmune inflammatory diseases; Immunology; In vitro assays; In vivo models of inflammation.

#34 Using large-scale genetic data and complied analytical strategy to understand the etiology and sex disparity of multiple sclerosis

Type of recruitment

Doctoral student, 4 years
Visiting doctoral student, 12 months
Postdoc, 24 months
Visiting researcher, 12 months

Project title

Using large-scale genetic data and complied analytical strategy to understand the etiology and sex disparity of multiple sclerosis

Supervisor

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Department of Clinical Neuroscience

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Qualifications of applicant

For PhD student / visiting PhD / visiting scholars

A. General eligibility requirement

You meet the general eligibility requirement for doctoral/third-cycle/PhD education if you:

1. have been awarded a second-cycle/advanced/master qualification (i.e. master degree) or

2. have satisfied the requirements for courses comprising at least 240 credits of which at least 60 credits were awarded in the advanced/second-cycle/master level, or

3. have acquired substantially equivalent knowledge in some other way in Sweden or abroad.

B. Specific eligibility requirement

You meet the specific eligibility requirement for doctoral/third-cycle/PhD education if you show proficiency in English equivalent to the course English B/English 6 at Swedish upper secondary school.

C. Skills and personal qualities

We are seeking a highly motivated person with an interest of using a compiled analytical strategy to understand disease etiology. The successful applicant needs to be fluent in English, have excellent communication skills and the ability to interact effectively and work productively in a team. The candidate is supposed to have a solid background in medicine or epidemiology together with a basic understanding but a strong motivation and a clear interest in genetic epidemiology and statistical analysis.

A master's degree in epidemiology or other areas of life science is preferred.

Excellent English in oral and written communication is required.

Previous research experience in epidemiology or data science will be a plus.

Programming skills using R and other statistical software, as well as experience with large datasets will be a plus.

##

Postdoctoral applicants should have completed or be in the process of completing a PhD or equivalent. Preferred fields of study and training include Genetic Epidemiology, Biostatistics/Statistics, Bioinformatics and Human Genetics. Programming skills using R and other statistical software, as well as experience with

large datasets, is strongly desired. The ideal candidate(s) will have demonstrated excellence in analysis of large-scale genetic data including genome-scale and Mendelian randomization analyses.

Background

Multiple sclerosis (MS) is an autoimmune neurodegenerative disorder in which damage of myelin and axons leads to a variety of neurological deficits. The disease is more prevalent in Nordic countries and among women. Despite epidemiological studies have identified several MS-associated environmental risk factors, it remains difficult to determine which of the many lifestyle changes that have occurred during the past are responsible for onset of MS later on. The observational nature of conventional epidemiological studies usually hinders causal interpretation, as the validity of results could be plagued by measurement error, confounding and reverse causality.

Current genetic discoveries in several heritable yet modifiable human complex traits (i.e. smoking, alcohol drinking, physical activity, dietary pattern, obesity and more) have provided an unprecedented opportunity to conduct Mendelian Randomization (MR), an approach that uses genetic variants as instrumental variables (IV) to make causal inference based on observational data. Complementing to MR which uses only a handful of index variants, another powerful way to understand the relationship underlying complex traits is to explicitly quantify their shared genetic basis. To the best of our knowledge, no study has been conducted to systematically and comprehensively investigate the causal relationship between environmental factors and MS utilizing these new possibilities.

Research project description

Questions & hypotheses

To interrogate biological mechanisms underlying disease onset and to inform prevention strategy, we propose to use the extensive genetic information available for 47,429 MS cases and 68,374 controls, as well as publicly available GWAS summary statistics on several modifiable environmental exposures based on millions of samples, to assess a putative causal relationship and a shared genetic component between these factors and MS.

We hypothesize that modifiable environmental factors may play a causal role in the development of MS. Specifically, we raise our research questions as follows, which also corresponds to three doctoral studies:

1. Are modifiable environmental exposures that commonly occurs in everyday life causally associated with MS? We will interrogate a wide range of environmental factors covering lifestyle (i.e. smoking, alcohol drinking, coffee consumption, physical activity), nutritional (i.e. dietary pattern, vitamin intake) and psychosocial factors (i.e. education, depression, anxiety). We will use both summary- and individual-level genetic data to address this question.

2. Is there a shared germline genetic basis between modifiable environmental exposures and MS? We will quantify both overall (genome-wide) and local genetic correlation (by regions).

3. Does the detected causal inference and genetic correlation differ by sex (male vs. female)? When data allows, we will perform a sex-specific analysis to understand sex disparity of MS (i.e. why MS strikes women 2-3 times more than men).

Methods & techniques

Large-scale GWAS(s) have been conducted for a multitude of heritable and modifiable human complex phenotypes. We will interrogate a wide range of environmental factors with a significant genetic component. We will collect summary-level genetic data for IV-exposure from publicly available resources. As an active partner to the International Multiple Sclerosis Genetic Consortium, we have full access to summary statistics of the hitherto largest meta-GWAS conducted in MS on 47,429 cases and 68,374 controls. We will retrieve IV-outcome associations from this genetic data. In addition to summary-level statistics, our group manage and supervise three large-scale population-based MS epidemiological studies totaling 19,000 individuals – the largest MS samples in the world with concomitant information on genetic and environmental factors.

We will conduct a two-sample MR using summary-level genetic data to test for a potential causal relationship between exposures and risk of MS, applying a number of MR approaches. We will cross-validate our main analyses (two-sample MR) through a genetic risk score (GRS)-based approach using individual-level data. We will calculate genome-wide genetic correlations between each exposure and MS, using an algorithm implemented in the statistical software LDSC and examine local (regional) genetic correlation using rho-HESS.

Research group

The student will be part of the Genetic Epidemiology research group at the Department of Clinical Neuroscience (CNS) where the supervisor works.

The host institute CNS provides a comprehensive institutional source of support and infrastructure to achieve proposed research and pedagogical goals. Our group offers an outstanding environment for neurological research, with a strong multidisciplinary network involving MS experts, immunologists and genetic epidemiologists with extensive experience in studying complex traits and autoimmune diseases. We hold regularly well-organized activities for doctoral students including journal clubs, seminars and study circles. The proposed doctoral education will therefore be conducted in a strong research environment characterized by an atmosphere of collaboration and substantial shared infrastructural support.

Supplementary information

Supervision will take place continuously during the whole doctoral period. Practical issues and project progress will be evaluated during weekly meetings in the Genetic Epidemiology group together with the supervisors who will also be available for daily consultation. In addition, the student will have scheduled meetings with main supervisor biweekly to discuss progress, current challenges and to plan upcoming analyses. The supervisor team and the student will have progress meetings every 6 months. All supervisors are available for meetings at the request of student to discuss research and study (e.g., choose courses).

The student will join the excellent academic environment of Karolinska Neuroimmunology and Mutliple Sclerosis centre, which is a close network of established PIs at CMM with a track-record of successful collaboration within the field of neuroimmunology. The student will join weekly KNIMS meetings which typically comprise a scientific presentation followed by discussions with the purpose to improve the quality of science through exchange of practical and theoretical knowledge as well as presentation and communication skills.

The long-term goal of supervision is to motivate the student to adopt a reflective, analytical and critical approach to his/her doctoral dissertation. The supervisors will create an open climate where the student feels free to ask questions and to form his/her own independent line of thinking and questioning.

Key words

Genetic epidemiology, neurological disease, multiple sclerosis, autoimmune disorder, mendelian randomization, genetic correlation, omics data.

#35 Interactions between immune cells and cancer-associated fibroblasts in pancreatic cancer

Type of recruitment
Postdoc, 24 months

Project title
Interactions between immune cells and cancer-associated fibroblasts in pancreatic cancer

Supervisor
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Qualifications of applicant
The applicant should have a doctoral degree in the field of immunology or related discipline, ideally with first author publications in recognized peer-reviewed journals. Experience with multi-color flow cytometry and related software packages is a prerequisite. Hands-on experience in fluorescence microscopy, cell sorting, cell culture and insights into bioinformatic analyses is meriting. In addition, excellent proficiency in both spoken and written English is necessary. The candidate should have the ability to work independently and as part of a team and should be able to coordinate the work of students in the lab.

Background
Pancreatic ductal adenocarcinoma is one of the most aggressive types of cancers with a 5-year survival of only 9 %. Pancreatic tumors are characterized by a dense stroma of activated cancer-associated fibroblasts (CAFs) which encapsulates and surrounds the tumor nests. Tumor-specific T cells have the capacity to kill tumor cells, but the immunosuppressive tumor microenvironment prevents T cells from mediating their cytotoxic functions and CAFs are likely involved in dampening T cell-mediated immunity. Recent studies and our own data show that T cells are present in pancreatic tumors, but that the majority of the T cells are localized in the fibroblast-rich stroma with little interaction with malignant cells. This could partly be explained by that CAFs secret chemokines which are involved in retaining the T cells within the stroma.

Research project description
The primary aim of our research is to understand the interactions between T cells and stromal cells in the tumor microenvironment of human pancreatic

adenocarcinoma. The long term goal is to identify factors that can be targeted to improve T cell immunity and increase their interaction with malignant cells. To this end, we use human tumor tissue samples from patients undergoing surgery for pancreatic cancer to investigate T cells and CAFs.

We characterize different T cell subsets in pancreatic tumors and adjacent normal tissue by multi-color flow cytometry. The expression of co-inhibitory marker, chemokine receptors and markers of tissue residency will be examined. Certain T cell subsets will be sorted and analyzed further to examine their functional responses and we also plan to determine TCR repertoires by next generation sequencing.

The spatial localization of T cells in relation to stroma and tumor nests will be investigated with immunohistochemistry and fluorescence microscopy. To better understand the role of chemoattractive factors for positioning of T cells inside the tumor, we are investigating secretion of chemokines and cytokines within the tumor by multiplex protein assays and examine associations to T cell infiltration. In vitro cell cultures and 3D models will further be used to examine how tumor-derived CAFs affect the function and migration of T cells.

Significance: Immunotherapy has revolutionized the treatment of some solid cancers, but it has so far been unsuccessful in pancreatic cancer. CAFs have emerged as important regulators of immune cells in the tumor microenvironment. Chemokines secreted in the tumor microenvironment may play an important role in directing T cells in the tumor microenvironment, and a better understanding of such complex and dynamic network systems is required to develop more powerful treatment strategies for pancreatic cancer patients. These studies can add information about how cell composition and chemokine secretion patterns affect the outcome for patients with pancreatic cancer, which can lead to new combination treatment modalities for this devastating type of cancer.

Research group

The Kaipe group is interested in immune cells in cancer and pregnancy, with a specific focus on interactions between T cells and other cells in the tissue microenvironment. The group currently consists of one PhD-student who is investigating T cells and CAFs in pancreatic cancer, one postdoc focusing on placental immunology, and one part-time technician. We share lab and office space as well as scientific activities with two other groups focusing on T cell immunity in cancer. We also work in close collaboration with research physicians at Karolinska University Hospital.

Supplementary information

Key words

T cells, cancer-associated fibroblasts, pancreatic cancer, chemokines, immunology, stroma, cytokines, tissue resident

#36 Tumor associated macrophages as targets for immunotherapy

Type of recruitment
Doctoral student, 4 years

Project title
Tumor associated macrophages as targets for immunotherapy

Supervisor
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Department of Microbiology, Tumor and Cell Biology

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Qualifications of applicant
The student should have a Masters in biology or similar education.

Background
It has been known for one hundred years that the immune system has the capacity to recognize and kill tumors. However, it is only recently that immunotherapy is taking its place alongside surgery, radiotherapy and chemotherapy as an option for cancer treatment. The reason that immunotherapy has taken so long to come into its own is that tumor antigens are for the most part “self” and therefore are not recognized by the immune system. In addition, tumors evolve mechanisms for evading immune recognition. Now, targeting T cells with checkpoint inhibitors has been shown to release the breaks on the immune system, resulting in enhanced T cell attack against tumors. Although this therapy has opened new avenues for treatment, many patients respond poorly to the treatment and some types of cancer such as pancreatic cancer do not respond at all. Tumor-associated macrophages (TAMs) have been identified as the major hurdle as they are blocking the efficiency of immunotherapy by preventing T cells from killing tumor cells. We recently discovered that antibodies targeting MARCO, a pattern-recognition receptor of the scavenger receptor family expressed by TAMs, can be used to therapeutically modify TAM function. Doing so enhanced anti-tumor responses in mice and prevented metastases. In this PhD project we now propose to target human TAMs as a novel approach to immunotherapy.

Research project description
Aim 1. Develop antibodies that target MARCO and other TAM specific targets for immunotherapy: To develop tumor targeting anti-human TAM antibodies, we will start with the MARCO receptor as the lead target and then expand to other

receptors of the SR family and receptors belonging to other families identified in Aim 3. We have already generated monoclonal antibodies (mAbs) to the human MARCO receptor (hMARCO) by serial immunization in mice with soluble recombinant hMARCO protein. We have screened hybridomas for binding to hMARCO, either by ELISAs or by flow cytometry using cells expressing hMARCO. We have also tested the hybridomas for cross-reactivity with SRs and are currently mapping the epitopes recognized by these mAbs using blocking experiments and recombinant proteins. The PhD student will test the activity of these antibodies in vitro, and we will set up and develop novel in vitro assays for evaluating human macrophage polarization. As a starting point, the readout in these assays will be based on findings from our mouse studies, in which the tumor-killing anti-MARCO antibody triggered phenotypic changes in TAMs that could be measured by flow cytometry or as changes in gene expression.

Aim 2. Investigate the use of antibodies to TAMs for treatment purposes in mouse models of cancer and use human macrophages in polarization and activation assays: Using multiple readouts (combining changes in gene expression, phenotype and metabolism), we will setup in vitro cultures of human macrophages of three different origins: (1) Human macrophage cell lines; (2) Monocyte-derived macrophages obtained from buffy coats from healthy individuals; (3) and (3) Primary TAMs from surgically removed melanoma tumors.

Aim 3: To investigate the use of anti-TAM antibodies as an imaging tool to evaluate specific TAM content in tumors for clinical application and for target discovery: In this aim, the PhD student will use the new antibodies to further evaluate hMARCO-expressing TAMs, other TAMs and MDSC populations in human cancer. We also aim to discover other myeloid targets including SRs on hMARCO-expressing subpopulations to be tested in assays described in this proposal. We will characterize the location of hMARCO-expressing TAMs in relation to other TAMs and immune cells within the tumor using fluorescently marked antibodies. Gene expression signatures will also be compared to survival data from the Swedish Cancer registry and we will determine how treatment outcomes, patient survival and biomarkers correlate with TAM phenotype and hMARCO expression. We will study a cohort of non-small cell lung cancer patients, with Dr Johan Botling (Uppsala University) and Pancreatic cancer samples will be obtained from patients followed by Prof. Matthias Löhr at Karolinska Hospital in Stockholm who is also co-supervisor for the PhD student. Finally, we collaborate with Prof. Rolf Kiess

Research group

The research group currently consists of 2PhD students and 2postdocs.

Supplementary information

Key words

Immunology, Macrophages, Cancer.

#37 Involvement of autophagy in small vessel disease using CADASIL Notch3 disease animal models

Type of recruitment
Doctoral student, 4 years
Postdoc, 24 months

Project title
Involvement of autophagy in small vessel disease using CADASIL Notch3 disease animal models

Supervisor
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Department of Neurobiology, Care Sciences and Society

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Qualifications of applicant
Molecular and cell biology, mouse handling experience, basic Neuroscience and or vascular biology knowledge

Background
CADASIL is a hereditary SVD associated with age-dependent cognitive impairment. In CADASIL, vascular changes such as degeneration of VSMCs and thickening of vessels may reduce blood flow and affect vasodilatory responses to cause lacunar infarcts and microinfarcts in grey and white matter and ultimately stroke. CADASIL is linked to mutations in a single gene, NOTCH3. To date more than 200 CADASIL-causing mutations in NOTCH3 gene have been reported The Notch3 receptor, predominantly expressed in VSMCs and pericytes and is important for the development and function of vasculature and in particular of VSMCs. The pathological hallmark of CADASIL is granular osmiopholic material (GOM) deposits seen by electron microscopy, which are specific to CADASIL and therefore used as diagnostic marker. The major component of GOM consists of aggregated extracellular Notch3 (Notch3 ECD). Remarkably mutations resulting in loss or gain of a cysteine residue in EGF-like repeats, leading to GOM formation, are pathogenic. This clearly shows that misfolded Notch3 ECD rather than altered Notch3 signaling per se may contribute to CADASIL pathology. However, the mechanisms underlying Notch3 ECD accumulation and vascular degeneration are unknown.

The prominent feature of Notch3 protein aggregation into GOMs in CADASIL suggests that autophagy is involved but yet not explored, which is our aim to elucidate in this application using a combination of state-of-the art CADASIL and autophagy mouse models.

Research project description

1. To investigate the impact of autophagy on Notch3 pathology aggregation using mouse model with autophagy-deficient VSMC.

This will be achieved by studying Atg7 cKO mice crossed with Notch mouse models R182C-TgN3. The CADASIL mouse model R182C-TgN3 expresses CADASIL-mutated Notch3 under the endogenous promoter thereby restricting the expression of Notch3 to the affected cells. These mice develop pathology from five months of age. To specifically delete autophagy in SMC, we will cross mice lacking the Atg7 gene, (Atg7 Flox/Flox) with mice that expresses Cre under the smooth muscle actin promoter (SM22-Cre). These mice will then be crossed with the CADASIL mouse model (R182C-TgN3) and by that we will develop novel in vivo mouse models that can be used for in-depth studies of the importance of autophagy in the vascular niche. The analysis of the mice will include immunohistochemistry, proteomics and electronmicroscopy of the brain and retina vasculature. Since the vasculature in the retina is affected at an early stage in CADASIL patients and also easily dissected from the mice, it is an optimal tissue to analyze for autophagic markers and vessel degeneration. Meanwhile the mouse models are being generated we will investigate how VSMC from retina and brain from the respective CADASIL mouse models express the autophagy markers LC3 and p62 at different ages. Moreover, we will isolate primary cerebral VSMC from our CADASIL mouse model and analyze how they respond to knock-down of the Atg7 gene in the presence and absence of Notch3 ligand in parallell, to the cerebral VSMC from CADASIL patients. We will use two systems, of which the first one is to culture the VSMCs in plates that have been coated with immobilized ligand Jagged1 and the second one is to perform co-culture of VSMCs with HEK293 cells expressing Jagged1. We will also stain human brain slices from CADASIL patients and analyze Notch3 metabolism, including transport and localization) and endocytosis in parallel with the autophagy markers LC3 and p62.

2. To develop a p62-based gene therapy treatment of CADASIL mouse model

In a gene therapeutic approach to treat Notch3 pathology we will inject a modified adeno-associated virus 2 (AAV2) that contain two linear peptides to specifically target VSMC. This AAV contain the p62cDNA in order to augment autophagy activity in R182C-TgN3 mice. Injection will be done before and after onset of the disease for preventive and therapeutic assessment. p62 gene therapy has been previously used successfully to treat AD-related pathologies in AD mouse models. By injecting AAV-p62 into the mouse tail vein, we will be able to reach the Notch3 aggregates in the vessels. After 3 months of treatment, the effects on Notch3 aggregation, GOM formation and improved VSMC survival will be assessed. Taken

together, the data is expected to give us knowledge of the role of autophagy in CADASIL and reveal whether the pathologies can potentially be treated by gene therapy.

Research group

Helena Karlström, Assoc.Prof, Group leader, Head of Division of Neurogeriatrics

ShaoBo Jin, PhD, Senior Lab Manager

Katrine Dahl Björnholm, PhD, Postdoctoral fellow

Daniel Oliveira, PhD student

Supplementary information

Key words

Neurodegeneration, Stroke, Small vessel disease, CADASIL, autophagy, Notch signaling, vasculature

#38 Uncovering body-site dependent skin cell diversity in health and disease

Type of recruitment
Doctoral student, 4 years

Project title
Uncovering body-site dependent skin cell diversity in health and disease

Supervisor
Maria Kasper, Associate Professor
Department of Cell and Molecular Biology

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Home page: http://kasperlab.org

Qualifications of applicant
We seek a student with a background in molecular biology, biomedicine, medicine or equivalent, who has a strong interest in skin biology, wet-lab work and learning programing languages (R and/or Python) needed to analyze single-cell transcriptomic data. The candidate should have a good team spirit, be self-motivated, and bring a keen interest in solving intricate scientific questions (in tissue biology). Experience in working with molecular biology techniques, confocal microscopy, FACS, and the isolation and culture of primary cells, as well as basic programming skills are a strong plus. The student is required to have a good team-work ability and communication skills in English (written and verbal).

Background
Skin is the largest human organ and contains an intricate variety of cell types that assure tissue architecture and proper skin function, such thermoregulation and hair growth. An imbalance of cell types and/or molecular signalling often results in disease. Across the body, skin composition differs in thickness, hair growth, sebaceous and sweat gland density, microbiota exposure and disease susceptibility. However, a molecular understanding for how cell types and genetic programs vary with skin regions, and molecular alterations in disease, is currently lacking. Building upon our labs expertise, this PhD project will molecularly dissect and functionally investigate body-site differences in mouse and human skin using a wide range of methods such as single-cell transcriptomics, FACS, imaging techniques, lineage-tracing mouse models and computational biology.

Research project description
The overall aim is to uncover skin-cell diversity across body sites and it’s impact on skin phenotype and function (e.g. hair density, thickness, sebum release). Emphasis

is on studying human skin with complementary use of mouse models, to address potential molecular and cellular mechanisms experimentally. We will utilize isoform-resolution scRNA-seq, FACS, single-molecule mRNA staining, computational analyses and mouse models to trace, activate or deplete specific cell populations in the skin.

The PhD project is anchored upon - but not limited to - the following two aims:

Aim 1. Charting body-location dependent cell-type diversity in healthy human skin. We will profile and analyze full-thickness skin at different anatomical body locations using scRNA-seq with isoform resolution.

Aim 2. Revealing new cell-type specific functions using mouse models. Complementary to Aim 1 and guided by results therein, we will use mouse models to trace, activate or deplete specific cell populations in the skin to study their respective function in vivo.

Research group

With our research – rooted within the fields of skin and stem cell biology – we aim to answer fundamental questions about tissue homeostasis, repair and regeneration. We use single-cell transcriptomics, computational biology, in vivo lineage-tracing and in situ spatial mappings, to uncover the cellular behavior and molecular signals of individual cells in skin during health, repair and cancer development (key lab references: Joost et al. 2016; Joost et al. 2018; Sun et al. 2020; Joost et al. 2020). The overall aim is to understand human skin disorders, improve early cancer detection and uncover new regenerative strategies to restore skin. We are a young and dynamic research team with a well-established collaborative network of experts in, for example, single-cell transcriptomics and human skin diseases (http://kasperlab.org). The group is located within an environment hosting a broad repertoire of technologies including good access to high-end core facilities.

Supplementary information

Key words

skin, stem cells, regenerative medicine, human tissue, mouse models, single-cell RNA sequencing, spatial mapping, computational analysis

#39 Skin and hair follicle regeneration

Type of recruitment
Visiting doctoral student, 12 months
Postdoc, 24 months
Visiting researcher, 12 months

Project title
Skin and hair follicle regeneration

Supervisor
Maria Kasper, Associate Professor
Department of Cell and Molecular Biology

E-mail: maria.kasper@ki.se
Phone:
Home page: http://kasperlab.org

Qualifications of applicant
The Postdoc, visiting student or researcher, should have a background in medicine, molecular biology, or equivalent, with a strong interest in skin biology and regenerative medicine. The candidate should have a good team spirit, be self-motivated, and bring a keen interest in solving intricate scientific questions (in tissue biology). Experience in working with molecular biology techniques, confocal microscopy, FACS, isolation and culture of primary cells and mouse models, as well as basic programming skills are a plus. The candidate is required to have a good team-work ability and communication skills in English (written and verbal).

Background

Research project description
We are born with all the hair follicles that we will ever have in our life. These structures are maintained by different types of cells (such as keratinocytes and fibroblasts) that work together to create hair. Hair follicles form in the embryo thanks to complex molecular signals, which include a molecular cascade of signaling pathways. After birth however, most of these embryonic molecular signals are shut down to avoid conflicting messages; inappropriate activation of these embryonic signals in adult skin, for instance, can lead to tumor development. This means that our skin loses the ability to make new hair follicles, and if skin is severely damaged it cannot regrow hair or produce the associated sebaceous glands that keep skin moisturized. Being able to create new hair in adult skin would be both functionally and aesthetically beneficial for patients in need (e.g.: burn victims). Overall, it would also help to understand if and how it is possible to reactivate developmental programs after birth.

The overall aim of this project is to uncover molecular signals and technical tools that can help to improve skin regeneration by, for example, restoring hair follicles. To tackle this aim, the candidate will make use of our knowledge gained from single-cell transcriptome analyses of mouse and human skin, as well as utilize our established mouse models and skin reconstruction assays. Furthermore, the candidate is encouraged to explore own ideas and use his/her own knowledge to work on skin restoration strategies.

Research group

With our research – rooted within the fields of skin and stem cell biology – we aim to answer fundamental questions about tissue homeostasis and regeneration. We use modern techniques such as single-cell transcriptomics, computational biology, in vivo lineage-tracing and in situ spatial mappings, to uncover the cellular behavior and molecular signals of individual cells in skin during health, repair and cancer development (key lab references: Joost et al. 2016; Joost et al. 2018; Sun et al. 2020; Joost et al. 2020). The

overall aim is to understand human skin disorders, improve early cancer detection and uncover new

regenerative strategies to restore skin. We are a young and dynamic research team with a well-established collaborative network of experts in, for example, single-cell transcriptomics and human skin diseases (http://kasperlab.org). The group is located within an environment hosting a broad repertoire of technologies including good access to highend core facilities.

Supplementary information

Key words

skin, regenerative medicine, mouse models, human tissue

#40 Decoding and therapeutic exploration of extracellular niche in brain pathology

Type of recruitment
Postdoc, 24 months

Project title
Decoding and therapeutic exploration of extracellular niche in brain pathology

Supervisor
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Qualifications of applicant
Requirements: a highly motivated postdoctoral fellow with a Phd in systems biology and bioinformatics. Experienced in analyzing single cell transcriptomics-, proteomics datasets and in developing multi omics pipelines. Knowledge in machine-learning, developmental biology and various CNS cell-types is an advantage. The working language in the lab is English and the postdoctoral fellow is expected to be able to socialize and communicate science in English.

Background
Traumatic brain injury (TBI) in children and adults, associated with cerebrovascular dysfunction/neurodegeneration and significant long-term disabilities, has been suggested a trigger for cognitive decline in children and dementia later in life (eg. Alzheimer´s disease, AD and Parkinson with dementia, PDD). While prevention of sequelae following blood-brain barrier (BBB) breakdown constitutes the key therapeutic strategy, good diagnostic tests and pharmacological treatments are so far lacking for mild and severe TBI, partly due to incomplete understanding of intercellular signalling, the extracellular matrix (ECM) and its associated molecules (matrisome).

Research project description
Aim: To understand the crosstalk between the different cell types of the blood-brain-barrier (BBB) and other neural cells in human to ameliorate the TBI phenotype and prevent its sequelae that lead to cognitive decline in children and to dementia later in life. Method: A system biology approach is applied where we define single cell ECM signatures across all human brain cell types of the neurovascular niche using sensitive single cell transcriptomic and proteomic methods on primary tissue from healthy human embryonic to adult brain, as well as

from patient samples including extracellular vesicles (EVs) from blood and CSF (TBI vs AD/PDD). The brain matrisome is decoded by bioinformatics and pattern recognition machine learning tools and compared to healthy human data but also to e.g. our previously generated ECM data in Wnt compromised brain vessels and microglia after brain-insult. We are about to develop a unique microphysiological BBB system for functional testing and disease modelling in which human 3D cortex spheroids, comprised of the six major brain-cell types can be genetically (CRISPRCas9), mechanically and pharmacologically manipulated. Relevance: These results will provide important insights into ECM biology in child-/adult brain health and disease and aspire to pave the way for novel prognostic/diagnostic tools, biomaterials and therapies toward mechano-medicine.

Research group

Project participants: PI in Neurovascular Biology and Health. 1 postdoctoral fellow in proteomics and 1 student in brain organoids, transcriptomics and bioinformatics. We have active collaboration with other strong research groups and facilities within and outside Biomedicum that allow an interdisciplinary platform, technological knowledge transfer and also access to clinically relevant material.

Supplementary information

Key words

Brain-matrisome, Systems Biology, Brain-Pathology, Blood-Brain-Barrier, Neural Cells, Developmental biology, Wnt

#41 Uncovering regulatory elements during organismal development and diseases

Type of recruitment
Postdoc, 24 months

Project title
Uncovering regulatory elements during organismal development and diseases

Supervisor
Claudia Kutter, PhD, Associate professor
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Qualifications of applicant

- Proven experience in working with eukaryotic gene regulation, genome/transcriptome-wide studies and/or RNA biology
- Demonstrated familiarity with sequencing data analysis and/or genome assembly/comparison as well as statistics and modelling approaches
- Excellent skills in computer programming (primarily Python, R, UNIX) and knowledge of biological database systems
- Wish to integrate computational and experimental approaches
- Enthusiastic, highly motivated, collaborative, scientifically adventurous, curiosity-driven candidate
- Bringing independent and original ideas into the project are welcome.
- Previous records of independent research as well as productive interactions within a multi-disciplinary team environment (e.g. first- and/or co-author publications in high profile journals) are beneficial
- Good communication skills (proficiency in spoken and written English).

Background

Numerous genome-wide studies in diverse cancers have indicated that molecular programs dictating developmental processes are repurposed in cancer cells and trigger the expression of transcripts manner to promote cancer progressio. Altering gene expression programs requires to remodel the chromatin state of the genome. This is achieved by modifying histones at distinct position that either allow or prevent transcriptional regulators to access DNA and consequently lead to gene activation or repression, respectively. Despite intensive research, the molecular mechanisms that control how the genome is deployed to define cell functionality in normal liver development remain elusive.

The purpose of the proposed project is to decipher chromatin signatures and regulatory roles of regulatory RNAs during normal embryonic and postnatal organ development. By identifying regulatory elements that determine molecular and cellular patterns at specific time points during organ development, we will test whether cancer cells reactivate developmental programs to promote cancerogenesis. Uncovering novel regulatory molecular pathways that are repurposed in cancer allows to identify diagnostic and therapeutic targets essential for clinical intervention and treatment.

Research project description

Radical changes in the physiological function of organs during development have been well. The shift in organ function is the result of a sophisticated alteration in gene expression programs. The instructions to execute a specific developmental program are embedded in the DNA and its accessibility relies on an active (“open”) chromatin state at promoter and enhancer regions. While promoters reside in close proximity to the transcriptional start site (TSS) of developmental genes, enhancers can control genes often located hundreds of kilobases from the TSS. The architectural protein CCCTC- binding factor (CTCF) organizes the genome by bridging genetic regions in form of 3D loops and therefore allowing promoter-enhancer interactions. Signatures of a specific chromatin state can remain through cell divisions in order to maintain cell identity. Controlled modulation of these signatures allows the cell to differentiate and commit to new physiological function. However, the signatures indicative for normal developmental programs might become repurposed and contribute to the development of cancer cells.

Experimentally using Chromatin Immunoprecipitation sequencing (ChIP-seq), active gene promoters can be identified by mapping regions enriched for trimethylated lysine 4 of histone H3 (H3K4me3) and acetylated lysine 27 on histone H3 (H3K27ac), which marks sites of transcription initiation. Similarly, enhancer regions can be mapped by acetylated lysine 27 on histone H3 (H3K27ac) and monomethylated lysine 4 of histone H3 (H3K4me1). Open chromatin regions can be also demarcated by Assay for Transposase-Accessible Chromatin using sequencing (ATAC-seq). The actual set of genes that are activated and produce RNA transcripts are profiled quantitatively by using total RNA-sequencing.

Studying the dynamics of gene activation and transcription is relevant for increasing our understanding of the underlying molecular mechanism that govern organ development and whether these mechanisms get utilized by the cancer cell.

The project addresses three main research questions:

1. which chromatin signatures predefine cell-type specific functions during organ development,

2. how do lncRNAs contribute mechanistically to organ development and

3. why can hard-wired molecular developmental programs get unhinged and contribute to cancerogenesis

Research group

The successful candidate will be part of a multidisciplinary and collaborative research team active within the fields of functional and comparative genomics, chromatin and RNA biology. The roles of noncoding RNAs are interrogated genome- and transcriptome-wide by employing a combination of next generation sequencing technologies and high-throughput genetic screening approaches, developing experimental and computational methods, along with additional biochemical, molecular and cell biological methods. The group uses an integrative and collaborative approach, and works closely with experimental and computational groups. The group owns a Next Generation sequencer facilitating quick and controlled data provision. Additional professional training is available through summer schools and workshops. The group is located at SciLifeLab in Stockholm, a national center for large-scale life science research with an advanced technological infrastructure.

Supplementary information

Key words

Genomics, transcriptomics, evolutionary biology, CRISPR technology, RNA binding proteins, RNA biology, transposon biology, long noncoding RNAs, transfer RNAs, small RNAs

#42 Advancement of studying RNA and protein interaction at the single cell level

Type of recruitment
Visiting researcher, 12 months

Project title
Advancement of studying RNA and protein interaction at the single cell level

Supervisor
Claudia Kutter, PhD, Associate professor
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Qualifications of applicant
- Proven experience in working with eukaryotic gene regulation, genome/transcriptome-wide studies and/or RNA biology
- Excellent skills in molecular biology
- Demonstrated familiarity with sequencing data analysis and/or genome assembly/comparison as well as statistics and modelling approaches
- Wish to integrate experimental and computational approaches
- Enthusiastic, highly motivated, collaborative, scientifically adventurous, curiosity-driven candidate
- Bringing independent and original ideas into the project are welcome
- Previous records of independent research as well as productive interactions within a multi-disciplinary team environment (e.g. first- and/or co-author publications in high profile journals) are beneficial
- Good communication skills (proficiency in spoken and written English).

Background
The human body consists of hundreds of highly specialized and morphologically diverse cells, yet virtually every cell in the body contains the same genetic information. To exert cell-specific functions, high fidelity mechanisms restrict the expression and processing to only a particular set of genes and transcripts. Abnormal cell behavior as seen in many fatal human diseases, such as cancer, is often the consequence of aberrant transcripts formation.

Deep sequencing technologies have revealed that up to 85% of the human genome is transcribed of which less than 3% encode for protein-coding genes and more than 97% for noncoding RNAs (ncRNAs). Many ncRNAs function as potent modifiers of gene expression. RNAs regulate molecular processes by interacting with protein

partners, called RNA binding proteins (RBPs), often in a combinatorial fashion. RNA-protein interactions are dependent on the RNA structure, which however is largely unreadable from the sequence content alone. Therefore, the binding and processing capacities of these protein partners remain poorly explored on a transcriptome-wide level. Some RBPs can become pathogenic when mutated. For example, DICER, TDP-43 or TERC contribute to oncogenesis, neurologic disorders or premature aging, respectively. These studies have highlighted the importance of RBPs in transcriptome regulation and have contributed to our understanding of their roles in human disease phenotypes.

Research project description

RBP deregulation affects noncoding and protein-coding RNA processing. To gain mechanistic insights in molecular mechanisms and disease regulation, the Kutter laboratory has developed a sophisticated new methodology, called PRIDE-seq. This method allows to study the interaction of RBPs and RNAs in a rapid, robust and scalable manner. PRIDE-seq is an exhaustive and unbiased transcriptome-wide approach to investigate the regulatory mechanisms of mammalian RBPs in ncRNA processing beyond mRNA. The group has already benchmarked this method to currently available methods, showing strong advantages. It allows understanding the impact of mutations on RNA species, among many other applications.

Since the method has been employed successfully on pools of cells, this project aims to adjust this methodology onto to the single cell level.

This approach allows to:

• classify RNAs based on differences in their transcription and processing by RBPs

• measure global gene expression levels (including ncRNAs) quantitatively

• determine transcript fate dependent on molecular pathways affected

• dissect specific or combinatorial roles of RBPs and cooperative RBP interaction

• reveal the rate and evolutionary turnover of RBP binding

• identify conserved binding motifs and structural features (RNA folding) within the transcript sequence

When PRIDE-seq is optimized for the single cell level, the findings will provide mechanistic insights in disease regulation and hold great potential in discovering disease markers for future therapeutic developments.

Research group

The successful candidate will be part of a multidisciplinary and collaborative research team active within the fields of functional and comparative genomics,

chromatin and RNA biology. The roles of noncoding RNAs are interrogated genome- and transcriptome-wide by employing a combination of next generation sequencing technologies and high-throughput genetic screening approaches, developing experimental and computational methods, along with additional biochemical, molecular and cell biological methods. The group uses an integrative and collaborative approach, and works closely with experimental and computational groups. The group owns a Next Generation sequencer facilitating quick and controlled data provision. Additional professional training is available through summer schools and workshops. The group is located at SciLifeLab in Stockholm, a national center for large-scale life science research with an advanced technological infrastructure.

Supplementary information

Key words

Genomics, transcriptomics, evolutionary biology, CRISPR technology, RNA binding proteins, RNA biology, transposon biology, long noncoding RNAs, transfer RNAs, small RNAs

#43 Clinical and genetic studies of papillary thyroid carcinoma

Type of recruitment
Doctoral student, 4 years

Project title
Clinical and genetic studies of papillary thyroid carcinoma

Supervisor
Catharina Larsson, Professor
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Qualifications of applicant
The candidate may have medical education with some experience from molecular biology work or laboratory experience / or have basic education within biomedicine. The candidate should have the required educational background for admission to doctoral education at Karolinska Institutet.

The candidate should be motivated and have an interest in cancer research, as well as having good communication skills and proficiency in English. Previous research experience in the field of cancer research is considered as an advantage for this project.

Background
Papillary thyroid carcinoma (PTC) frequently show hotspot mutations of BRAF or carry fusion genes resulting from chromosomal rearrangements that leads to abnormal tyrosine kinase activity. Familial forms have been reported and there is a significant group of PTC patients with onset at early ages. However, the driver genes and associated mechanisms involved are largely unknown.

We and others have reported that activation of the telomerase complex and it´s TERT component are highly important for the development of aggressive thyroid tumors and have clinical implications. Specifically, promoter mutations in the telomerase gene TERT are common and associated with shorter telomeres, shorter patient survival, loss of radioiodine uptake and with transformation to highly lethal

anaplastic thyroid carcinoma. Additional mechanisms of TERT activation are anticipated in PTC and remains to be elucidated.

In previous studies we observed an intimate relationship between the ETS family transcription factor GABPA and DICER1 in the microRNA machinery in multiple human cancer types including PTC. GABPA expression inhibited metastatic behavior in vitro and reduced GABPA expression in tumors was associated with metastases and short survival of PTC patients, in agreement with a tumor suppressor function. Furthermore, effects on specific microRNAs were observed, the extent and effects on potential microRNA-targets remains to be elucidated.

Research project description

The PhD project is proposed to include the following three studies:

1) Identification of genetic predisposition for PTC

To further elucidate the genetic background of PTC a large pedigree with PTC is studied where several family members from three generations were diagnosed with PTC at 15-60 years of age, strongly supporting a dominantly inherited genetic predisposition in this family. From whole-genome sequencing data, candidate gene mutations will be selected based on predicted effects and rarity in the general population. Following verification, the possibility of their involvement in PTC in general will be assessed. Patogenicity of mutations will be evaluated from possible effects on tumor phenotypes in vitro in PTC cells and expression in PTC tumors from adult as well as young PTC patients.

2) Elucidation of TERT activating alterations in PTC

These studies aim to elucidate the involvement and additional mechanisms of TERT activation in PTC outside of TERT promoter mutation. Gene dosage and aberrant methylation density will first be evaluated according to our observations in other types of thyroid and endocrine tumors. Since TERT expression is more common than TERT mutation, expression of functional TERT full-length transcript will be analysed to elucidate its possible additive prognostic value for PTC. Another central question is where in the tumor development TERT activation occurs and whether it can precede progression to more aggressive disease or anaplastic cancer.

Upregulation of ETS factors by BRAF mutation and MAP kinase activation is believed to contribute to TERT expression and stabilization of telomerase as well as

other tumor-related effects. Here the TCGA database is used to identify ETS factors which expression correlates well with poor outcome, BRAF mutation and TERT expression. An ETS factor of interest that can be verified by similar analyses in the Karolinska cohort of PTC is of interest as a possible therapeutic target and as a clinical additional marker. ETS candidates will therefore be further studied for its effect together with TERT on in vitro tumor phenotypes using PTC cell lines with different combinations of TERT and BRAF genotypes.

3) Studies of DICER1 related effects on microRNAs and PTC clinical features

DICER1 is a down-stream effector of the ETS factor GABPA with tumor suppressor consequences. Here, the effects of GABPA / DICER1 downregulation in PTC will be studied concerning specific microRNAs and their targets. microRNAS and predicted targets who´s expression correlate with GABPA and DICER1 expression are of special interest to study further for possible effects on PTC clinical features and patient outcomes.

Research group

The research group Medical Genetics is presented at the homepage. The group includes four research teams with overlapping projects and an overall goal to explain tumor initiation and malignification focusing on initiating and acquired events and their cellular effects and influence on the natural course of the disease as well as how these can be applied to improve clinical workup and handling. In the research team of Catharina Larsson there are presently two PhD students working on thyroid and adrenal cancer as well as affiliated clinically employed MD PhDs in the fields of pathology and oncology.

Supplementary information

The PhD student will be registered at the Department of Oncology-Pathology at KI and have full-time activity in the research group of Catharina Larsson. Catharina Larsson is MD Professor and a full-time researcher with expertise in experimental, molecular and translational research on thyroid and other endocrine tumors, and daily available for questions and discussions. The PhD student will also be co-supervised by other senior researches with expertise in complementary aspects of the PhD project.

The daily activities will be carried out in the group´s laboratory in Bioclinicum, a novel experimental research centre in the Karolinska University Hospital located centrally in the Stockholm region.

Key words

Thyroid, cancer, prognostic marker, genetic predisposition, telomerase, microRNA

#44 Gut-brain axis mediators in neuropsychiatric disorders

Type of recruitment
Doctoral student, 4 years

Project title
Gut-brain axis mediators in neuropsychiatric disorders

Supervisor
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Qualifications of applicant
The following qualifications are required: Experimental techniques including cell culturing with assays of proliferation and migration, RNA extraction, RT-PCR, Western blot, immunohistochemistry, immunofluorescence, and some experience of bioinformatic and statistical analyses. Personal characteristics including being enthusiastic, thorough and responsible, and with the ability to work in teams and solve minor practical problems independently.

Background
Attention-deficit hyperactivity disorder (ADHD) has high comorbidity with autism and is commonly treated with stimulants having side effects. Stimulants have at high doses been proposed to cause inflammation and blood-brain barrier (BBB) hyperpermeability in rodent brain. Gastro-intestinal (GI) symptoms are reported to be overrepresented in ADHD and autism. ADHD and autism have a high comorbidity also with immune-mediated conditions, like atopic dermatitis, asthma. Immune activation peripherally and in cerebrospinal fluid has been consistently reported for autism, however, it is not well explored for ADHD. ICAM-1 and VCAM-1 are expressed predominantly by endothelial cells and are considered central to leukocyte–endothelial cell adhesion and inflammation into the surrounding tissue. Elevated levels of ICAM-1 have been reported in affective disorders, and that may relate to ICAM-1s role in regulating BBB permeability. The upregulation of cellular adhesion molecules (e.g. ICAM-1 and VCAM-1) cause endothelial dysfunction which is an independent risk factor for cardiovascular disorder.

In autism, there is evidence for a dysfunctional gut bacterial microbiome and improvements by probiotic interventions and fecal transplantation. Likewise, feces from patients with autism, depression or schizophrenia transferred to the rodent

intestine produced patient-disorder-related behaviors and biochemical modulations. However, the gut-brain axis in ADHD is quite unexplored.

Research project description

The overall project aim is to explore if levels of gut microbiome metabolites in blood and urine (i) have a role in endothelial dysfunction in ADHD patients, and (ii) are associated with ADHD symptoms, autistic traits and emotional dysregulation in pediatric and adult patients with ADHD. We hypothesize that there is a vascular endothelial dysfunction in ADHD, associated, on the one hand, with pharmacological stimulant treatment, and, on the other hand, with comorbid autistic traits, and that these associations are in part driven by gut microbiome metabolites impairing the vascular endothelium affecting also the blood-brain barrier. We further hypothesize that normalizing the gut microbiota with a synbiotic protects the vascular endothelium and reduces autistic symptoms and emotion dysregulation and in young and middle-aged persons with ADHD.

Using a large randomized placebo-controlled trial of a synbiotic intervention (dietary fibres and lactic acid bacteria) in children and adults with ADHD we found markedly elevated plasma levels of endothelial dysfunction markers (sICAM-1 and sVCAM-1), especially in those treated with stimulants, and that these marker levels correlated strongly with plasma levels of short chain fatty acids (SCFAs) produced by the gut bacteria upon digestion of fibres. SCFAs are proposed to mediate part of the communication from the gut to the brain and to influence the intestinal and blood-brain barrier permeability and brain microglia. These SCFAs and adhesion molecules correlated also with level of autistic traits and were suggestively reduced by the synbiotic intervention. These findings will soon be included in a thesis by CSC-KI PhD-student Liu Yang. This current project proposal will build on the findings by Liu Yang.

The following studies will be included:

Study I) To investigate the effect of physiological levels of SCFAs on adhesion molecules (ICAM-1 and VCAM-1) and other endothelial function markers in vascular endothelial cells in vitro. While certain SCFAs, at levels far above physiological range, have been reported to protect against vascular inflammation, it is unknown if effects occur at physiological SCFA levels.

Study II) To explore the whole microbiome metabolome in plasma and/or urine samples from the 154 RCT completers and 61 healthy controls and its relation to the already measured levels of the vascular endothelium adhesion molecules and other measured plasma immune activity markers found upregulated in ADHD with autistic traits. There are several bacterial metabolites known to influence barriers, such as bile acids.

Study III) To explore the above microbiome metabolome in relation to the psychiatric symptom profiles, the gut microbiome species profile in the RCT completers, and the effect of the synbiotic intervention. The feces microbiome has been sequenced covering both bacteria, fungi and viruses.

Study IV) To determine effects of physiological levels of functional metabolites, detecte

Research group

The Translational psychiatry research group has 27 members, including 7 doctoral students. Some of us are clinically active and our research builds on clinical patient data and large epidemiological registry data. Our research goal is to provide an evidence-based risk factors and biomarkers for improved diagnosis and treatment of psychiatric disorders.

Supplementary information

This KI supervisor is research group leader and Departmental director of research education.

Key words

Gut-brain axis, psychiatry, probiotics, vascular endothelium, microbiome, metabolome

#45 Epidemiological studies of metabolic related determinants of cardiovascular event fatality

Type of recruitment
Postdoc, 24 months

Project title
Epidemiological studies of metabolic related determinants of cardiovascular event fatality

Supervisor
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Qualifications of applicant
We are looking for an independent researcher with a solid background in epidemiology. Knowledge of statistical analysis-methods and statistical programs is necessary. An interest in, and documented experience from, cardiovascular research is an advantage.

Background
In the cardiovascular epidemiology field of research, there is often an implicit idea that fatal cardiovascular disease (CVD) events may have different aetiology than non-fatal. However, relatively few studies have aimed at investigating such differences. Further, most previous studies of factors influencing fatality of cardiovascular events were restricted to hospitalized cases, thus not considering out-of-hospital deaths. Even though victims of fatal CVD events to a large degree share atherogenic traits with those who survive, and the epidemiology of fatal CVD to a great extent should parallel that of nonfatal, it is important to understand possible differences. To be capable of rising to the challenge of preventing out-of-hospital deaths from a first CVD event we need increased knowledge about predicting factors and underlying biological mechanisms in the aetiology.

Previous studies that considered both in- and out-of-hospital CVD-related deaths have associated fatality of coronary events with increasing age, prior CVD, diabetes, low physical activity, low-grade inflammation, and genetic susceptibility among other factors. Studies of stroke fatality are more limited. Our own research has

contributed to confirm the association between diabetes and a fatal outcome of a first coronary event. Further, we found that hypertension, hyperlipidemia, overweight and prior diagnosis of angina pectoris or intermittent claudication did not associate with increased fatality.

Research project description

The overarching aim is to contribute to the scientific knowledge forming the basis for cardiovascular preventive strategies, with a special focus on how to prevent out-of-hospital deaths from a first cardiovascular event.

The project specifically aims at assessing the association between metabolic related risk markers and the fatality of future incident first-time cardiovascular events, in men and women respectively. Both in-hospital and out-of-hospital deaths are considered. We will study the most common CVD diagnoses – coronary heart disease and stroke – but also less common ones such as aortic aneurysms.

The metabolic risk factors to be assessed include well-known biomarkers of a disturbed lipid metabolism, such as apolipoproteins A1 and B, and low-grade inflammation such as leukocyte count and haptoglobin. In addition, pro-inflammatory fatty acids will be studied.

An underlying hypothesis is that inflammatory markers associate with more severe CVD than do lipid biomarkers.

The studies are based on different study materials including the large AMORIS (Apolipoproteins-related mortality risk) cohort (https://ki.se/en/imm/amoris), the 60YO (Cohort of 60-year-olds) (https://ki.se/en/imm/the-cohort-of-60-year-olds), the SHEEP (Stockholm Heart Epidemiology program) (https://ki.se/en/imm/the-stockholm-heart-epidemiology-program-sheep) and national registers. In addition, the planned research will be based on the FORCE (Fatty acids and outcomes research) collaborative effort (https://nutrition.tufts.edu/research/projects-initiatives/force-fatty-acids-and-outcomes-research-consortium), where our group participates with data from the 60YO (n=4232).

A prerequisite for population-based studies of factors that may influence event fatality is access to large epidemiological materials which we have in this project.

The AMORIS includes around 8000 individuals who resided in the larger Stockholm area at the time of the baseline investigations which took place during the period 1985-1992. Cause specific mortality has been identified through linkage to the National Cause of Death Register up to 2019. Likewise, all hospitalizations (from 1987 to 2019) have been identified through the Swedish National Patient Register.

The SHEEP is a population-based case-control study of risk factors for first-time acute myocardial infarction. The study base comprised all Swedish citizens resident in the Stockholm county 1992-1994 who were 45-70 years of age and were free of previous clinically diagnosed myocardial infarction. The number of cases included is 2246. Out of those, 603 were considered fatal; the majority were autopsied. Questionnaire data covering a wide range of exposure areas were collected from the participants. For fatal cases, a close relative was asked to fill in the questionnaire. Through linkage with the AMORIS cohort, we expect to retrieve pre-event data on metabolic biomarkers for about 30% of the well-characterized cases.

Research group

The Unit of Cardiovascular and Nutritional Epidemiology at the Institute of Environmental Medicine, Karolinska Institutet, is a workplace with an open and friendly atmosphere which stimulates scientific research discussions. We work in an interdisciplinary way with both questionnaire-based research and research on biomarkers to understand and to investigate mechanisms behind the development of chronic diseases. Our overarching aim is to strengthen the scientific basis for different primary prevention approaches.

Supplementary information

The post doc researcher we hope to hire would be a member of Leander´s research group. This research group also includes a post doc researcher engaged in research with the field of nutrition and cardiometabolic risk markers, a biostatistician with vast expertise from epidemiological research, and a doctoral student engaged in research on women´s health with focus on sex hormones. The post doc researcher to be hired would be warmly welcomed and stimulated to participate in various collaborations, both within the unit and outside. Leander will show great commitment to tutoring.

Key words

Epidemiology; cardiovascular disease; case-fatality; biologic markers; metabolic pathways; inflammation; dyslipidemia; coronary heart disease; cerebrovascular disease

#46 Regulation of recovery from a DNA damage checkpoint

Type of recruitment
Doctoral student, 4 years

Project title
Regulation of recovery from a DNA damage checkpoint

Supervisor
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Qualifications of applicant

Fluent communication in written and spoken English.

Masters level education in a relevant subject.

Substantial experience of lab work with positive track-record.

Experience in cell handling, molecular biology, image analysis/programming is an advantage.

The key qualification concerns motivation and interest for the field of study.

Background
How human cells commit to recover from a DNA damage insult and resume proliferation is a fundamental question that currently is poorly understood. It is also a question at the heart of both tumor development and cancer treatment.

Many current cancer treatments function by damaging a cell's DNA. These treatments may become more efficient if combined with compounds targeting cellular signaling. Understanding the signaling that determines cell fate after DNA damage is therefore key to predict which compounds to combine with genotoxic anti-cancer treatment.

Whether a cell resumes proliferation or enters senescence after DNA damage in G2 phase depends on the interplay between two major signaling networks: cell cycle signaling and DNA damage dependent signaling. The lab is studying different aspects of these signaling networks and in particular how they interact over time.

For a recent review from the lab, please see Lemmens and Lindqvist, Journal of Cell Biology 2019.

Many of the key proteins involved in these networks are known. However, clearly targets are missing. In particular, there are several rare genetic conditions that impacts on cell proliferation in which the gene is identified but the mechanism remains unclear. This PhD project aims at studying the interplay between cell cycle and DNA damage dependent signaling in human cell lines, with a particular focus on G2 phase and genes mutated in rare genetic conditions with proliferation defects.

Research project description

The project is a continuation of our ongoing efforts to understand how cell cycle signaling and DNA damage dependent signaling interact. It both involves a cooperation with a postdoctoral fellow and a senior scientist in a large scale project (Aspect 1), and independent exploration of novel functions of genes mutated in human disease (Aspect 2).

Aspect 1. Study the regulation of DNA damage checkpoint recovery from G2 phase in human cells.

A. Characterize signaling of key cell cycle and DNA damage proteins over time in single cells.

Two main methods are used. First, individual cells are followed by time-lapse microscopy. The cells either contain fusion proteins between endogenous proteins and fluorescent proteins, making it possible to follow expression levels and localization over time. Or, the cells express reporter constructs to study cellular signaling. Second, cells are fixed and subjected to quantitative immunofluorescence, and trends over time are estimated by a method we have invented. For examples of methods and existing cell lines please see Jaiswal et al. EMBO journal 2017 and Lemmens et al Molecular Cell 2018.

B. Study importance of signaling events for checkpoint recovery.

The quantitative data from A is included in a mathematical model of the combined signaling of cell cycle and DNA damage dependent signaling, performed by a senior scientist in the lab. Predictions from this model are tested experimentally by the PhD student. The setup in A is combined with perturbation by addition of small molecule inhibitors, transfections of siRNA or creation of degron cell lines. In addition, methods as Cloning, Western Blot and FACS are used.

2. Study the involvement of genes mutated in rare monogenic diseases with proliferation defects for recovery from a DNA damage response.

A. In collaboration with the lab of Outi Mäkitie, we will culture fibroblast cell lines derived from patients with monogenic proliferative disorders, such as cartilage-hair hypoplasia

(CHH), mulibrey nanism, and overgrowth symptom. Using time-lapse microscopy and FACS, the student will determine how these cells proliferate and how they recover from DNA damage. For an example of how these methods are employed on CHH cells, please see Vakkilainen et al, Scientific Reports 2019.

B. Patient cell lines that show a defect will be studied further. First, the mutation will be reverted by CRISPR/Cas9 to test specificity. Second, the gene/protein will be studied using similar tools as for Aspect 1. This includes creating fusion proteins with fluorescent proteins and tagging with degron sequences. Depending on which gene/protein is selected for further analysis, additional suitable methods will be employed.

Research group

The group currently consists of PI, one senior researcher, one postdoctoral fellow, and one PhD student. Frequently, a master student project is ongoing. The character of the group is international, and all members are currently from different countries. The group is situated in the Biomedicum building at Karolinska Institutet, and shares lab and office space with the groups of Marianne Farnebo, Olle Sangfelt, and Nico Dantuma, who all perform research in nearby research fields. A range of resources are nearby, such as imaging and FACS facilities.

Supplementary information

Relevant publications from the lab include:

doi: 10.3390/cells9092126

doi: 10.1083/jcb.201909032

doi: 10.1038/s41598-019-50334-6

doi: 10.1016/j.molcel.2018.05.026

doi: 10.15252/embj.201696082

doi: 10.1111/acel.12588

A full set of publications is available at lindqvistgroup.org

Key words

cell cycle, DNA damage, checkpoint, cancer, rare genetic disorders, signaling, microscopy.

#47 Impact of premenstrual disorders on women's health and working life

Type of recruitment

Doctoral student, 4 years
Visiting doctoral student, 12 months
Visiting researcher, 12 months

Project title

Impact of premenstrual disorders on women's health and working life

Supervisor

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Qualifications of applicant

We look for a highly motivated student/researcher with a background in epidemiology, medicine, public health, psychology, biostatistics, or other relevant field. Experience with statistical software (e.g., SAS, STATA, or R) or programming languages will be a merit.

Background

Premenstrual disorders (PMDs), including premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD), affect millions of women of reproductive age around the world. The estimated prevalence of PMS is 20%-30%, while PMDD ranges from 2.1% to 6.4%. Although the symptoms restrict to the days before menstruation, these chronic and cyclic condition may have a profound impact on long-term quality of life. Our recent studies illustrated that women with PMDs often had first symptom onset before age 20 and are at 80% increased risk of suicidal behavior. Yet, the burden of living with PMDs from young ages is poorly documented in women's health and working life.

Research project description

In this proposal, we will utilize a register-based national cohort including women with PMDs (N>20,000), their unaffected sisters and population controls, as well as a population-based longitudinal cohort, LifeGene (N=30,000), in Sweden to assess the impact of PMDs on women's working life and wellbeing. Specifically, we will 1) evaluate the risks of unemployment, sick leave, and disability benefit claims among women with PMDs, compared to women without PMDs; 2) examine the risks of psychiatric and cardiometabolic disorders, and premature deaths in PMD women, compared to women without PMDs; and 3) examine if pharmaceutical treatment

reduces long-term disease burden in women with PMDs. Our data will comprise follow-ups up to 20 years, ascertainment both through clinical management and questionnaire self-assessment, as well as of subtypes (PMS and PMDD), and linkages to working-/health-related outcomes.

This proposal leverages the unique Swedish register resources and a large-scale prospective cohort to address common, debilitating yet under-studied conditions among young women. Our findings will be the first to illustrate the negative impact of PMDs on long-term health and wellbeing, and may provide concrete evidence for health policies targeted to improve the quality of life among women living with PMDs.

Research group

Our research program is to study women's mental health over the life course and to bridge the gap between Obstetrics/Gynecology and Psychiatry. Leveraging high-quality large-scale population-based cohorts from Sweden, China, Denmark, Iceland, and US, we aim to understand the underlying biological mechanisms affecting women's mental health and potential health consequences using register, questionnaire, and omics data.

Supplementary information

Co-supervisors:

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University of Iceland
Harvard T.H. Chan School of Public Health
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Prof. Elizabeth R. Bertone-Johnson
University of Massachusetts Amherst
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Key words

Epidemiology; Public health; Women's health; Obstetrics and Gynecology; Psychology; Psychiatry; Premenstrual disorders; Mental health

#48 Viral oncoprotein-mediated RNA regulation in Merkel cell carcinoma

Type of recruitment

Doctoral student, 4 years
Postdoc, 24 months

Project title

Viral oncoprotein-mediated RNA regulation in Merkel cell carcinoma

Supervisor

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Qualifications of applicant

We are seeking a highly motivated student/postdoc who has a strong interest in RNA biology and cancer research. The applicant should have good communication skills and ability to interact effectively and work productively in a team of researchers. Emphasis will be placed on personal ability and previous experience of laboratory work. Excellent ability to express themselves in speech and writing, including scientific writing in English is a requirement. The candidate should have a MSc (for doctoral student) or PhD (for postdoc application) in molecular biology or biomedicine. Previous experience in the fields of tumor virology and RNA biology would be a merit for this project.

Background

Merkel cell carcinoma (MCC) is an aggressive skin cancer with high recurrence and mortality rates. About 80% of MCC tumors harbor integrated Merkel cell polyomavirus (MCPyV) genome with a mutation in the large T-antigen, expressing truncated large T and small T antigens. These viral oncoproteins are required for neoplastic transformation and maintenance of cell growth, supporting the importance of these viral oncoproteins in MCC pathogenesis. Still, how these viral oncoproteins contribute to tumorigenesis is not fully understood.

Research project description

Our previous work demonstrated that MCPyV T-antigens post-transcriptionally regulate microRNA expressions via the DnaJ domain of viral T-antigens. However, the mechanism how the viral T-antigens regulate microRNAs remains unknown. We recently discovered that the viral T-antigens interact with RNA binding protein that regulates microRNA processing. In this project, we will elucidate the mechanism

how the interaction between viral T-antigens and the RNA binding protein contributes to mRNA stability/translation and selective microRNA processing. This project will employ a broad range of cell and molecular biology techniques to understand the viral-mediated RNA-protein interaction and their functional consequences. This work will uncover novel mechanisms how MCPyV oncoproteins can regulate RNA expression and microRNA processing, which may lead to greater insights for the role of MCPyV in infection and tumorigenesis.

Research group

Our research team is working on viral oncogenesis in Merkel cell carcinoma. The team currently consists of PI, one postdoc and one PhD student. We are located at the Cancer theme of BioClinicum, and actively collaborating with basic scientists and clinicians locally and internationally.

Supplementary information

Key words

Merkel cell polyomavirus, RNA binding protein, gene regulation, miRNA, DICER1, Merkel cell carcinoma, cancer, non-coding RNA

#49 The molecular and cellular basis of pathological lipid accumulation in atherosclerosis and liver disease

Type of recruitment

Doctoral student, 4 years
Visiting doctoral student, 12 months
Postdoc, 24 months
Visiting researcher, 12 months

Project title

The molecular and cellular basis of pathological lipid accumulation in atherosclerosis and liver disease

Supervisor

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Qualifications of applicant

Applicants for the 4-year PhD course must satisfy the Karolinska Institutet entry requirements for Doctoral students. For all applicants, we are interested in recruiting scholars who enjoy working as a team in determining molecular mechanisms behind disease pathology. For the positions, full training will be provided in the experimental techniques. We encourage individuals from all biological backgrounds to apply, particularly those with interests in Immunology, Endocrinology, Metabolism, Bioinformatics and Molecular Biology. However the most important qualities are curiosity, determination and a positive attitude.

Background

Tissues require triglycerides, phospholipids and sterols as substrates for energy metabolism, hormone synthesis and cell membrane production, and can take up these circulating lipids from plasma if required. However, predisposing genetic mutations or increased dietary intake can lead to excess storage of lipids in organs. This can result in tissue damage, as inappropriate lipid accumulation in tissues disturbs normal physiology, especially if the lipids are modified, for example through oxidation. Notably, lipid-loading (steatosis) marks the onset of non-alcoholic fatty-liver disease (NAFLD) and the sub-intimal retention of lipoproteins triggers atherosclerosis plaque formation, which is the major cause of cardiovascular disease. Over the last 30 years, thousands of studies have implicated the immune system in the pathology of diseases caused by dyslipidemia.

However, a critical gap in our knowledge is understanding the immunological processes that characterize the initiation of these disorders, particularly the interplay between the parenchyma, resident phagocytic cells and the immune system.

Research project description

A dyslipidemic and pathogenic lipoprotein profile cannot be induced in wild-type mice. To circumvent this, current mouse models of atherosclerosis are based on congenital defects in lipoprotein metabolism inspired by familial hypercholesterolemia patients. These models are born with elevated plasma cholesterol levels and are therefore at allostasis. Hence the initiating response to dyslipidemia cannot be inferred from these strains and they are refractory to capturing the physiology of disease commencement. We have solved this experimental bottle-neck by creating two mouse strains that allow us to induce an acute state of dyslipidemia through conditional deletion of Apolipoprotein E, or conditional ectopic expression of human gain-of-function PCSK9.

For this CSC application, we intend to create a cellular and molecular map of the initiation of atherosclerosis and NAFLD. Our inducible models of atherosclerosis have been additionally crossed with mice expressing mCherry-tagged Apolipoprotein B. This will allow detection of the cells that retain lipoproteins and their isolation ex vivo. The project will involve bulk RNA-seq, single cell RNA-seq and spatial transcriptomics to determine gene expression changes. Molecular mechanisms are determined by ATAC-seq and ChIP-seq. Confocal microscopy and advanced imaging technique combined with established histological approaches are used to assess organ pathology. These studies will be complemented by experimental approaches that target cell types or specific genes in the context of disease initiation, with a strong emphasis on immune and phagocytic cells. By deleting defined immune cell types, or inhibiting specific putative pathogenic or protective genes, the project will provide insight into how we can attempt therapeutic interventions to prevent atherosclerosis or improve outcomes following establishment of NAFLD.

Research group

The current research group consists of 2 postdocs, 1 PhD student and 1 technician. The group is further part of the Cardiovascular Medicine unit at the Department of Medicine. We are approximately 60 people from all over the world that creates a supportive and interactive environment for all of our international employees.

Supplementary information

The project is part of recently funded Leducq transatlantic Network in cardiovascular disease: https://www.fondationleducq.org/network/b-cells-in-cardiovascular-disease/ As part of this project, there will be opportunities for the scholars to perform research exchanges at Harvard University, Cambridge

University, Icahn School of Medicine at Mount Sinai, University Of Vienna and University of Virginia. Recent publications from the main supervisor: Liu et al Journal of Experimental Medicine 2020 Nov 2;217(11):e20200147, Sedimbi et al Proc Natl Acad Sci U S A. 2020 Apr 21;117(16):9054-9063, Centa et al Circulation 2019 May 21;139(21):2466-2482, Centa et al Arterioscler Thromb Vasc Biol. 2018 Aug;38(8):e145-e158, Habir et al Frontiers in Immunology 2017 Oct 24;8:1387, Dahdah et al Arthritis and Rheumatology 2017 Oct 17, Centa et al Arterioscler Thromb Vasc Biol. 2016 Jan;36(1):25-36, Malin et al Nature Immunology. 2010 Feb;11(2):171-9.

Key words

Dyslipidemia, Immunology, Metabolism, Atherosclerosis, NAFLD

#50 Role of Group 2 Innate Lymphoid Cells in a mouse model of atopic march

Type of recruitment
Postdoc, 24 months

Project title
Role of Group 2 Innate Lymphoid Cells in a mouse model of atopic march

Supervisor
Itziar Martinez Gonzalez, Assistant professor
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Qualifications of applicant
The candidate must be a highly motivated researcher with experience in mouse models and flow cytometry. Background in type 2 immunity will be valuable. The candidate is expected to be organised, have excellent communicating skills and work well in a team.

Background
Allergic inflammation, typically found in asthmatic patients, is characterised by a type 2 immune response. Susceptible individuals are sensitised by direct contact with an allergen, which triggers the release of alarmins by the damaged epithelium. These alarmins activate the innate immune system, including ILC2s, which produce the type 2 cytokines IL-5 and IL-13 and subsequently the adaptive immune response. Chronic lung allergic inflammation is mediated by long-lived antigen-specific memory Th2 cells, which respond stronger during subsequent encounters with the same allergen. However, antigen-specificity cannot explain all allergic reactions. I have found that allergen sensitisation elicits the generation of long-lived antigen non-specific memory ILC2s. Memory ILC2s are more readily stimulated by unrelated allergen challenge than naïve ILC2s and enhance allergic lung inflammation.

A significant proportion of asthmatic patients start their atopy early in life, most often with the development of atopic dermatitis (AD), a type 2 disease in the skin where ILC2s has been shown to play a role. The pathogenesis that underlie the progression of allergy (or atopic march) from AD to asthma is poorly understood and cannot be explained only by the presence of antigen-specific memory Th2 cells. I hypothesise that antigen non-specific memory ILC2s may contribute to the pathogenesis of atopic march by mediating non-specific allergic responses.

Research project description

The goal of this proposal is to identify the role of ILC2s in the atopic march. In parallel to what we have recently described for memory ILC2s in the lung, we hypothesize that upon skin sensitization, some of the activated skin ILC2s acquire memory-like properties. Memory ILC2s enter the circulation and upon further allergen inhalation are recruited to the lung and enhance allergic lung inflammation. Of note, we have found increased frequency of memory ILC2s in the blood of lung sensitized mice, indicating their ability to circulate in the organism. Also, increased numbers of ILC2s have been found in atopic dermatitis (AD) lesions from patient samples and mouse models of AD show that skin ILC2s become activated. The specific aims are as follows:

Aim 1: To characterize ILC2 activation and memory generation in an AD mouse model.

Aim 2: To evaluate the role of skin memory ILC2s in allergic lung inflammation.

Aim 1: We will apply topical treatment of the vitamin D analog calcipotriol to sensitize the skin of the mouse and induce AD. Number and activation of skin ILC2s and histopathological changes will be determined using multi-color flow cytometry and confocal microscopy. Next, we will reproduce the memory lung ILC2 model in the skin. Briefly, mice will receive topical calcipotriol (or vehicle as control) and when ILC2s have returned to resting state, mice will be re-challenged by skin cytokine injection. Activation of skin ILC2s and AD features will be compared between the control and skin sensitized mice. We anticipate that ILC2 activation and AD inflammation will be increased in skin sensitized mice compared to control. This high-responsiveness will be confirmed by further in vitro stimulation with cytokines as well as upon in vivo transplantation into naive mice. This aim will allow us to demonstrate that memory ILC2s can be generated in the skin.

Aim 2: First, we will model atopic march by inducing lung allergic inflammation in AD mice. Mice will be skin sensitized with topical calcipotriol or skin cytokine injection (or vehicle as control) and once ILC2s return to resting state, the mice will receive an intranasal administration of an allergen or cytokine. Blood and lung will be harvested after the intranasal administration and ILC2 number and activation will be analyzed. Moreover, allergic lung inflammation will be assessed as shown

before. We anticipate that skin-sensitized mice will have a stronger lung allergic inflammation compared to control. We will assess the relevance of memory ILC2s in the enhanced allergic lung inflammation by reproducing the atopic march model in the T-cell deficient Rag1-/- mouse, tracking skin-derived ILC2s in the blood and lung in the atopic march model and by in vivo transfer experiments. Altogether, this sub aim will indicate whether memory ILC2s mediates lung allergic inflammation in AD mice.

Research group

Itziar Martinez Gonzalez, PhD: Team leader

Sergio Martinez-Høyer, PhD: post doctoral fellow

Laura Mathä, PhD: post doctoral fellow

Supplementary information

Key words

Group 2 Innate Lymphoid Cells

Allergic inflammation

Immunological memory

Atopic March

#51 Identifying compounds that enhance T cell-mediated recognition of human melanoma cells

Type of recruitment
Postdoc, 24 months

Project title
Identifying compounds that enhance T cell-mediated recognition of human melanoma cells

Supervisor
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Qualifications of applicant
We are looking for a dedicated and goal-oriented researcher that is able to work independently and in collaboration with others. Expertise with immunological and cellular techniques is strongly preferred, for example isolation of primary immune cells (e.g. PBMC, T cells, monocytes), flow cytometry and cytotoxicity assays. Also highly desirable is a theoretical background in immunology, oncology or cancer immunotherapy.

Background
Immunotherapy has revolutionized treatment of melanoma patients in the past decade, with notable success being achieved by immune checkpoint inhibitors for example. However, many immunotherapies still fail to induce clinical benefit in large patient groups, creating an urgent need for novel approaches that can improve efficacy of cancer immunotherapy. A root cause of inefficacious responses to immunotherapy is poor tumor immunogenicity, which renders T cell-mediated tumor recognition ineffective. Importantly, many tumors employ reversible resistance mechanisms against interferon-gamma (IFNγ), a crucial cytokine that is produced by T cells to promote target cell immunogenicity. Therefore, novel approaches to restore or amplify IFNγ-responsiveness of tumor cells would be highly attractive, as they would most likely strongly sensitize tumor to T cell-mediated immune attack. Knowing this, we here propose a project that aims to identify small-molecular compounds that can enhance human melanoma immunogenicity and recognition by T cells. Compounds identified in this approach could be developed towards the clinic as a monotherapy or as a combination with other immunotherapies.

Research project description

The initial part of this research project will be done using Jurkat cells, an immortalized line of human T lymphocytes without any endogenous T cell receptor (TCR). However, these Jurkat cells have been transduced with a TCR specific for peptides derived from either Tyrosine or MART-1, both well-known melanoma antigens. A first step will be to identify melanoma cell lines that overexpress Tyrosinase and/or Mart-1, using flow cytometry after staining for each of these three markers with commercially available antibodies. Subsequently, Tyrosinase- or MART-1-specific Jurkat cells will be tested on these melanoma cell lines for functional antigen recognition. At this point, it will also be evaluated to what extent pre-treatment of these melanoma cell lines with IFNγ can enhance recognition by Jurkat cells.

In this way, we aim to identify melanoma cell lines that, both at baseline and after IFNγ treatment, are relatively weakly recognized by Jurkat cells. In a next step, these melanoma cell lines will be used to identify compounds that can enhance T cell-mediated recognition of human melanoma cells. This will be done by both hypothesis-driven and unbiased approaches, using drugs with restricted modes of action or larger chemical libraries. In all these approaches, melanoma cells will be seeded in multiple well plates and pre-treated with selected small-molecular compounds, either alone or in combination with IFNγ. Subsequently, Jurkat cells are added to each well and cocultured with melanoma for 24 hours. Finally, interleukin-2 (IL-2) in the supernatant will be detected as a measure for tumor recognition by the Jurkat cells.

In a next step, selected compounds that most strongly enhanced tumor recognition by Jurkat cells in the setup above, are studied further to validate their effect and to unravel their exact mechanism of action. An important aim will be to verify if treatment of melanoma cells with these selected compounds affects key indicators of tumor immunogenicity, such as expression of HLA class I and PD-L1. In addition, selected compounds will be studied for their ability to block melanoma dedifferentiation, which can be induced by IFNγ and coincides with immune resistance. These same aspects will also be studied in a co-culture model of human melanoma cell lines with paired autologous tumor-infiltrating T cells (TIL), a valuable and very clinically relevant model that is well-established in our group.

If time permits, possible next steps in this project could consist of testing selected compounds in xenograft mouse models, making use of the same pair(s) of melanoma cell lines and autologous TIL that were used for in vitro validation.

Ultimately, and if fully justified by all pre-clinical data, compounds with very clear in vitro and in vivo abilities to enhance tumor recognition by autologous T cells may be evaluated in melanoma patients, as part of the clinical trials done by our group at the Karolinska University hospital.

Research group

A successful candidate will work in the Immune and Gene Therapy group headed by Professor Rolf Kiessling at the Department of Oncology-Pathology. His group, currently consisting of a PhD student, two post-docs, one assistant-professors and two technicians, has been supported by the Swedish Research Council, Wallenberg Foundation and the Swedish Cancer Foundation, among others.

The group is a part of the prominent Oncology-Pathology department, which consists of researchers working on different aspects of cancer, including genetics, epidemiology and immunology and has great access to clinical cohorts and experimental models. The group is located at Bioclinicum, a brand new and recently opened building directly adjacent to the new Karolinska University Hospital. Bioclinicum houses various research departments that bring together internationally recognized leading experts from basic and clinical research on common diseases from Karolinska Institutet and University Hospital.

Supplementary information

Key words

Cancer Immunotherapy; Immunology; Translational Medicine; Melanoma

#52 Mapping the distribution of protein coding genes in the mammalian central nervous system

Type of recruitment
Doctoral student, 4 years

Project title
Mapping the distribution of protein coding genes in the mammalian central nervous system

Supervisor
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Department of Neuroscience

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Qualifications of applicant
The candidate student should have master degree in biomedicine or biotechnology and an interest in Neuroscience and should have enough neuroscience background to define a project theme. The candidate student should have a basic understanding of next generation sequencing methods, data and data analysis methods. Furthermore, the student must be able to communicate and discuss ideas and results in English (written and oral).

Background
In the human protein atlas (HPA) project (proteinatlas.org) we aim to map and visualize protein expression and distribution in all major tissues and organs. The project started in 2003 and a first draft of the Tissue-based map of the human proteome was published in 2015. Our current activities are focused on generating a higher resolution zooming in on tissue and organ domains and single cells. The brain profiling group within the human protein atlas has the mission to generate a more complete overview of the mammalian brain by analyzing more brain regions and more species (human, mouse, pig, macaque, rat). In a collaborative project between HPA and BGI in China we are utilizing latest mRNA and single cell sequencing methods to reveal the transcription landscape of the brain. With the antibodies generated within the human protein atlas we can further study these proteins in details linking them to cells, cellular compartments and function.

Research project description
The student will utilize the transcriptomics data that is recently generated at Karolinska Institute and BGI to extract novel information about the molecular organization of the brain. The student will use bioinformatic tools, but the main

focus will be on 1) data integration (different omics data sets) and 2) neurobiology (gene to function). The sequencing experiments will be finalized during 2020 generating a data set with over 2,000 samples of human, pig, macaque, and mouse brain. The exact outline and theme of the doctoral project has not yet been defined and will be based on a shared interest of student and supervisor. Based on the goals of the human protein atlas project and the samples used for our sequencing experiments, project themes should focus on fundamental biological questions and not so much on disease. To perform her/his/they study the student will be trained in neuroscience, molecular biology, immunofluorescence, advanced microscopy and image analysis.

Research group

The HPA brain profiling group is located at the biomedicum at the karolinska Institute. The group consists of researchers, research assistants and students with backgrounds in neuroscience and/or molecular biology. Furthermore, as part of the human protein atlas project there is a lot of interaction with the bioinformatics, cell profiling and tissue profiling groups.

Supplementary information

Key words

Transcriptomics, brain atlas, protein distribution

#53 Single-cell profiling of immune responses to SARS-CoV-2 vaccination.

Type of recruitment
Postdoc, 24 months

Project title
Single-cell profiling of immune responses to SARS-CoV-2 vaccination.

Supervisor
Benjamin Murrell, Assistant professor
Department of Microbiology, Tumor and Cell Biology

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Qualifications of applicant
The recruit must have training in basic immunology, and experience with single-cell technologies (especially 10X) will be strongly favored. The recruit should also have the ability to work with large datasets in R, Python, or Julia.

Background
Details about the T-cell and B-cell responses to SARS-CoV-2 immunization are still unknown. The Murrell lab is heading a consortium that is, in part, investigating SARS-CoV-2 immunization strategies and analyzing the development of antibody responses that neutralize SARS-CoV-2 and prevent infection. New technologies, combining antigen oligo-tagging with single-cell RNAseq, allow the simultaneous profiling of multiple immune cells and their antigen specificities.

Research project description
Various protein immunization strategies have been shown to elicit potent neutralizing antibody responses against SARS-CoV-2 (eg. Mandolesi et al, BioRxiv, 2020). A deeper understanding of how such responses arise may provide clues for how to encourage them to be more potent and longer lasting, generating long-lived plasma cells.

To properly understand the dynamics of how B-cells and T-cells respond to immunization of model animals, we will simultaneously study, at the single-cell level, both the transcriptomics of antigen-specific immune cells, as well as the genetic component of the adaptive immune system: the TCRs and BCRs of these cells. We are in the process of developing computational approaches for examining

the differentiation trajectories of immune cells, aided by their TCRs and BCRs, understanding how various effector and memory compartments develop.

Besides capturing the transcriptomic and genetic state of individual cells, single-cell RNAseq can also profile antigen specificity by capturing specific oligos that have been conjugated to antigens of interest, providing a high-dimensional readout of the antigen specificity of each immune cell. We have developed multiple tagging strategies for multiple SARS-CoV-2 antigens, which will be used to understand the phenotypic diversity and function of antigen-specific immune cells in high-throughput.

Different immune compartments and different sampling times will be studied, attempting to capture key transitions between transcriptional states, characterizing the transcriptional causes and consequences of functional diversification of the immune responses that drive antibody development, and the establishment of immune memory and long-lasting antibody responses.

Research group

The Murrell lab mixes computational and laboratory expertise to study viruses and our immune responses against them. Currently, the lab is strongly focused on SARS-CoV-2. Besides the PI, the lab currently comprises a postdoc virologist, a wet-lab technician, a posdoc mathematician, a bioinformatician, and a lab manager.

Supplementary information

Key words

Immunology, Virology, Vaccines, Single-cell, SARS-CoV-2

#54 Brain mechanisms underlying detail-focused perception in autism and synesthesia – a twin study.

Type of recruitment
Doctoral student, 4 years

Project title
Brain mechanisms underlying detail-focused perception in autism and synesthesia – a twin study.

Supervisor
Janina Neufeld, Assistant professor
Department of Women's and Children's Health

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Qualifications of applicant
The successful candidate needs to demonstrate excellent written and spoken English skills, very good scientific writing skills in English, strong statistics skills and has a background in Psychology, Cognitive Science or a related field. Further, at least basic knowledge about autism and other neurodevelopmental disorders, brain development and brain imaging techniques is required. The candidate should demonstrate curiosity, critical thinking and the ability to independently come up with ideas, questions and solutions. Knowledge about sensory processing and synesthesia and experience with R (https://www.r-project.org/), brain imaging and programming (e.g. in Python or Matlab) are highly meriting.

Background
Autism Spectrum Disorder (ASD) is a neurodevelopmental condition characterized by social and communication impairments alongside restricted/repetitive patterns of behavior. It is further associated with altered sensory processing including hyper- or hypo-responsiveness to sensory stimuli and a detail-focused attentional style. Interestingly, people with synesthesia, a non-pathological sensory condition where certain sensory inputs (e.g. sounds) lead to additional internal sensations (e.g. color), show a remarkably similar profile of altered perception as observed in ASD, including also a more detail-focused perceptual style. Further, while synesthesia is prevalent in ~4% of the general population, it seems to be more common among people with ASD.

Altered functional connectivity and brain activation patterns, especially in occipital, parietal and prefrontal brain regions, might underlie the more detail-focused processing style in ASD. However, the results are largely inconsistent, due to variability in study designs and a lack of control over confounding variables. Very few autism brain connectivity studies applied a twin design, which enables implicitly controlling for a large number of confounders. Comparing monozygotic (MZ) and dizygotic (DZ) twin pairs further allows estimating the impact of genetic vs environmental influences. Studying ASD and synesthesia in conjunction enables differentiating condition-specific from shared brain alterations.

Research project description

This PhD project will focus on altered brain activation and connectivity associated with detail-focused visual processing in ASD and synaesthesia applying a twin design. The project will build on two ongoing twin studies, the Roots of Autism and ADHD twin Study (RATSS) and the Synesthesia & Autism Twin Study (SATS). In RATSS, 209 twin-pairs and 2 sets of triplets (~15% diagnosed with ASD) have already been assessed. SATS assesses twins discordant for ASD or synesthesia, respectively, and typically developing twins (at least 20 twin pairs per category, total n = 120). The student will be involved in the brain imaging data acquisition for RATSS and SATS, but also have access to the data that have already been acquired before the start of the PhD project.

Study 1 will be a systematic review over fMRI studies using visual detail processing tasks (eg visual search etc.) in autistic and typically developed individuals, with the purpose to generate a systematic overview over the brain mechanisms underlying detail-focused attention during visual processing in ASD and beyond. With help of the supervisors, other academic staff and search experts at the Karolinska Institutet library, the PhD will perform a systematic literature review and meta-analyses, registered in PROSPERO.

In study 2 the aim is to investigate the neural correlates of detail-focused visual processing in ASD for the first time in a twin sample (SATS). After identifying brain activation patterns underlying the disembedding processes in a visual task (the Leuven-Embedded Figured Test), the student will model the functional connectivity analysis between these regions and compare these findings between twins diagnosed with ASD vs their undiagnosed co-twins and TD controls.

Study 3 aims to investigate patterns of altered brain connectivity that are associated with a more detail-focused visual style but occur independently from task performance in a large twin cohort (RATSS). Structural connectivity will be assessed using fiber tractography on DTI data while functional connectivity at rest will be estimated using independent component analysis and time series correlations on RS fMRI data. Connectivity correlates of a detail focused visual style

will then be compared between MZ and DZ twins in order to estimate the genetic influence on them.

Study 4 is identical to study 2 in the design, but assesses a different twin sample (from SATS). Here, twins with synesthesia will be compared to their co-twins and TD twins. In a second step, the student will investigate the overlap of these contrast patterns with the group contrasts from study 2 (ASD>co-twins & ASD>TD) in order to identify the shared and non-shared alterations associated with ASD and synesthesia.

Research group

The Center of Neurodevelopmental Disorders at Karolinska Institutet (KIND), is a competence center focusing on research, development and education, offering regular seminars and large interdisciplinary collaboration network. There is access to all infrastructure necessary to conduct the project.

The main supervisor, Janina Neufeld (PI of SATS) is expert in ASD, synesthesia and brain imaging research and leads the synesthesia research team within KIND. Co-supervisor Sven Bölte (PI of RATSS) is the head of KIND and an internationally recognized ASD expert. The co-supervisors Peter Fransson (Department of Clinical Neuroscience at Karolinska Institutet) is expert in brain imaging (especillay resting state functional connectivity) and co-supervisor Tessa van Leeuwen (Donders Institute for Brain, Cognition and Behaviour, Radboud University Nijmegen, the Netherlands) contributes with her expertise in synesthesia, vision research and brain imaging (effective functional connectivity).

Supplementary information

There are currently three PhD students and one research assistant at KIND who primarily work with the RATSS study, and three research assistants and one external postdoc within the SATS, in addition to the PIs (Sven Bölte and Janina Neufeld). Further, there is a range of clinical and research personnel working with aspects of RATSS and both RATSS and SATS a supported by many national and international (e.g. US, UK, Australia, Germany, the Netherlands) research collaborations.

Key words

Autism, synesthesia, brain imaging, MRI, visual processing, detail focus, connectivity

#55 Crosstalk between mitochondrial dynamics and brain tumor biology

Type of recruitment

Visiting doctoral student, 12 months
Visiting researcher, 12 months

Project title

Crosstalk between mitochondrial dynamics and brain tumor biology

Supervisor

Monica Nistér, Professor senior
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Qualifications of applicant

Background in medical sciences/biomedicine/ molecular biology/biotechnology/life sciences

Experimental skills in basic molecular biology, protein detection, cell culturing, knock-out and knock-down techniques, immunofluorescence and confocal microscopy, measurements of cellular energy metabolism

Fluency in oral and written English

Background

Mitochondria are essential organelles of eukaryotic cells. Although they are originally known as the powerhouse of the cell for supplying cellular energy, it is now accepted that mitochondria virtually are a hub for numerous signaling pathways impacting a variety of cellular processes. Mitochondrial dysfunction has been linked to numerous diseases

Mitochondria are highly dynamic organelles that constantly change their morphology through fusion and fission events, referred to as mitochondrial dynamics, which is controlled by a set of mitochondria-shaping proteins. Mitochondrial dynamics regulates not only the shape of mitochondria, but also mitochondrial function of mitochondria. Although the specific mechanisms involved are far from clear, it has been appreciated that these dynamic morphological transitions of mitochondria govern cell fate decisions and switch cells between life and death. Dysfunction of mitochondrial dynamics has been associated with aging and a variety of human diseases, such as neurodegenerative diseases, diabetes, cardiovascular disease and cancer.

Cancer cells manifest two particular properties distinct from healthy cells. Accumulating data indicate that escaping cell death and using aerobic glycolysis reflect mitochondrial functional abnormalities in cancer.

Research project description

Emerging evidence suggests that abnormal mitochondrial dynamics occurs in cancer, potentially contributing to tumor development by establishing resistance to chemotherapy, aerobic glycolysis and other cellular processes in cancer cells. Increasing evidence suggests that dysregulation of mitochondria-shaping proteins occurs in different types of human cancer such as glioblastoma, leukemia, breast carcinoma and renal cell carcinoma. To better understand the role of mitochondrial dynamics in brain tumor biology, this research plan will involve manipulation of mitochondrial dynamics in human brain cancer cells and glioma stem cells.

Gliomas represent the most frequent form of primary brain tumors in adults. Although it is still unclear whether abnormal mitochondrial dynamics takes place in most human gliomas, there is growing evidence indicating that mitochondrial dynamics plays an important role in brain tumors. For example, we previously showed that the mitochondrial inner membrane protein MTGM (also called Romo1), which is involved in the regulation mitochondrial dynamics, is upregulated in several types of brain tumors. Mutation/deletion of the gene PARK2, a gene that encodes the E3 ubiquitin ligase Parkin, has been reported in glioblastoma and is a regulator of mitochondrial dynamics and mitophagy. Drp1, a key regulator of mitochondrial fission, is involved in hypoxia-induced migration of human glioblastoma U251 cells and plays a role in controlling brain tumor initiating cells. These data implicate that mitochondrial dynamics may represent a therapeutic target for brain tumors.

The cancer stem cell hypothesis suggested that current therapies which are extremely cytotoxic to the bulk of highly proliferative tumor cells fail to kill the relatively quiescent and resistant cancer stem cells (CSCs), thereby allowing these cells to survive and drive tumor recurrence. For this reason, we will explore the sensitivity of several human glioma cell lines to apoptotic and mitophagic stimuli and evaluate the correlation between drug sensitivity and expression levels of the mitochondria-shaping proteins. We will further isolate glioma stem cells (GSCs) from gliomas, and compare the sensitivity to apoptotic and mitophagic stimuli between the isolated GSCs and their original cell population. We will also evaluate potential effects of manipulating mitochondrial dynamics by overexpression and knockdown (shRNA)/knockout (CRISPR/Cas9-based gene editing) techniques on apoptotic resistance, mitophagy, gliosphere formation, self-renewal and differentiation of GSCs. Cell culture, plasmid- and shRNA/siRNA-based transfection, CRISPR/Cas9-based gene editing, western blotting, as well as immunofluorescence and confocal microscopy will be used in this work. We believe that these studies will contribute to a better understanding of the potential roles of dysfunctional mitochondrial dynamics in brain tumor biology.

Research group

Monica Nistér, MD, PhD, professor senior

Jian Zhao, PhD, researcher

Rong Yu, PhD post doc

Min Guo, PhD

Li Yi, visiting PhD student

Supplementary information

Key words

mitochondrial dynamics, cancer, apoptosis, autophagy, oxidative phosphorylation, glycolysis

#56 Development of biomarkers and diagnostics of inflammatory osteolysis

Type of recruitment
Doctoral student, 4 years

Project title
Development of biomarkers and diagnostics of inflammatory osteolysis

Supervisor
Tuomas Näreoja, Assistant professor
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Qualifications of applicant
We are seeking a highly talented and enthusiastic PhD-student with preferrably a background in 3D model development, immunoassay development and bone biology and/or cell biology. Candidates with extensive experience in stem cell research, cell signaling advanced cell culture protocols and experience with single-cell transcriptomics and cell sorting are encouraged to apply. Knowledge in bone remodeling, osteoclastogenesis, OB differentiation OB-OC – coupling and osteocyte cultures is preferable. State-of-the-art experience with high-content imaging, transcriptomics or image analysis is a merit. The successful candidate should be self-motivated and able to keep herself/himself informed on developments of the relevant research field, and also, have excellent interpersonal and communication skills and organizational skills. The candidate must be able to integrate well into the group and the international and multidisciplinary research environment as a whole. Excellent knowledge of spoken and written English is a requirement. The selected candidate will be a part of a team, and collaborate closely with other members of the lab.

Background
Total hip arthroplasty (THA) is a quality of life restoring surgical procedure in orthopedics and annually more than 2 million patients undergo THA worldwide. However, more than 100000 patients annually have to undergo a risky and costly revision surgery due to periprosthetic aseptic osteolysis (PPO) and additionally 25000 more due to periprosthetic joint infections (PJI). This despite continual improvements in surgical technique and implant design. Osteolytic lesions around well-fixed orthopedic implants are both notoriously abundant and difficult to detect and are, 7–14 years after surgery, present in 10-70 % of hips. Moreover, in the absence of diagnosis the condition is impossible to treat. Therefore, it is urgent

for us to figure out the mechanism of inflammatory osteolysis and provide more precise diagnosis and treatment [1-2].

Monocytes and macrophages also play a role in normal bone formation and healing through crosstalk between two cell types [3-5] and the mesenchymal stem cells present in the bone marrow. Proinflammatory M1 phenotype involves in attacking pathogens, while anti-inflammatory M2 phenotype takes part in tissue repair and parasite infection. Up to now, some studies [5] show close interaction between macrophage polarization and inflammatory osteolysis, suggesting that new biomarkers could be found by studying their relationship.

Research project description

This proposal describes how we work on inflammatory osteolysis in molecular level. By using in vitro 3D bone cultured model, we try to identify the biomarkers for diagnostics and potential therapeutic targets.

WP1 Hypothesis: Successful 3D model of bone requires all Ocys, OBs and OCs, but also, loading and niches with different stiffness to support co-cultures. In an in vitro model of female bone remodeling cyclic estrogen stimulation causes cyclic changes in bone remodeling that need to be accounted for. Stimulation a human 3D model of bone with inflammatory cytokines can in short time-span model osteoinflammatory conditions that take months to develop. In WP1 we analyze the secretome of 2D cultured PBMCs and 3D in vitro model with Ocys, OBs and OCs under cyclic estrogen and inflammatory stimulus, and compare these to genetic markers, sera and synovial fluid from known cases of PPO and PJI.

WP2. Studies demonstrate that macrophage activation and subset types play a crucial role in inflammatory osteolysis [3-5]. Immunoregulatory effects of MSCs are triggered by TNF activation of NFB pathway. Hypothesis 2: Preventing the formation of inflammatory OCs and FBGCs, and migration of monocytes to the tissue are viable strategies of treating conditions involving inflammatory bone loss. We characterize monocyte fate under osteoclastogenic, osteoprotective, and diverse inflammatory stimuli and elucidate signaling affecting these processes on single cell and population level. Identify inflammation sustaining cascade, potential biomarkers and find druggable targets that may reverse the self-amplifying cycle of inflammatory osteolysis.

WP3: Hypothesis 3: Signaling between inflammatory OCs, FBGCs and other bone cells involves previously unidentified biomarkers and measuring the secretome of all bone cells enables elucidation of changes in the bone remodeling balance and the balance in pro- and anti-inflammatory signals, which may be used to build ratios of biomarkers. Composite biomarkers, i.e. ratios that describe changes in the balance of inflammatory cytokines and bone remodeling parameters, provide more sensitivity to detecting inflammatory osteolysis than single biomarkers. Composite

biomarkers are less susceptible to individual variation than any single biomarker. They reflect balance and are not sensitive to metabolic activity of the patient. Use ratios that define changes in the balance of inflammation/healing, mineralization/resorption and infection/chronic inflammation. With the ELISA-panel we can diagnose patients presenting discomfort at the implant site before any macroscopic signs of osteolysis are present.

Aim 3A. We will include more cases and, identify possibly interfering conditions. Furthermore, we estimate how do co-morbidities e.g. diabetes, obesity and rheumatoid arthritis affect classification of patients to PJI and PPO groups. 3B. Early diagnosis of implant failure. A cohort with prospective follow-up for 10 years.

Research group

Since 2018, my lab's research is built on three interconnected cornerstones I Further development of an in vitro model of bone, II Fundamental cell biology of osteoclasts (OC) and III Development of serological diagnostics for PPO and PJI. My group belongs to a bone biology research environment consisting of groups Prof. G. Andersson and ass. prof. S. Windahl. I have obtained 950000 € external funding during 2017-2019 as a main applicant, and the KI group is able to support the clinical objectives. I have published 36 original research papers. My research team currently includes 2 postdocs and 2 PhD-students.

A postdoc Talita Stessuk (h-index 9), an expert in development of bone in vitro models, bioprinting and OC biology. A postdoc Janne Koivisto (h-index 8), expert in hydrogel development and 3D cell culture. PhD-student Suchita Desai (defense 2022) expert in development of in vitro models to study bone cells and an exchange PhD-student Haifeng Hu (Shanxi University).

Supplementary information

[1] Trehan SK, et al. HSS Journal. 2018 14(2):148-152.

[2] Deirmengian C et al, Clin Orthop Relat Res. 2014;472(11):3254-3262.

[3] Vi L, et al. J Bone Miner Res. 2015;30(6):1090-1102.

[4] Alexander KA, et al. J Bone Miner Res. 2011;26(7):1517-1532.

[5] Gao XR, et al. Cell Cycle. 2018;17(17):2134-2145.

Key words

Bone biology, cell biology, biomarkers, 3D in vitro model, transcriptomics, in vitro - diagnostics

#57 Identification of regulatory modules and key factors that drive B-cell differentiation

Type of recruitment
Doctoral student, 4 years
Visiting doctoral student, 12 months
Postdoc, 24 months
Visiting researcher, 12 months

Project title
Identification of regulatory modules and key factors that drive B-cell differentiation

Supervisor
Qiang Pan-Hammarström, Professor for clinical immunology
Department of Biosciences and Nutrition

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Phone:
Home page:

Qualifications of applicant
PhD students (4 years) or visiting students (1 year)

The applicant is eligible to apply if he or she has obtained a master's degree in the fields of Medicine, Biology, Genetics, Oncology and Immunology, or related fields, and fulfils all academic entry requirements set by the Karolinska Institutet. Good knowledge of molecular biology, stem cell biology, immunology, genetics, documented experience in cell culture, FACS, the CRISPR/Cas 9 technology or skills in analysing large-scale sequencing data especially ATAC and single cell RNA-seq data, is an advantage.

Postdoc (12-24 months) or Visiting researcher (12 months)

The applicant is eligible to apply if he or she has obtained a PhD in the fields of Medicine, Biology, Stem Cell Biology, Genetics, Bioinformatics, and Immunology, or related fields.

Good knowledge of molecular biology, stem cell biology, immunology, genetics, documented experience in cell culture, FACS, the CRISPR/Cas 9 technology or skills in analysing large-scale sequencing data especially ATACseq and single cell RNA-seq data, is an advantage.

The applicants for all positions should be talented and highly motivated students or researchers who are able to work within a team environment. Furthermore, the candidate should possess excellent communicating and writing skills in English.

Background

B-cells play an important role in adaptive immunity against pathogens through the production of antibodies. B-cells develop from hematopoietic stem cells in the bone marrow in a stepwise process during which they generate a broad repertoire of unique B-cell receptors through a somatic recombination process referred to as V(D)J recombination.

After the first phase of precursor B-cell development, antigen-dependent peripheral B-cell differentiation takes place in blood and peripheral lymphoid organs. Two additional immunoglobulin gene diversification processes occur in peripheral lymphoid organs: class switch recombination (CSR) and somatic hypermutation (SHM). CSR allows a previously rearranged Ig heavy-chain variable domain to be expressed in association with a different constant region, leading to production of different isotypes, where SHM may increase the Ig affinity by accumulation of mutations in the ariable domain encoding genes.

While our knowledge about B-cell development in mice is relatively advanced, B-cell development in humans is less well-characterized. The current markers and B-cell subset definitions are imprecise and little is known about the B-cell subset distribution and clonal evolution in various secondary lymphoid organs.

Research project description

A number of subprojects will be included in this proposal:

1. Characterization of B-cell subsets from bone marrow and secondary lymphoid tissues

We plan to make a systematic analysis of B-cell subpopulations in the bone marrow, peripheral blood and secondary lymphoid organs in normal individuals, using unbiased, single-cell profiling approaches. Characterization of the different subpopulations according to their transcriptional profiles and clonalities will be performed subsequently.

2. Recapture the B cell development process by inducible pluripotent stem cells

We plan to develop the method for differentiation of iPSC cells to early stage of B cells, recapturing the B-cell development process in vitro. iPSCs will be generated from both normal individuals and patients with inborn errors of immunity. In addition to monitoring the cell differentiation process by cell surface staining and single cell RNA-seq, V(D)J recombination and BCR repertoires will also be studied.

3. Identification of critical transcription factors for B-cell development using unbiased CRISPR-based activation screen system

We plan to develop an unbiased activation screen system to identify transcription factors that are crucial for the for B-cell lineage differentiation as well as for late B cell development, including the CSR processes. The identified key factors will be further validated by CROP-seq and other relevant functional studies.

Research group

https://ki.se/en/bionut/we-study-human-b-cells-in-health-and-disease-qiang-pan-hammarstrom

Supplementary information

Key words

B cell, antibody gene diversification, iPSC cells, CRISPR screen, inborn errors in immunity

#58 Iron metabolism and ferroptosis in calcific aortic valve disease.

Type of recruitment
Doctoral student, 4 years

Project title
Iron metabolism and ferroptosis in calcific aortic valve disease.

Supervisor
Sven-Christian Pawelzik,
Department of Medicine, Solna

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Phone: +46 73 717 09 97
Home page: https://twitter.com/TransCardio

Qualifications of applicant
Applicants to this position must hold (or are expected to hold at the start of the PhD period) a Master's degree in molecular life sciences, medicine, or related disciplines. The applicants should be highly motivated and able to work independently and in a structured manner. Previous research experience, especially expertise in basic cellular and molecular biology techniques, cell culture, flow cytometry, immunohistochemistry, and animal work, is advantageous. Additional experience with bioinformatics and competence to analyze omics data is beneficial. Excellent language skills in verbal and written English are a requirement. The successful applicant should be a creative and team-minded person with a strong sense of responsibility, who can constructively interact within an international research team.

Background
Calcific aortic valve disease (CAVD) is the most common valvular heart disease, characterized by valvular sclerosis that may advance to aortic stenosis (AS). AS causes a progressive obstruction of the aortic valve (AV) due to inflammation, extracellular matrix (ECM) remodeling, and calcification of the valve leaflets. If untreated, AS may lead to myocardial hypertrophy, left ventricle dilation, heart failure, and mortality. There is currently no other treatment available but replacement of the diseased tissue with a prosthetic valve.

AV tissue consists of two principle cell types, a single layer of valvular endothelial cells (VEC) on each side of the valve, and valvular interstitial cells (VIC), which make up the majority of the tissue and determine the structure and function of the AV.

Osteoblastic differentiation of VIC is considered a key step in CAVD development. Osteoblast-like VIC promote the pathological remodeling of the valvular ECM and subsequent tissue calcification.

Intra-leaflet hemorrhage due to neovessel formation and extravasation of blood into the AV tissue is common in CAVD and associated with a rapid progression of the disease. Recent evidence suggests that the accumulation of iron due to intra-leaflet hemorrhage accelerates valvular calcification, but the pathophysiological mechanism of iron accumulation in the AV remains largely unexplored.

Research project description

We have previously shown that iron can be taken up by VIC in a pro-inflammatory environment. Iron uptake leads to increased proliferation of VIC but a reduced production of elastin. Furthermore, iron uptake by VIC results in substantial changes in the expression of genes involved in iron metabolism. It significantly increases the expression levels of the iron storage protein ferritin, the scavenger receptor for the hemoglobin-haptoglobin complex CD163, and the heme oxygenase HMOX1. Calcified AV tissue expresses lower levels of the iron exporter ferroportin-1 than non-calcified AV tissue. Iron metabolism may thus play an important mechanistic role in CAVD progression.

Iron plays a pivotal role in a recently discovered form of regulated cell death termed ferroptosis. At biochemical, morphological, and genetic level, ferroptosis is distinct from other forms of regulated cell death. A hallmark of ferroptosis is a cell morphology with intact nuclei, small mitochondria displaying ruptured outer membranes, and the absence of membrane blebbing. Ferroptosis is triggered by oxidative stress, which can be generated by iron via the Fenton reaction and has been shown to contribute to CAVD.

The aim of this project is to establish a role for ferroptosis in human CAVD, to elucidate biochemical pathways involved in ferroptosis in correlation to disease burden and cell calcification, respectively, and to identify molecular targets that can be exploited to interfere with ferroptosis.

We will use bioinformatics tools in combination with an established global transcriptomics databank of human AV tissue to study pathways of iron metabolism and ferroptosis in CAVD and to identify connected signaling pathways. We will furthermore investigate human AV tissue for the expression of key ferroptosis

proteins using immunohistochemistry and for morphological signs of ferroptosis using electron microscopy. Using various pharmacological intervention strategies, we will dissect the ferroptosis pathway on a molecular level in primary cultures of isolated VIC under control and osteogenic conditions. In a mouse model of hemodynamic stress-induced CAVD, we will investigate the effect of anti-ferroptosis treatment on disease burden as assessed by echocardiography, histology, and biochemical analysis.

There is a great need to develop a medication treatment of CAVD to a delay disease onset, attenuate its progression, or even reverse signs of the disease. This exploratory project has the potential to explore a novel pathway related to CAVD and to demonstrate in a proof-of-concept study its capacity to develop drugs that interfere with the underlying molecular mechanism.

Research group

Our research group belongs to the Cardiovascular Research Unit of the Dept of Medicine Solna (MedS) and is a productive and innovative team of 6-8 members, headed by Magnus Bäck, MD, PhD, Prof. of Cardiology. We have longstanding expertise in cardiovascular and translational research and are internationally recognized experts in the field of CAVD. The main supervisor in this project, Sven-Christian Pawelzik, PhD, has extensive experience in cardiovascular and inflammation research.

Our laboratory is located in the NEO research building, a newly built hub for translational research on Karolinska Institute's Flemingsberg campus, in direct proximity to Karolinska University Hospital Huddinge. It is equipped with all necessary resources to support this project. We actively collaborate with groups both throughout the clinical and the academic branches of Karolinska Institute, including research teams located in the Center for Molecular Medicine (CMM), Bioclinicum, and Biomedicum.

Supplementary information

Key words

Calcific aortic valve disease, aortic stenosis, ferroptosis, iron, inflammation

#59 Modelling mRNA life from synthesis to decay

Type of recruitment
Visiting doctoral student, 6 months

Project title
Modelling mRNA life from synthesis to decay

Supervisor
Vicent Pelechano, Assistant professor/Senior researcher
Department of Microbiology, Tumor and Cell Biology

E-mail: vicente.pelechano.garcia@ki.se
Phone: +46 72 856 49 04
Home page: http://pelechanolab.com

Qualifications of applicant
We aim to recruit visiting PhD student (6 months). The candidate will have the opportunity to learn and develop a variety of computational and experimental genome-wide tools. Applicants to this position should possess adequate experience in computational biology, molecular biology, genomics or RNA biology. Preferred experience also includes familiarity with NGS data handling eukaryotic transcription and RNA degradation. A strong interest in interdisciplinary technology development, and novel and creative thinking abilities are essential. 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.

Background
One of the biggest challenges in biology is to understand how apparently identical cells respond differently to the same stimulus. Most of our knowledge of transcriptional regulation is based on the study of mRNA expression level changes. However, the abundance of a mRNA is not enough to understand its functional consequence. Each gene expresses multiple transcript isoforms using alternative promoters, exons and terminators. In some cases, those alternative isoforms have divergent, or even antagonistic, consequences. In addition to transcription, gene expression is also shaped by translation and mRNA degradation. Translation is required for protein production and is often miss regulated during disease development. mRNA degradation is essential for cellular adaptation as, by controlling the turnover of mRNA molecules, it allows remodelling of gene

expression. In the last years we have discovered that translation and mRNA degradation are highly connected and often co-regulated in a intricated way that we do not fully understand. With the development of high-throughput approaches, now we have tools to start dissecting the functional relevance of those subtle variations (i.e., telling apart “noise” from functional relevant differences). To understand how gene expression complexity contributes to divergent cellular phenotypes, it is necessary to study from the transcription process to the production of functional proteins.

Research project description

To deliver an integrated view of how the intrinsic complexity of gene expression contributes to cellular adaptation, our group combines the development of novel genome-wide tools with the investigation of transcription and post-transcriptional regulation. By following the life of mRNAs from transcription to decay we aim to improve our understanding of gene expression regulation in health and disease. We are particularly interested in understanding the crosstalk between translation and mRNA decay. mRNA translation is a highly regulated process with multiple layers of control. Although translation initiation has been considered the rate-limiting step, and thus has been more intensively studied, recent evidence suggests that translation elongation and mRNA degradation is also highly regulated. Our lab has shown that mRNA degradation is often co-translational, where a 5’-3’ exonuclease follows the last translating ribosome [1]. Following this initial discovery, we have now developed an improved experimental [2] and computational [3] approaches that facilitates the investigation of this process across organism. The use of 5’P degradome sequencing offers thus an ideal window to study factors that control ribosome-dependent mRNA stability.

This project will focus on the development of a genome-wide computational model to integrate the different steps of gene expression, from mRNA synthesis, to processing, translation and mRNA decay. The candidate will integrate NGS data from multiple sources combining RNA-Seq and 5PSeq with RNA metabolic labelling. We will use the derived model to predict regulatory features controlling RNA life in Saccharomyces cerevisiae. This work will reveal novel feature controlling the balance between translation-independent and co-translation mRNA decay. By applying this model to a dynamics system (i.e. stress), we will also improve our knowledge regarding the dynamic remodelling of the transcriptome. The candidate will use the developed mathematical model to make predictions regarding gene expression regulation. Those predictions will be experimentally validated in collaboration with other members of our team.

A quantitative dissection of mRNA life in budding yeast will offer new perspectives regarding gene expression that will be used to understand better gene expression in pathogenic fungi and humans.

1. Pelechano, V. *, Wei, W*. & Steinmetz, L. M. Widespread Co-translational RNA Decay Reveals Ribosome Dynamics. Cell 161, 1400–1412 (2015).

2. Zhang, Y. & Pelechano, V. High-throughput 5'P sequencing reveals environmental regulated ribosome stalls at termination level. bioRxiv 2020.06.22.165134 (2020) doi:10.1101/2020.06.22.165134.

3. Nersisyan, L., Ropat, M. & Pelechano, V. Improved computational analysis of ribosome dynamics from 5'P degradome data using fivepeseq. bioRxiv 2020.01.22.915421 (2020) doi:10.1101/2020.01.22.915421.

Research group

Our lab is located at the Science for Life Laboratory (https://www.scilifelab.se). SciLifeLab is equipped with state-of-the-art instrumentation and core facilities for NGS and high-throughput biology, and thus is the ideal place to develop the project we propose. Our lab is composed by 4 PhD students at different stages of their education that combine experimental and computational work, 6 postdoctoral researchers 2 technicians and a senior lab manager with expertise on RNA biology, bioinformatics, yeast biology, clinical genomics and epigenetics (http://pelechanolab.com). This will provide the candidate with additional support, practical supervision and opportunities for collaboration.

Supplementary information

The candidate will work in strong collaboration with the group of our colleague Prof. Wei Wu (CAS Key Laboratory of Computational Biology and Shanghai Institutes for Biological Sciences, http://www.picb.ac.cn/weiLab/index.php). The candidate is expected to participate in our ongoing collaboration funded by STINT and NSFC: "Joint China-Sweden Mobility Programme: Transcriptome complexity in human disease".

Key words

RNA-Seq, mathematic modelling, Computational Biology, mRNA life, bioinformatics

#60 Genome-wide investigation of mRNA life.

Type of recruitment
Visiting researcher, 3 months

Project title
Genome-wide investigation of mRNA life.

Supervisor
Vicent Pelechano, Assistant professor/Senior researcher
Department of Microbiology, Tumor and Cell Biology

E-mail: vicente.pelechano.garcia@ki.se
Phone: +46 72 856 49 04
Home page: http://pelechanolab.com

Qualifications of applicant
We aim to recruit a visiting researcher (3 months) with a PhD in a relevant area. The candidate will have the opportunity to learn and develop a variety of computational and experimental genome-wide tools. Applicants to this position should possess adequate experience in computational biology, molecular biology, genomics or RNA biology. A strong interest in interdisciplinary technology development, and novel and creative thinking abilities are essential. 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.

Background
One of the biggest challenges in biology is to understand how apparently identical cells respond differently to the same stimulus. Most of our knowledge of transcriptional regulation is based on the study of mRNA expression level changes. However, the abundance of a mRNA is not enough to understand its functional consequence. Each gene expresses multiple transcript isoforms using alternative promoters, exons and terminators. In some cases, those alternative isoforms have divergent, or even antagonistic, consequences. In addition to transcription, gene expression is also shaped by translation and mRNA degradation. Translation is required for protein production and is often miss regulated during disease development. mRNA degradation is essential for cellular adaptation as, by controlling the turnover of mRNA molecules, it allows remodelling of gene expression. In the last years we have discovered that translation and mRNA degradation are highly connected and often co-regulated in a intricated way that

we do not fully understand. With the development of high-throughput approaches, now we have tools to start dissecting the functional relevance of those subtle variations (i.e., telling apart “noise” from functional relevant differences). To understand how gene expression complexity contributes to divergent cellular phenotypes, it is necessary to study from the transcription process to the production of functional proteins.

Research project description

To deliver an integrated view of how the intrinsic complexity of gene expression contributes to cellular adaptation, our group combines the development of novel genome-wide tools with the investigation of transcription and post-transcriptional regulation. By following the life of mRNAs from transcription to decay we aim to improve our understanding of gene expression regulation in health and disease. We are particularly interested in understanding the crosstalk between translation and mRNA decay. mRNA translation is a highly regulated process with multiple layers of control. Although translation initiation has been considered the rate-limiting step, and thus has been more intensively studied, recent evidence suggests that translation elongation and mRNA degradation is also highly regulated. Our lab has shown that mRNA degradation is often co-translational, where a 5’-3’ exonuclease follows the last translating ribosome [1]. Following this initial discovery, we have now developed an improved experimental [2] and computational [3] approaches that facilitates the investigation of this process across organism. The use of 5’P degradome sequencing offers thus an ideal window to study factors that control ribosome-dependent mRNA stability.

This project will focus on the development of a genome-wide computational and experimental model to integrate the different steps of gene expression, from mRNA synthesis, to processing, translation and mRNA decay. The candidate will learn experimental technologies required to generate and integrate NGS data from multiple sources combining RNA-Seq and 5PSeq with RNA metabolic labelling. We will use the derived model to predict regulatory features controlling RNA life in Saccharomyces cerevisiae. This work will reveal novel feature controlling the balance between translation-independent and co-translation mRNA decay. By applying this model to a dynamics system (i.e. stress), we will also improve our knowledge regarding the dynamic remodelling of the transcriptome. The candidate will combine nolve experimental insights with mathematical models to make predictions regarding gene expression regulation. Those predictions will be experimentally validated in collaboration with other members of our team.

A quantitative dissection of mRNA life in budding yeast will offer new perspectives regarding gene expression that will be used to understand better gene expression.

1. Pelechano, V. *, Wei, W*. & Steinmetz, L. M. Widespread Co-translational RNA Decay Reveals Ribosome Dynamics. Cell 161, 1400–1412 (2015).

2. Zhang, Y. & Pelechano, V. High-throughput 5'P sequencing reveals environmental regulated ribosome stalls at termination level. bioRxiv 2020.06.22.165134 (2020) doi:10.1101/2020.06.22.165134.

3. Nersisyan, L., Ropat, M. & Pelechano, V. Improved computational analysis of ribosome dynamics from 5'P degradome data using fivepeseq. bioRxiv 2020.01.22.915421 (2020) doi:10.1101/2020.01.22.915421.

Research group

Our lab is located at the Science for Life Laboratory (https://www.scilifelab.se). SciLifeLab is equipped with state-of-the-art instrumentation and core facilities for NGS and high-throughput biology, and thus is the ideal place to develop the project we propose. Our lab is composed by 4 PhD students at different stages of their education that combine experimental and computational work, 6 postdoctoral researchers 2 technicians and a senior lab manager with expertise on RNA biology, bioinformatics, yeast biology, clinical genomics and epigenetics (http://pelechanolab.com). This will provide the candidate with additional support, practical supervision and opportunities for collaboration.

Supplementary information

The candidate will work in strong collaboration with the group of our colleague Prof. Wei Wu (CAS Key Laboratory of Computational Biology and Shanghai Institutes for Biological Sciences, http://www.picb.ac.cn/weiLab/index.php). The candidate is expected to participate in our ongoing collaboration funded by STINT and NSFC: "Joint China-Sweden Mobility Programme: Transcriptome complexity in human disease".

Key words

RNA-Seq, genomics, gene expression, mRNA life, bioinformatics

#61 Transcriptional complexity and RNA metabolism as a readout for personalised medicine.

Type of recruitment

Visiting doctoral student, 6 months

Project title

Transcriptional complexity and RNA metabolism as a readout for personalised medicine.

Supervisor

Vicent Pelechano, Assistant professor/Senior researcher
Department of Microbiology, Tumor and Cell Biology

E-mail: vicente.pelechano.garcia@ki.se
Phone: +46728564904
Home page: http://pelechanolab.com

Qualifications of applicant

We aim to recruit visiting PhD student (6 months). The candidate will have the opportunity to learn and develop a variety of computational and experimental genome-wide tools. Applicants to this position should possess adequate experience in computational biology, molecular biology, genomics or RNA biology. Preferred experience also includes familiarity with NGS data handling eukaryotic transcription and RNA degradation. A strong interest in interdisciplinary technology development, and novel and creative thinking abilities are essential. 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.

Background

One of the biggest challenges in biology is to understand how identical genetic information encoded in the genome generates diversity between cells and tissues. Gene expression is the fundamental process whereby genetic information is expressed to control cellular identity and plasticity; defects in this process have been associated with numerous diseases. To adapt to changes in the environment cells and organism must alter their gene expression program, often involving changes in RNA abundance. However, in recent years, our view of RNA has markedly changed, from regarding these molecules solely as intermediates of genetic information to appreciating their variety of functions that are independent

of their protein-coding potential. The development of high-throughput approaches has revealed pervasive transcription in all genomes that have been investigated so far. This has uncovered a highly interleaved transcriptome organization that involves thousands of coding and non-coding RNAs and has challenged our traditional definitions of genes and functional regions of the genome.

Research project description

Our group has developed a variety of genome-wide approaches to study gene expression, and to improve clinical analysis. We investigate the complexity of overlapping human transcript isoforms simultaneously sequencing both the 5' and 3' ends of each RNA molecule (TIF-Seq)[1]. We have now improved our published approach to make it suitable for the study of complex mammalian genomes (TIF-Seq2) [2]. Our work in Chronic Myeloid Leukaemia (CML) has identified many "transcriptionally fused" transcripts (conjoined) with potential to produce fused proteins and to rewire gene expression regulation. Those novel transcripts are present both in commonly used cell lines (K562) and patient cohorts. However, we do not know up to what degree those conjoined isoforms are associated with disease progression and could be use as biomarkers. In additions to the study of the functional consequences of transcriptional complexity, our group is also interested in understanding the control of RNA degradation. We have previously showed the widespread existence of co-translational mRNA degradation in eukaryotes and how that process allows studying ribosome dynamics by sequencing mRNA degradation intermediates (5P-Seq) [3-5].

As starting point for this project, we hypothesize that signatures of full-length and "in degradation" mRNA would be useful indicators to report the physiological status of the cells, and thus potentially help with patient stratification. The selected candidate will combine the use of TIF-Seq2 with long-read sequencing approaches and RNA degradome sequencing to investigate the functional consequences of transcriptome complexity. The candidate will study both cellular systems as well as clinical samples. Special focus will be placed on the development of novel computational tools to investigate the transcriptional complexity in human cells.

1. Pelechano V*, Wei W*, Steinmetz LM. Extensive transcriptional heterogeneity revealed by isoform profiling. Nature. 2013 May 2;497(7447):127-31

2. Wang J, Li B, Marques S, Steinmetz LM, Wei W, Pelechano V. TIF-Seq2 disentangles overlapping isoforms in complex human transcriptomes [published online ahead of print, 2020 Aug 20]. Nucleic Acids Res. 2020;gkaa691. doi:10.1093/nar/gkaa691

3. Pelechano, V. *, Wei, W*. & Steinmetz, L. M. Widespread Co-translational RNA Decay Reveals Ribosome Dynamics. Cell 161, 1400–1412 (2015).

4. Zhang, Y. & Pelechano, V. High-throughput 5'P sequencing reveals environmental regulated ribosome stalls at termination level. bioRxiv 2020.06.22.165134 (2020) doi:10.1101/2020.06.22.165134.

5. Nersisyan, L., Ropat, M. & Pelechano, V. Improved computational analysis of ribosome dynamics from 5'P degradome data using fivepeseq. bioRxiv 2020.01.22.915421 (2020) doi:10.1101/2020.01.22.915421.

Research group

Our lab is located at the Science for Life Laboratory (https://www.scilifelab.se). SciLifeLab is equipped with state-of-the-art instrumentation and core facilities for NGS and high-throughput biology, and thus is the ideal place to develop the project we propose. Our lab is composed by 4 PhD students at different stages of their education that combine experimental and computational work, 6 postdoctoral researchers 2 technicians and a senior lab manager with expertise on RNA biology, bioinformatics, yeast biology, clinical genomics and epigenetics (http://pelechanolab.com). This will provide the candidate with additional support, practical supervision and opportunities for collaboration.

Supplementary information

The candidate will work in strong collaboration with the group of our colleague Prof. Wei Wu (CAS Key Laboratory of Computational Biology and Shanghai Institutes for Biological Sciences, http://www.picb.ac.cn/weiLab/index.php). The candidate is expected to participate in our ongoing collaboration funded by STINT and NSFC: "Joint China-Sweden Mobility Programme: Transcriptome complexity in human disease".

Key words

RNA-Seq, transcript isoforms, Computational Biology, mRNA life, bioinformatics

#62 Dynamic Changes in Functional Brain Connectivity over the course of Alzheimer's Disease

Type of recruitment
Postdoc, 24 months

Project title
Dynamic Changes in Functional Brain Connectivity over the course of Alzheimer's Disease

Supervisor
Joana Pereira, Assistant Professor
Department of Neurobiology, Care Sciences and Society

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Home page: https://staff.ki.se/people/joaper

Qualifications of applicant
The ideal candidate should have the following qualities:

- A PhD in neuroimaging, computational science, engineering, physics, medicine, statistics, neuropsychology or a related field;

- Experience in statistical techniques, programming, or scripting;

- Experience with functional magnetic resonance imaging, diffusion tensor imaging, positron emission tomography or other neuroimaging techniques;

- Clinical or research experience with aging and/or neurodegenerative disorders;

- Good writing and communication skills in English;

- Good record of scientific publications.

Background
Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the accumulation of toxic proteins in the brain such as amyloid and tau. There is growing evidence showing that the accumulation of these proteins damage brain connectivity in AD by decreasing the strength of functional connections between the anterior and posterior cingulate as well as other areas of the default-mode network. To this date, no studies have provided a reliable brain connectivity marker

to predict progression to AD. This could be due to the fact that current methods analyze brain connectivity by assuming it is a constant process that does not change over time.

Research project description

The aim of this project is to apply new methods that analyze brain connectivity as a highly dynamic process across different stages of AD. This will be performed by combining resting state functional magnetic resonance imaging with graph theory methods in different cohorts of patients and healthy controls. Once the dynamic brain network changes have been identified, their relationship with amyloid, tau and cognitive dysfunction will be assessed. In addition, it will also be possible to apply machine-learning algorithms in this project as well as combine the data with anatomical brain connectivity measures derived from diffusion tensor imaging.

Research group

I currently lead a research team of 1 PhD student and 2 Postdocs, and I am also the co-supervisor of 5 PhD students at Karolinska Institute and the University of Gothenburg. My team is working with brain connectivity measures derived from different neuroimaging techniques in patients with Alzheimer's disease and Parkinson’s disease. Our current projects are focused on the assessment of network topology in different disease stages as well as their relationship with biomarkers derived from the cerebrospinal fluid and clinical measures. In addition, I have a large network of collaborators in Sweden and abroad.

Supplementary information

Key words

Brain Connectivity, Alzheimer’s disease, Neuroimaging, Graph theory, Machine learning

#63 Adverse outcomes in offspring of parents with psychiatric disorders: A population-based register study

Type of recruitment
Doctoral student, 4 years

Project title
Adverse outcomes in offspring of parents with psychiatric disorders: A population-based register study

Supervisor
Erik Pettersson, Senior Researcher
Department of Medical Epidemiology and Biostatistics

E-mail: erik.pettersson@ki.se
Phone: +46 76 009 24 55
Home page: https://staff.ki.se/people/erpett

Qualifications of applicant
Qualifications include an interest or background in psychiatry, psychology, public health, epidemiology, causal inference, or statistics. Experience with (logistic/probit) regression, survival analysis, factor analysis, structural equation modeling, family-based studies, and fixed effects regression or within-between analysis is useful. It is also helpful to have experience using softwares such as SAS, R, Stata, OpenMx, lavaan, or Mplus.

Background
Because mental health problems are so prevalent, many offspring are exposed to parents with psychiatric disorders. A population-based survey study estimated that 12 percent of Canadian children, corresponding to over half a million, live with a parent with a psychiatric disorder. This is important because children exposed to parents with mental health problems not only display a greater degree of mental health problems, but also have lower scores on intelligence tests and are even at increased risk of dying in childhood and young adulthood.

Nevertheless, past research is limited in three ways. First, many studies have relied on smaller self-report samples, which can lead to low precision and recall bias. Second, most studies have explored only a single disorder among parents and a single outcome in the offspring at a time, even though comorbidity is the norm rather than exception in psychiatry. Third, many studies have failed to account for

potentially important unobserved confounders, including genetics and shared environmental factors.

The goal of this project is to examine a wide range of adverse outcomes in offspring of parents with psychiatric disorders. We will rely on Swedish population registers to derive precise estimates while minimizing recall bias. Furthermore, we will fit a general factor model to the offspring outcomes to separate common from unique aspects, and adjust for potential unmeasured confounding using a children-of-siblings framework.

Research project description

The exposures are psychiatric disorders among parents extracted from the National Patient register, which captures all inpatient admissions since 1973 and outpatient admissions since 2001. We will include schizophrenia, bipolar disorder, depression, anxiety, substance abuse, and alcohol misuse.

The outcomes are extracted from various Swedish registers, and include psychiatric disorders, suicide, injuries due to accidents, prescription of psychiatric medication (e.g., stimulants, antipsychotics, antidepressants, etc.), income, social welfare recipiency, unemployment, general intelligence test scores, junior high school grade point average, intellectual disability, criminal victimization, and criminal convictions. Relying on these exposures and outcomes, the goal of this project is to answer four research questions:

Research question 1: What are the associations between parent psychopathology and offspring adverse outcomes?

To address this question, we will regress each offspring adverse outcome onto each parental psychiatric disorder. This will allow for identifying whether any psychiatric disorder in the parents is particularly problematic, and also if any outcome is especially susceptible to parental mental illness.

Research question 2: Do these associations remain after adjusting for unmeasured confounds (genetic or shared environmental) within families?

To address this question, we will fit the same model as above, but in a fixed effects regression format using a children-of-siblings design. If the associations were to remain after adjusting for unmeasured time-constant confounds shared within

families, then that would indicate that treatment of parental psychiatric disorders might alleviate offspring adverse outcomes.

Research question 3: Are the associations between parent psychopathology and offspring adverse outcomes attributable to general comorbidity?

To address this, we will fit a general factor model to capture both common and unique aspects of the adverse outcomes in the offspring, and regress this factor model on the exposures. If there are associations with the common factor, then that would indicate that the risk is broad rather than specific. If, on the other hand, there are associations with the unique factors, then that might highlight potential pathways shared by only a subset of the outcomes.

Research question 4: Do the associations with the general factor model remain after adjusting for unmeasured confounds (genetic or shared environmental) within families?

To address this, we will fit the same model as above, but in a fixed effects regression format using a children-of-siblings design. If the associations remain after adjusting for unmeasured time-constant familial confounds, that would indicate that treatment might alleviate common and/or unique aspects of the adverse outcomes.

Research group

The main supervisor, Researcher Erik Pettersson, combines multivariate techniques and family-based causal inference designs within a structural equation modeling framework to study the general factor of psychopathology and its etiology. He has published such papers as first author in high impact outlets such as World Psychiatry, Molecular Psychiatry, and JAMA Psychiatry.

Co-supervisor Professor Paul Lichtenstein is leading world expert on psychiatric epidemiology. He has extensive experience using the Swedish population registers to apply family-based designs to rule out unmeasured confounds. He has published in high impact journals such as JAMA, Lancet, and the New England Journal of Medicine as the lead author.

Supplementary information

Key words

Psychiatric epidemiology

Family-based causal inference designs, Mental health problems, Psychiatric disorders, Psychiatric comorbidity, General factor of psychopathology (p-factor)

#64 Investigation of risks inherent to assisted reproductive technologies in clinical and experimental studies

Type of recruitment
Doctoral student, 4 years
Postdoc, 24 months

Project title
Investigation of risks inherent to assisted reproductive technologies in clinical and experimental studies

Supervisor
Kenny A. Rodriguez-Wallberg, Associate professor in Obstetrics and Gynecology and Lecturer in Reproductive Oncology
Department of Oncology-Pathology

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Qualifications of applicant
The applicant for the PhD position must hold (or expected to hold in 2021) a Bachelor in Medicine (major) with additional education (residency or master) in Obstetrics and Gynecology.

The applicant should have:

Clinical experience in obstetrics and gynecology

Laboratory experience with cell lines culture

Experience with molecular biology techniques , qPCR, DNA isolation, Western Blot, Immunofluoresecence, immunohistochemistry.

Experience with microscopy/histology

Experience with enzyme activity determination

Knowledge of diagnostic clinical and molecular methods used in early pregnancy

Interest in infertility and assisted reproductive techniques

For the postdoc position the applicant should have training in clinical or experimental embryology and assisted reproductive technologies including micromanipulation of gametes and embryos.

Background

Our research team is dedicated to the investigation of infertility, fertility preservation strategies and fertility treatments and the impact of clinical variables and interventions using assisted reproductive techniques on relevant clinical outcomes.

Our research activity is clinically oriented, and our projects are integrated into the clinical work, aiming at answering questions that can improve the counselling of patients and the quality of healthcare, and increase the efficacy and safety of medically-assisted reproductive treatments and medical interventions aimed at fertility preservation.

The research team accounts with multidisciplinary expertise and a laboratory for translational fertility preservation at Karolinska Institutet. Our projects currently encompass clinical, epidemiological and translational research.

https://ki.se/en/onkpat/research-team-kenny-rodriguez-wallberg

Research project description

Epidemiological research indicates that medically assisted reproductive treatments may be associated to an increased risk of pregnancy and neonatal complications. The role of infertility can not be ruled out in most of the studies and the use of specific methods involved in fertility treatments, such as the use of frozen thawed embryos or embryos at blastocyst stage seem to be associated with specific elevated risks.

In this project, clinical epidemiological and experimental research is planned to investigate these risks.

The doctoral project will focuse on:

1) the long-term follow-up of children conceived through assisted reproductive treatment in a clinical cohort

2) the investigation of differences in growth and development among children conceived through assisted reproduction vs naturally conceived children

3) molecular changes detected in embryos - experimental setting

The postdoctoral project will focus on experimental embryology to investigate changes in protein profile expression at different stages of development.

Research group

Our research team belong to the larger research group Jonas Bergh at Karolinska Institutet.

The Research Team Kenny Rodriguez-Wallberg includes 4 PhD with MD degree and one with major in pharmacology. There are 8 postdocs including 7 clinical postdocs and one molecular biologist.

Supplementary information

Key words

infertility, assisted reproductive technology, embryology, clinical outcome, experimental study, pregnancy, oocytes, fertilization, embryos

#65 Immunometabolic mechanisms in human and murine models of mitochondrial dysfunction

Type of recruitment

Doctoral student, 4 years

Project title

Immunometabolic mechanisms in human and murine models of mitochondrial dysfunction

Supervisor

Joanna Rorbach, Assistant professor
Department of Medical Biochemistry and Biophysics

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Home page:

Qualifications of applicant

Highly motivated, creative and curious students with an interest in molecular biology and immunology are encouraged to apply. The candidate should be interested in understanding fundamental cellular mechanisms and show a willingness to develop their own research questions. The ability to work well in the team environment is a prerequisite.

Applicants should hold a masters' degree (or equivalent) in biology, biochemistry, chemistry or another relevant life science. Excellent laboratory skills in molecular biology are required, with experience in the area of immunology being advantageous.

Background

A growing number of findings highlight the crucial role of mitochondria as signalling organelles dictating immunological fate. Over the past five years, studies of the role of mitochondrial metabolism in the immune system have been undergoing a much-needed renaissance, leading to the emergence of immunometabolism field. Indeed, recent work has shown that complex interactions between several metabolic pathways are essential for T-cell activation, differentiation and memory formation, B-cell and dendritic cell activation macrophage polarization, and inflammasome activation. Understanding these pathways, and manipulating cellular metabolism, may therefore, be beneficial when it comes to enhancing or tempering immunity. Indeed, novel immunotherapeutics hold much promise as interventions for a range of complex human disorders - such as cancer, obesity, and infectious and autoimmune diseases. However, considering the emerging importance of

immunometabolism, surprisingly little is yet known about the effects of primary mitochondrial defects on human immunity.

Research project description

The objective of this research is to understand how mitochondrial deficiencies affect immune system function, in humans. To do this, we will employ cutting-edge methodologies (including mass cytometry and transcriptomics) to delineate with unparalleled resolution any defects present in haematopoietic subsets from the peripheral circulation of Primary Mitochondrial Disorders patients. These approaches will be followed by functional studies, including modelling any observed phenotypes in murine models.

Results arising from this study could have important clinical implications for determining the immunological capacity/susceptibility of PMD patients, especially as efforts to provide quantitative metrics of immunity are entering the clinic. Moreover, a description of these processes will yield further insight into the emerging field of immunometabolism and will potentially open new avenues for immunotherapies.

The specific objectives of the project are:

1. To investigate the quantitative differences between different sub-populations of immune cells in the peripheral blood of PMD patients, compared to healthy controls.

2. To characterise the activation and differentiation capacities of purified immune subsets isolated from mitochondrial disease patients.

3. To carry out analyses of immunological phenotypes in mouse models of mitochondrial dysfunction, validating and extending results arising from our human studies.

Research group

The doctoral study will be placed in the laboratory of Joanna Rorbach that comprises 3 PhD students and 3 postdoctoral scientists. The laboratory is embedded in the Division of Molecular Metabolism, consisting of 3 research groups. Currently, the division includes 7 PhD students and 15 postdocs, with administrative and laboratory assistance from two scientific coordinators and two research assistants. All three research groups investigate mitochondrial biology in a collaborative manner, sharing equipment and expertise.

Supplementary information

Key words

#66 Prenatal and early-life causes of neurodevelopmental disorders using genetically informative designs

Type of recruitment
Doctoral student, 4 years

Project title
Prenatal and early-life causes of neurodevelopmental disorders using genetically informative designs

Supervisor
Mina Rosenqvist, Assistant professor
Department of Medical Epidemiology and Biostatistics

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Home page: https://staff.ki.se/people/minryd

Qualifications of applicant
We are looking for a doctoral student with a background in epidemiology, biostatistics, public health, psychiatry or other relevant field, with an interest in psychiatric epidemiology research and methodology, strong analytical competence and good collaboration and communication skills in English. Prior knowledge in epidemiology or biostatistics; experience working with large data sets; and experience of using statistical software (such as SAS or STATA) is meriting.

Background
Neurodevelopmental disorders such as attention deficit hyperactivity disorder (ADHD), autism spectrum disorders (ASD) and intellectual disability (ID) are common lifelong disorders with childhood-onset which are associated with adverse outcomes throughout the lifespan. It is therefore important to identify causes of these disorders. While some studies have suggested that prenatal and early environmental factors are potential causes of such neurodevelopmental disorders, it is challenging to distinguish the effect of prenatal/early-life environment from genetic influences.

Research project description
The aim of the project is to identify potential prenatal and early-life environmental causes of neurodevelopmental disorders, such as ADHD, ASD and ID. The project offers an opportunity to work on a unique large-scale linkage of population-based health registers in Sweden, using advanced genetically informative study designs. The available linkage includes around 1.5 million children born in Sweden, who are

followed up in the registers with regard to clinical diagnoses of ADHD, ASD, and ID. Family-based study designs, where the risk of the outcome among exposed individuals is compared with their unexposed family members, will be used to control for unmeasured genetic and environmental confounding, whereas twin studies will be used to estimate the relative contribution of genetic and environmental influences. There is also an opportunity for the student to be involved in the development of other novel genetically informative designs and to apply these in the project.

The research project is a part of a larger program investigating prenatal and early-life causes of neurodevelopmental problems, conducted in collaboration with researchers from other international research institutes. A variety of educational courses are available for PhD students to increase their expertise throughout these years.

Research group

The psychiatric epidemiology group at the department of Medical Epidemiology and Biostatistics comprises more than 20 members, including professors, assistant professors, postdocs, and doctoral students. We have an interdisciplinary research team from various backgrounds, including epidemiology, biostatistics, sociology, and psychiatry. The group is largely concerned with the causes, consequences, and treatment of neurodevelopmental and psychiatric disorders. Research within the group is based on nationwide Swedish health registries and large cohort studies.

Supplementary information

Key words

neurodevelopmental disorders, prenatal exposure, early exposures, genetically informative study designs

#67 Exercise induced immune modulation – consequences for tumor progression and responsiveness to checkpoint inhibition.

Type of recruitment
Doctoral student, 4 years
Postdoc, 24 months

Project title
Exercise induced immune modulation – consequences for tumor progression and responsiveness to checkpoint inhibition.

Supervisor
Helene Rundqvist, Researcher
Department of Laboratory Medicine

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Home page:

Qualifications of applicant
We are looking for a candidate with documented experience in tumor biology, flow cytometry and functional characterization of immune cells. A keen interest in science and the ability to interact effectively and work productively in a team as well as a good ability to communicate in English is required. Emphasis will be placed on personal skills, knowledge and abilities, as well as on documented previous work.

To qualify for a post doctoral position the applicant must hold a doctoral degree (PhD) or a foreign qualification deemed equivalent to a doctorate in medicine or biology.

Background
The benefits of exercise for patients with a cancer diagnosis are increasingly recognized. We and others have shown that exercise interventions after a cancer diagnosis reduce symptom burden and hospitalization, enhance physical functioning, and improve health related quality of life (Fong, Ho et al. 2012, Furmaniak, Menig et al. 2016, Mijwel, Backman et al. 2017, Mijwel, Backman et al. 2018, Mijwel, Cardinale et al. 2018).

Recent epidemiological studies suggest that a high level of physical activity after diagnosis can reduce the risk of recurrence and mortality (Cormie, Zopf et al. 2017)

and a large number of studies, including our recent publication in elife (Rundqvist et al . 2020), show reduced tumor growth in exercising animals .

Suggested mechanisms for the anti-neoplastic effects of exercise include; weight control, endocrine effects, decreased systemic inflammation and improved immune cell function , although there is little or no consensus on the subject.

High levels of infiltrating cytotoxic CD8+ T-cells and NK cells have been shown to predict a favorable clinical outcome in several cancer diagnoses. Interestingly, the short-term stress of a single bout of physical exercise induces a transient release of immune cells into the circulation. We hypothesize that acute exercise enhances immune function and thereby promote anti-tumoral immune responses.

Research project description

The specific aims of the current proposal are:

- to describe how T-cell numbers and function is altered by exercise

- to investigate the effects of exercise on responsiveness to immune checkpoint blockade therapy in established mouse models.

In the recent years, we have established mouse models with a robust anti-tumoral response to exercise, and shown that Cd8+ T cells mediate a substantial part of the exercise effect. For the proposed project we intend to perform a closer characterisation of splenic, lymph node and tumor infiltrating CD8+ populations in exercising animals with the purpose of identifying the traits of a “trained T-cell”. Specifically, expression of functional markers, metabolic profiling and assessments of mitochondrial function will be investigated.

The short-term stress of a single bout of physical exercise induces a transient release of immune cells into the circulation. In rodent models and healthy human subjects, this systemic recruitment is true for granulocytes, monocytes, and NK-cells as well as both CD4+ and CD8+ T-cells (Gustafson, DiCostanzo et al. 2017). Findings from the animal models will be confirmed through isolation of T-cells from human subjects before and after acute exercise.

Responsiveness to immune checkpoint inhibition therapy in exercised animals will be evaluated by administrating aPD(L)1 and/or aCTLA4 antibodies to exercising and non-exercising animals and monitor tumor growth and survival, including characterisation of tumor infiltration ratios of regulatory T-cells as well as PD-L1 and CTLA-4 expressing cells that could alter the function/efficacy of the cytotoxic T-cell population.

Research group

The research at the Division of Clinical Physiology, Department of Laboratory Medicine in Huddinge aims to increase awareness of the link between physical

activity and health and spans from the whole-body level down to specific tissues and organs at the molecular level. The Rundqvist lab specifically focuses on the role of exercise in tumor progression. The lab consists of one post doctoral researcher, graduate student and undergraduate students. The research is carried out in close collaboration with medical doctors and exercise physiologists within the Division.

Supplementary information

Key words

Exercise, Immunology, Tumor biology

#68 Investigating transcriptional dynamics using single-cell genomics

Type of recruitment

Doctoral student, 4 years
Visiting doctoral student, 12 months
Postdoc, 24 months
Visiting researcher, 12 months

Project title

Investigating transcriptional dynamics using single-cell genomics

Supervisor

Rickard Sandberg, Professor in Molecular Genetics, Vice Head of department
Department of Cell and Molecular Biology

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Qualifications of applicant

Experienced in molecular biology or computational biology and with a strong interest in basic research and gene regulation.

Background

A core area of the lab is to develop and use single-cell genomics to explore transcriptional regulation and dynamics. The single-cell resolution has enabled the analysis of transcriptional bursting at the transcriptome-wide level. To get more temporal resolution, we recently developed metabolic labeling of newly transcribed RNA in single cells, which is a very powerful strategy for investigating the direct consequences of perturbations on transcriptional dynamics and regulation.

Key recent references:

Larsson et al. Nature 2019

Hendriks et al. Nature Communications 2019

Hagemann-Jensen et al. Nature Biotechnology 2020

Research project description

To develop experimental and computational strategies to study transcriptional processes transcriptome-wide at the resolution of individual transcriptional bursts, alleles. To determine the direct consequences of perturbations to transcriptional regulators and co-factors

Research group

Sandberg lab:

The lab typically consists of ten members, currently we are two PhD students, five postdocs and two staff scientists We operate a highly modern molecular biology lab, including several pipetting robots, nanodispensers, FACS, and NGS sequencing machines. Good computational infrastructure with several lab computing servers (with up to 400 cores each) and large-scale storage.

The lab is located in Biomedicum, a highly modern research facility at Karolinska Institutet that accommodates most basic research at Karolinska Institutet.

Supplementary information

Key words

single-cell genomics; transcription; gene regulation; sequencing

#69 Studies of a newly discovered adaptive NK cells in solid tumors

Type of recruitment
Doctoral student, 4 years

Project title
Studies of a newly discovered adaptive NK cells in solid tumors

Supervisor
Dhifaf Sarhan, Assistant professor
Department of Microbiology, Tumor and Cell Biology

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Qualifications of applicant
We are recruiting a doctoral student for a period of up to 4 years. We are looking for an ambitious student with strong enthusiasm towards science, with well communicating skills in English, to complement our interdisciplinary team. The successful applicant has completed a master's degree in translational medicine, (bio)medicine or similar topic and strong

background in immunology/tumor immunology. Preferably, the applicant should also have experience working with cell/tissue processing techniques, flow cytometry and analysis of flow cytometric data. Background in molecular cell biology and biochemistry, experience in immunofluorescence and immunohistochemistry methods, single cell RNA- Sequencing and associated analysis are also meritorious but not required.

Background
Natural Killer (NK) cells are innate immune cells able to reject hematological malignancies and correlate with better prognosis in solid tumors. However, conventional NK (cNK) cell anti-tumoral activity is limited by the immune suppressive tumor microenvironment (TME). We have recently discovered that an adaptive NK (aNK) cell subpopulation with immunological memory is able to resist immune suppression. Our research has exposed previously unrecognized mechanisms used by aNK cells to avoid immune suppression including downregulation of the immune checkpoint proteins. These aNK cells acquire memory and recall responses towards viral and bacterial infections. Markedly, our preliminary data suggest that aNK cells acquire recall responses towards several tumor types. Therefore, given their capacity to resist TME suppression and kill tumors otherwise resistant to cNK cells and memory capacity, aNK cells provide an

excellent new approach for cancer immunotherapy, possibly highly complementary to already available treatments. This PhD program has three complementary objectives. I) Identify antigen recognition strategies used by aNK cells; II) Study the molecular signature of aNK cells that drive memory; III) Characterize aNK cells in solid tumors and lymph nodes. I hypothesis that aNK cells use sophisticated antigen recognition strategy and a distinct network of intrinsic and extrinsic signaling contributing to acquire memory against tumors.

Research project description

Aim I: Identify antigen recognition strategies used by aNK cells

Aim II: Investigating intrinsic and extrinsic signaling that contribute to the establishment of aNK cell memory.

Aim III: Characterize aNK cells in solid tumors

Methods/techniques and Studies planned:

I: Our unpublished data indicate that aNK cells specifically recognize tumor antigens loaded on antigen presenting molecules through interaction with NK cell specific receptors. Using tumor lysate loaded antigen presenting cells (APC), monocyte-derived dendritic cells or activated B cells, resulted in superior tumor reactivity towards the specific tumors but not irrelevant tumors suggesting antigen specific responses in aNK cells. Here, structural studies will be performed to assess association of protein structure and recognition of the specific peptide complexes. I hypothesize that specific reconfiguration of the engaged receptors determines specific responses and memory formation in aNK cells. Most of the required cell culture systems have been already optimized and setup in my laboratory at Karolinska Institutet.

II: We would further evaluate the intrinsic and extrinsic signaling that contribute to the establishment of aNK cell memory. Gene and protein expression profiles that distinguish aNK cells from cNK cells, particularly the transcriptional landscape of changes associated with memory formation and recall responses against tumor specific antigens are expected to be determined. Single cell RNA-sequencing will be used to identify gene signatures differentially expressed in cNK and aNK cells after primary and secondary tumor exposure. From this part, we expect to map the signaling network associated with memory formation and recall responses in tumors.

III: We have previously developed an ex-vivo culture-system to study the phenotype and function of tumor infiltrating immune cells. Immune signature including metabolic profile and functional properties of tumor infiltrating aNK cells will be compared to those of aNK cells from blood and draining lymph nodes, and cNK cells by multiparametric cytometry, Seahorse analysis, and long-term live cytotoxicity assays. This project will be done with help of well-established

collaborations with national and regional. Overall, results from this part of the project will increase our understanding of aNK cell behavior in solid tumors.

Significance:

While cNK cells lack antigen specificity and are suppressed and dysfunctional in tumors, aNK cells exert many properties that are needed to develop a more effective therapeutic product including resistance to TME suppression and improved antigen recognition though selection and expansion. Such properties together with recall responses, will give early and long-lasting protection against tumors. This PhD project will provide new insights to innate memory against cancer in advanced solid often metastatic cancers, an area representing a challenge in cancer research and patient care.

Research group

The student will work in a stimulating laboratory environment with PhD students, postdoctoral fellows, researchers, and technical staff with ample experience in immunology and tumor immunology research. The research plan is designed that the student will work mainly in Sarhan's lab that has 1 PhD student, 1 Erasmus trainee, 1 master student, and 5 shared PhD students with other main supervisors. The student will occasionally work in the co-supervisors and collaborators laboratories throughout the education. Sarhan is working closely with Prof. Mikael Karlsson where the PhD student will interact with research fellows and shares laboratory. Prof. Adnane Achour will be one of the co-supervisors at the SciLife labs, where the student will be trained in studying receptor structure that lead to immunological responses. Also, Sarhan's laboratory is collaborating with several clinicians to provide clinical material and knowledge, where the PhD student will be interacting closely with.

Supplementary information

Sarhan is an assistant professor in tumor immunology/immunotherapy and the co-supervisors are professors in Immunology, Molecular Immunology respectively, and a senior oncologist/docent. As such, the supervisors' distinct expertise is complimentary to benefit the projects. The student will work in a multidisciplinary team with immunologist and oncologists, and collaborators. Although the student will benefit from working in an environment with basic, translational, and clinical scientists, initial hands-on supervision will be led by Sarhan and a PhD student and a researcher that will also be involved in projects. The supervision team is available on a daily and regular basis to discuss research findings, design of experiments, how to advance the projects, and for career development.

Key words

Innate memory, Tumor immunology, Immunotherapy, Tumor microenvironment

#70 Unlocking Vulnerabilities in malignant Paraganglioma and Neuroblastoma using single cell technology and integrated mass spectrometry

Type of recruitment
Doctoral student, 4 years

Project title
Unlocking Vulnerabilities in malignant Paraganglioma and Neuroblastoma using single cell technology and integrated mass spectrometry

Supervisor
Susanne Schlisio, Associate professor
Department of Microbiology, Tumor and Cell Biology

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Qualifications of applicant
We seek a PhD student to work on the analyses of a large-scale single-cell transcriptome project on childhood neuroblastoma and pheochromocytoma to understand heterogeneity and drug resistance of this malignancy.

Position-specific requirements: MSc.

Furthermore, the student should have educational background in cell biology, molecular biology, oncology, medicine. Previous experience in in vitro study including all cell-based methods is required. Other skills in using programming language for data analysis and experience with animal experiments will be considered as a merit. Furthermore, fluent English skills and team spirit are essential as well.

Background
Neuroblastoma (NB) is the most common pediatric solid tumor and represents 15% of all childhood cancer deaths. High cellular heterogeneity is a hallmark of NB, which may account for the wide range of clinical presentations and non-uniform response to treatment. In preliminary single cell analysis, we observed that neuroblastoma are highly heterogeneous in itself and resemble some stages of

neural crest differentiation into sympathetic neuroblast. Creating “comparative identity maps” using single cell analyses of tumors and healthy progenitor populations will allow us to identify the precise developmental and adult origin cell types and corresponding differentiation status for different subtypes of NB. The methodology we propose involves mapping individual tumor cells onto developmental or homeostatic trajectory to reveal the molecular processes leading to NB. We hypothesize that errors, bias, or aberrant delays in making key fate decisions can lead to these malignancies during self-renewal and/or development.

Identifying cell of origin of these sympathoadrenal malignancies will reveal the causes of disease heterogeneity and clinical behavior. From our preliminary tumor mice, we found two tumors consisting of both pheochromocytoma (PPGL) and NB components, and further characterized them as composite malignancies. This diagnosis has provoked the question if NB and PPGL might have a common progenitor.

Research project description

Aims:

1) Profiling tumor heterogeneity and immaturity on single cell resolution of human and mouse neuroblastoma and pheochromocytoma tumors.

2) Developing novel neuroblastoma and pheochromocytoma mouse models for identifying cancer cell of origin by tracing the cell lineage and tumor subpopulations.

3) Understanding drug resistance in malignant PCC/PGL and high risk NB: Integrating mass spectrometry combined with single cell analysis in primary, metastatic and relapse PPGL/NB.

Rational:

The neuroblastoma cell of origin is thought to be a developing sympathoblast, however, its precise cell of origin remains unknown. Single cell transcriptomics will identify gene expression clusters that are prominent in specific embryonic sympathoadrenal developmental stages in NB. Identifying the cell(s) of NB origin and their temporal development will provide mechanistic insight into: disease initiation, heterogeneity, progression, clinical behavior and spontaneous NB regression.

Questions:

1) Understanding the clinical heterogeneity of neuroblastoma: What distinguishes the “favorable” vs the “unfavorable” neuroblastoma?

2) What unique signatures can be found in the spontaneously regressing neuroblastoma?

3) Do neuroblastoma types and PPGL represent regulatory patterns in early or late embryonic sympathoblast/crest populations (SCP, Bridge, sympatho-verus immature chromaffin)?

4) Can we identify cell-of-origin subpopulations for neuroblastoma or PPGL initiation?

Research group

Associate Professor S. Schlisio: is a cancer biologist with extensive experience in sympathoadrenal nervous system malignancies, neuronal development and cancer mouse models. She performed her PhD studies at Duke University Medical School 2002. In 2008, she completed her postdoctoral research at the Harvard Medical School. As a postdoctoral researcher in the laboratory of Dr. William G. Kaelin, Jr. she was part of the team discovering how cells adapt to changes in oxygen availability and how this process is directly linked to cancer-discoveries that now have been recognized with award of the Nobel Prize to Dr. Kaelin. In In 2008, she was a recipient of an internationally competitive member position at the Ludwig Cancer Institute Stockholm to start her own research group. Since 2017, she is faculty at MTC, KI.

PhD students: Wenyu Li, Maria Arceo

Postdocs: Shuijie Li, Petra Bullova, Monika Plescher

Bioinformatician: Oscar Bedoya Reina

Funded by: ERC, KAW, VR, CF, BCF, ParaDiff

Supplementary information

The project will take advantage of the resources at Karolinska Institutet, including state-of-the-art mouse transgenic and imaging facilities. This will be complemented by use of national infrastructures provided by SciLifeLab for Single Cell Transcriptomics with the opportunity to perform a variety of protocols including 10X Genomics platform, Smartseq2. Imaging facilities include confocal, tumor visualization methods and super-resolution instrumentation. Important, Karolinska Institutet foster a close collaboration with the hospital site. Thus, we have the ability to work close with clinician and are able to retrieve large number of rare tumor material. The biobank at the Karolinska hospital has one of the largest PCC/PGL collections in Europe.

Key words

neuroblastoma, pheochromocytoma, oxygen sensing, tumor suppression

#71 Targeting p53 to kill tumor cells, reprogram cancer-associated fibroblasts and boost anti-cancer immune response

Type of recruitment
Postdoc, 24 months

Project title
Targeting p53 to kill tumor cells, reprogram cancer-associated fibroblasts and boost anti-cancer immune response

Supervisor
Galina Selivanova, Professor in Cell and Tumor Biology
Department of Microbiology, Tumor and Cell Biology

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Home page: https://ki.se/en/mtc/galina-selivanova-group

Qualifications of applicant
To qualify, the applicant must hold a Ph.D degree, preferably in cancer cell biology. The applicant must have at least 4 years of experience in molecular and cell biology and good knowledge of English.

The applicant should have experience with mammalian tissue culture techniques and molecular biology including DNA and RNA techniques, as well as biochemical methods. Preferred experience also includes immunoprecipitation, Western blot analysis, fluorescence microscopy, and flow cytomerty. Experience with high throughput methods, including transcriptomics and proteomics and/or bioinformatics is a plus. Solid experience and excellent track record in the research field will be considered a distinct advantage.

Background
p53 inactivation via mutations or enhanced degradation by Mdm2 is the most frequent alteration in human cancers, which underscores the key role of p53 as a major tumor suppressor. We discovered potent anti-cancer compound PRIMA-1/APR-246, reactivating mutant p53. It is now being tested in Phase III clinical trial.

Numerous studies have established that cancer progression and metastasis are controlled by tumor microenvironment (TME), including cancer-associated fibroblasts (CAFs) and immune cells, which creates a great medical need for the development of novel treatment modalities. Moreover, with the advent of immune

anti-cancer therapy it becomes imperative to understand how immune checkpoints are affected by novel target-specific drugs. While p53 reactivating molecules, discovered by us and others, have been shown to kill cancer cells, the question remains open how p53 reinstatement will affect CAFs and anti-cancer immune response.

Our ambition is to provide basis for innovative p53-based treatment strategies targeting both cancer cells and TME to generate synergistic anti-tumor effects that result in long term survival of patients. We will use small molecule reactivating mutant p53 (PRIMA-1/APR-246, discovered by us), as well as MDM2 inhibitors, in cancer cells and in animal models. Defining this concept, its mechanisms and implications for novel anti-cancer therapies form the main objectives of this project.

Research project description

Aims of the project:

I. Mechanistic studies to elucidate the mechanisms and factors leading to inactivation of p53 in cancer-associated fibroblasts (CAFs) resulting in conversion of TME to tumor-promoting state. We aim to identify factors and drugs which can reverse tumor-driving capabilities of TME to tumor-repressing ones;

II. Elucidation of the p53-regulated pathways modulating immunosurveillance, in cancer cells, in CAFs and in immune cells.

In order to address these challenging questions we will employ a comprehensive and multidisciplinary approach. We will apply cutting-edge molecular and cell biology methodologies, multi-omics analyses and systems biology analysis, combined with ex vivo 3D cell & tissue culture and in vivo animal models. We combine hypothesis-driven strategy with unbiased multi-omics approach and apply the analysis of publicaly available patient data sets (e.g., TCGA), as well as newly obtained data from patient material via my collaborations with clinicians in Sweden and abroad.

Our aims will be achieved through the following work packages (WP):

WP1. Identification and functional validation of the factors inducing mutant-like (ML)p53

WP2. Development of approaches to reprogram CAFs to normal phenotype

WP3. Targeting p53 to boost cancer cells' immunogenicity

WP4. Elucidation of the role of mutant p53 in immune surveillance of cancer

WP5. Pharmacological activation of p53 to activate NK cell-mediated cancer killing

My hypothesis is based upon unique unpublished work in a field in which I am an established international expert. This is an ambitious and challenging proposal, however, we will use highly parallel strategies to achieve our goals and use both unbiased multi-omics and hypothesis-driven research to ensure that no bottlenecks will form to the study progression.

Importantly, my lab has already obtained substantial preliminary results, underscoring the feasibility of the project. The majority of approaches and models described in this proposal have been already established in the lab or available via collaborations.

The expected major outcomes of the proposed study will be fundamental new knowledge of mechanisms of TME-dependent therapy escape, with the key outcome of identification of new targets for therapeutic intervention. Reprogramming of TME by targeting p53 could have an impact on the very concepts we use to treat cancer. An important implication of this new concept is that it will pave the way for rational combination of target-specific drugs to achieve high efficiency and to decrease the chance of de novo resistance to therapies. I envisage that this innovative program will promote clinical trials of the investigational compounds, including p53-targeting therapies and will help to stratify patient cohorts, allowing personalized cancer medicines for the benefit of patients.

Research group

Galina Selivanova, PhD, Professor

Sylvain Peuget, PhD, Assistant Professor

Madhurendra Singh, PhD, postdoc

Ali Rihani, PhD, postdoc

Gema Sanz Santos, PhD, bioinformatician

Xiaolei Zhou, PhD student

Supplementary information

Key words

cancer, p53, tumor suppression, inflammation, immunotherapy, tumor microenvironment, small molecules, cancer therapy

#72 Assessing of Motion-Cognitive Reserve with Virtual Reality and Wearable Sensing

Type of recruitment
Doctoral student, 4 years

Project title
Assessing of Motion-Cognitive Reserve with Virtual Reality and Wearable Sensing

Supervisor
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Department of Clinical Science, Intervention and Technology

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Qualifications of applicant
The main qualification expected on the PhD candidate is to have an engineering background in electrical engineering, computer sciences or biomedical engineering with experience in developing virtual reality scenarios in environments like Unity or equivalent. A strong mathematical background is required and formal education on data analysis and modelling is a plus.

Background
With an expected increase in the mean age and proportion of the population older than 65 years, the public health burden of cognitive impairment and dementia will become substantial. Cognition and the maintenance of mental, social and physical well-being in older age are crucial for healthy ageing. Alzheimer's disease (AD) is the most common cause of dementia in the elderly, accounting for over 70% of dementia cases in individuals ≥ 70 years of age. Clinicopathological studies suggest the presence of a long preclinical phase of AD, with AD pathology estimated to begin a decade or longer prior to the onset of cognitive symptoms. People with AD often suffer from motor- and cognitive disability, and such functional decline might impact on their motion and cognitive capacity also known as reserve (MCR) to function in everyday life conditions. Quantifying the MCR would allow the detection of subtle alterations in function and enable the prediction of future decline.

There is a strong scientific rationale for linking motor dysfunction to cognitive impairment, including the link between age-related motor problems and dementia due to AD. To assess such motion and cognitive capacitive, there are required both a model and a stress test methodology to quantify the limits of such capacity. Wearable sensing and virtual reality technologies have evolved to a point that can

be used to develop the evaluation tool that can support the development of such model, its test and its validation

Research project description

To date, the quantification of cognitive, motor or motor-cognitive reserves is not well established and MCR is considered an unmeasurable construct. We aim to address this shortcoming by developing an innovative technological platform to model and quantify the MCR construct with an index that may be used to identify those likely to suffer from motor-cognitive decline, well before those processes progress and become clinically detectable, offering a huge impact on healthcare systems and the well-being of many older adults.

To achieve such aim 3 objectives have been identified:

1. To develop a multimodal platform to assess motor-cognitive performance and physiological and neural responses to motor-cognitive tasks of increasing difficulty.

The MCR platform will be based on Virtual Reality (VR) and gaming technology that will expose subjects to a graded motor-cognitive 'stress test', challenging the subject's physiology in multiple domains that contribute to MCR and bring it to the 'tipping point' in which performance declines (i.e., motor, cognitive or both). The MCR platform's network of synchronized wearable sensors will measure motor performance, physiological measures (i.e., heart rate and skin conductance) and mental capacity in response to the graded difficulty levels of the test and identify compensatory brain mechanisms.

2. To develop a quantitative model that will be used to create the MCR index.

Measures obtained from the platform developed in objective 1 together with background measures such as, age, gender, education, physical activity and genetics will be analysed separately and then integrated into a multifactorial model. The physiological, cognitive and motor responses to the 'stress test' will be modelled, and the 'tipping points' will be estimated using new bio-statistical approaches developed for this purpose. The fine line demarcating the border of capacity at which performance begins to deteriorate can be referred to as "the moment of critical mass" and the difference or "distance" of this point(s) from basal function will be algorithmically defined and estimated, thereby determining

the subject's MCR index. Multimode regression approaches (normally nonlinear) will be used to further tune the classification problems.

3. To validate the MCR index in healthy adults and individuals at risk for motor-cognitive decline.

A cross-sectional study in healthy young and older adults and patients with well-defined motor and cognitive deficits (i.e., Parkinson's disease, and mild cognitive impairment) will address inter-subject variability and establish the MCR index. In addition, we will recruit individuals who have an increased risk for developing neurodegenerative diseases. The validation process will demonstrate the potential of this new platform and the novel MCR index in identifying populations at risk of unsuccessful ageing and neurodegeneration as compared to traditional measures and conventional testing

Research group

The research group in Biomedical engineering and Digital Health lead by Fernando Seoane counts premises at the Division of Functional Imaging and Technology with a newly appointed assistant professor PhD. Farhad Abtahi and affiliated senior researcher PhD Carlos Fernandez-Llatas. In addition, the research group is affiliated to the Karolinska University Hospital, where Prof. Seoane works as R&D coordinator within the division of Medical Technology Development and Management.

Supplementary information

This project will be run in collaboration with the division of clinical geriatrics at the Department of Neurobiology, Care Sciences and Society. The research at division of clinical geriatrics is multi-faceted focusing on neurodegenerative diseases, such as Alzheimer's disease, frontotemporal dementia and Parkinson's disease. The research is clinically oriented with an emphasis on diagnosis, prevention and treatment.

Key words

Alzhaimer, Dementia, Wearable sensors, multi-parametric modelling, virtual reality, data analysis.

#73 Feasibility study on applying Interactive Process Mining to Clinical Epidemiology Studies with Real World Data

Type of recruitment
Doctoral student, 4 years

Project title
Feasibility study on applying Interactive Process Mining to Clinical Epidemiology Studies with Real World Data

Supervisor
Fernando Seoane, Professor
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Qualifications of applicant
The students should have a degree in computer science with an excellent background in both mathematics and data analytics as well as proven experience in programming in Python, R or equivalent

Background
An aging population and improvements in medical interventions and healthcare systems have reduced mortality from several diseases, leading to an increased need for managing chronic conditions. Up to 30% of the population suffers from five or more disease conditions. Caring for chronic diseases and multimorbidity already accounts for more than 80% of the total health expenditure. The problem is systemic and jeopardizes the sustainability of public healthcare.

Managing patients suffering from multiple chronic diseases is a challenge of remarkable significance. The list of factors adding to such complexity is long but among others, we find:

a) Adverse drugs reactions caused by pharmacokinetic, pharmacodynamic drug-drug interactions between medications prescribed or medication toxicity caused by medication prescribed for one condition being adverse for another.

b) Incompatibility between therapies impairs patient therapy adherence.

c) Treatment of diseases using “one dose fits all” approach

From a data analytics and AI perspective, it is possible to infer models from the care pathways performing longitudinal analysis. Unfortunately, to establish meaningful causalities requires more than just finding correlations.

The Interactive Pattern Recognition framework was defined to make AI more explainable, by incorporating domain experts in the AI process. Interactive Process Mining has been identified as the most adequate technique to identify causalities in longitudinal records.

Research project description

This proposal aims at exploiting the opportunity provided by the current availability of healthcare Real World Data (RWD) combined with analysis and mining methodologies suitable for producing explainable AI in healthcare. The approach combines life science and information technology, using a multidisciplinary approach.

The main goal is to demonstrate how real-world data and biomedical knowledge can be integrated in a synergistic way through the interaction of data scientists and biomedical experts, creating an interactive methodology for information mining and hypothesis generation that produce explainable AI causality models easy to understand, accept and eventually adopt in line with healthcare.

To reach such a goal the following Intermediate objectives have been defined:

- To identify commonly used medications across the range of kidney function as well as patterns of use that may lead to increased risk of adverse events.

- To define adverse events of interest, prioritizing those, which may be potential sequelae of medication use, and test their associations with Chronic Kidney Disease (CKD) stage.

- Quantify and estimate risks of adverse events associated to medication use across CKD severity stages; characterize comorbidities or concomitant medications that alter risks and benefits.

To ensure the sucess of the project the following taks have been identified:

- To develop a platform based on Interactive process mining for identification of longitudinal trajectories within patient pathways.

- To develop a methodology for producing hypotheses from the results obtained from the process mining analysis of RWD.

- To characterize comorbidities or concomitant medications that alter risks for Adverse Drugs Reactions.

- To define, quantify and estimate risks of adverse events associated with medication use across different severity stages of common chronic conditions: focusing on CKD, and exploring the feasibility in hepatic impairment and elderly.

- To identify commonly used medications across the range of kidney function as well as patterns of use that may lead to increased risk for adverse events, considering the patient's age and sex.

The availability of the Real World Database SCREAM (Stockholm Creatinine Measurements) and the extensive work already done on it through traditional longitudinal data analytics methods provide us with the perfect opportunity to develop and validate an Interactive Process mining methodology customised for providing understandable clinical epidemiologic insights to improve care of CKD patients with comorbities.

This project will be executed in collaboration with Prof. Juan Jesus Carrero (https://staff.ki.se/people/jucarr) at the Department of Medical Epidemiology and Biostatistics at Karolinska Institutet the groups that he personally leads (https://staff.ki.se/orgid/510856).

Research group

The research group Biomedical Engineering and Digital Health lead by Professor Fernando Seoane counts with an assistant professor, PhD Farhad Abtahi and an affiliated Senior researcher PhD. Carlos Fernandez Llatas.

Supplementary information

As indicated in the description this PhD Thesis will be co-supervised in collaboration with Prof. Juan Jesus Carrero from MEB

Key words

Understandable Artificial Intelligence, Machine Learning, Clinical Epidemiology, Python programming, R programming

#74 Modelling high-dimensional genomics and omics data

Type of recruitment
Doctoral student, 4 years

Project title
Modelling high-dimensional genomics and omics data

Supervisor
Xia Shen, Dr.
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Qualifications of applicant
The scholar should have a BSc or MSc degree in biostatistics or a similar statistics subject. Programming skills in R and/or Python is required. Experience in linear mixed models and relevant algorithms is favourable. Candidates from top Chinese universities are favourable. Published research articles as the 1st or co-1st author in JCR Q2 or above journals are considered strong merits.

Background
Understanding the genetic architecture of complex traits using vastly available big data resources has become a central aim in current human genetics research. The resources cover not only individual-level data of the human genome, transcriptome, and proteome, etc. but also new types of summary-level data such as genome-wide association summary statistics. For instance, one technical breakthrough in analysing genome-wide summary-level data by our group is called high-definition likelihood (HDL; Ning et al. 2020 Nature Genetics). Via full likelihood modelling, the method can assess shared genetic architecture between complex traits and diseases by precisely estimating the genetic correlation parameter. Subsequent studies are needed to extend the model to different settings of parameterisation and molecular biology problems.

Research project description
This project aims to extend the HDL model to better fit the distribution of the genetic effects across the human genome. This involves partitioning the genome according to allele frequencies, linkage structures, functional annotations, and other perspectives of variant features. Integrating with transcriptome information, the extension can be applied to pinpoint regulatory gene networks, cell types, and human tissues underlying complex traits and diseases.

Research group

The research group at KI currently consists of 3 PIs and 3 PhD students, where Prof. Yudi Pawitan will be co-supervising this project. The group covers various aspects of high-throughput molecular data analysis. We aim to perform research that will ultimately generate a high impact in relevant biological areas.

Supplementary information

Co-supervisor contact information:

Yudi Pawitan

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Key words

Statistical Modelling, Genetics, Genomics, Omics

#75 Long-term prescribing of benzodiazepines in contemporary Sweden - predictors, consequences, and strategies to reduce unwarranted prescribing in primary care

Type of recruitment
Doctoral student, 4 years

Project title
Long-term prescribing of benzodiazepines in contemporary Sweden - predictors, consequences, and strategies to reduce unwarranted prescribing in primary care

Supervisor
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Qualifications of applicant
â€¢ A master degree related to the field of medical epidemiology, public health epidemiology, biostatistics, psychiatry, or similar.

â€¢ Documented research experience within the field of pharmacoepidemiology, psychiatric/psychological epidemiology, or substance use epidemiology, preferably with the use of large population-based registers.

â€¢ Proven record of carrying out statistical data analysis with focus on longitudinal modelling of register-based cohort data.

â€¢ Proven competence and proficiency in the use of analytic software (e.g., Stata or SAS).

â€¢ Knowledge and skills in qualitative research and intervention research are qualifying.

â€¢ Fluency in English.

â€¢ Excellent oral and written communication skills.

Having a medical education (e.g., Bachelorâ€™s degree education comprising medical subjects) is desirable and considered as a merit. In addition, the candidate should be able to take initiative, ensure that project goals are consistently met, be flexible to manage project effectively, and be comfortable having parallel activities. The applicant must be able to integrate well into the international and multidisciplinary environment. Personal suitability is therefore of great importance.

Background

Benzodiazepines and benzodiazepine-related z-drugs (BZD) are widely used psychotropic medications in Sweden and most prescriptions come from primary care. The guidelines limit BZD treatment to up to 2-4 weeks due to the high risk of dependency and severe adverse effects. Yet, unwarranted long-term BZD prescribing for a wide variety of psychiatric disorders is alarmingly common, mainly in young and the elderly patients, and among socially disadvantaged. This raises serious clinical and public health concerns since, in addition to dependence, long-term BZD use is associated with psychomotor and cognitive impairment (leading to traffic accidents and injuries), risk of stroke, brain malignancy, Alzheimerâ€™s disease, and dementia, that collectively increase all-cause mortality.

In Sweden, a major concern is that the recent increase in psychiatric morbidity along with organizational changes in the Swedish healthcare system that made primary healthcare services a â€˜first line of psychiatryâ€™ may further intensify BZD prescribing, particularly in primary care. The driving forces of long-term BZD prescribing are unknown and this hinders the development of preventive interventions. Therefore, it is crucial to equip the primary healthcare providers with evidence-based strategies for reducing long-term BZD prescribing to benefit patients and the Swedish society at large.

Research project description

The project aims to create an evidence base for identifying patients at risk of unwarranted long-term BZD prescribing and to devise strategies, directed to prescribers, for avoiding harmful BZD prescribing in primary care. To achieve this aim, a set of quantitative and qualitative studies will be conducted and followed by designing (together with prescribers) and piloting an intervention in primary care. The project will use a wide variety of the Swedish nationwide population-based registers, from which longitudinal data on clinical, pharmacological, prescriber-related, demographic, and socioeconomic characteristics will be collected for all individuals with the first BZD prescriptions issued in 2007-2017. Among BZD-recipients, the factors that predict and modify overall long- vs. short-term BZD prescribing as well as various prescribing trajectories (e.g., stable, accelerating, decelerating, occasional prescribing) will be explored. Then, the impact of distinct BZD prescribing patterns on the risk of adverse health outcomes will be quantified. As the next step, the project will explore and qualitatively assess the general

practitioners' experiences and perceptions of long-term BZD prescribing. Finally, an educational intervention will be designed (together with prescribers) and piloted in primary care with the aim to reduce long-term BZD prescribing in a routine clinical practice. The project will employ a wide range of advanced statistical methods (for the analyses of register-based data) as well as the thematic content analysis (for qualitative study) and mixed-effect regression (for assessing feasibility and acceptability of pilot intervention).

The project will lay foundation for further development of intervention to reduce unwarranted BZD prescribing. Hence, our project has a direct clinical implication and a considerable significance for both patients and healthcare providers, in particular at primary care level, where most BZD prescribing is initiated.

Research group

Our group conducts multi-disciplinary research (e.g., biological, clinical, social, epidemiological, and pharmacoepidemiological) in the area of psychiatric disorders, with a particular focus on obsessive-compulsive and related disorders. We are interested in understanding the risk factors and consequences of various psychiatric disorders, with a strong emphasis on clinically relevant questions that can inform prevention and intervention work. The group members have a well-established and on-going collaboration with leading research groups in psychiatric epidemiology and clinical trials in the US, UK and several Universities in Sweden, and an extensive network of leading national actors from government agencies responsible for health, medical services, and development of primary care services. Group home page: https://ki.se/en/cns/david-mataix-cols-research-group

Supplementary information

The student will assess relevant literature, prepare study protocols, acquire and manage data from large population-based registers, conduct statistical data analysis, and write scientific publications.

We offer an engaging and international research environment where student will have an opportunity to contribute to high quality research at international top level and work closely with top researchers in the field. The student will have an access to the unique data sources based on the Swedish population registers and get amazing training opportunities through attending PhD courses, research school, seminars and workshops on relevant topics.

Key words

Pharmacoepidemiology, benzodiazepines, mental disorders, psychiatry, register-based study, cohort, qualitative research, prevention, intervention

#76 Sleep and neuroimaging biomarkers: From healthy aging to Alzheimer's disease (SPIRE)

Type of recruitment
Postdoc, 24 months

Project title
Sleep and neuroimaging biomarkers: From healthy aging to Alzheimer's disease (SPIRE)

Supervisor
Shireen Sindi, Assistant professor
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Qualifications of applicant
We are seeking a highly motivated and innovative post-doctoral scientist to investigate novel neuroimaging biomarkers in the context of aging and dementia.

The duties involve:

- Conducting literature reviews
- Performing neuroimaging analyses
- Performing statistical analyses
- Writing research articles
- Presentation of findings in research conferences / seminars
- Integrate the expertise from different group members and collaborators

To qualify, the applicant must hold a doctoral degree in neuroscience / neurology and have a background in biomedicine or equivalent. Previous experience with neuroimaging and biomarker analyses is essential. A strong scientific background in neurodegenerative diseases and a strong publication record is highly desirable. Good documentation skills and effective planning to meet deadlines is crucial. The successful candidate should have a high level of responsibility and a problem-solving attitude. The candidate should be self-motivated a, driven, with good communication skills, and be able to work effectively in our multidisciplinary team. A high level of English, spoken and written, is a requirement. The CV will be assessed, and references are needed.

Background

Dementia is a major cause of disability/dependence among older adults. Globally, 50 million people have dementia, and this will triple by 2050. A third of dementia cases are preventable through lifestyle changes. Sleep disturbances were recently highlighted as an important dementia risk factor, and are a 'public health problem' with a range of health consequences, and societal/economic burdens. Aging is accompanied by changes in sleep physiology and patterns, and 50% of older adults report sleep problems. Sleep deprivation impacts brain structures/function in animal models (impairs hippocampal neurogenesis, neuronal plasticity, decreases hippocampal volume). Results on the associations between sleep disturbances and neuroimaging correlates among older adults are scarce, and inconsistent. The role of sleep in Alzheimer's disease (AD) has recently received considerable attention; it was discovered that only during sleep can the brain eliminate waste through the 'glymphatic systems', including Aβ clearance. The (limited) existing evidence from human studies supports this notion.

Dr. Sindi established the Multi-Center Sleep Study which showed that midlife and late-life sleep disturbances are associated with a higher risk for dementia and poor cognitive status in older adults. More recently she showed that sleep disturbances are associated with the speed of multimorbidity accumulation. The current project will investigate the neurological mechanisms underlying these associations

Research project description

The goal of SPIRE is to develop an in-depth understanding of biological mechanisms linked to sleep disturbances by using well-characterized Nordic studies (Total N=2000+), including validated sleep measures/actigraphy, data on a broad range of risk factors (sociodemographic, genetic, lifestyle, vascular, metabolic, psychosocial), data from the most successful lifestyle intervention trial for the prevention of dementia and cognitive decline (FINGER) and its successor (MIND-AD), and detailed measures of several neuroimaging correlates (MRI, fMRI, DTI, MEG, PET, CSF AD biomarkers).

More specifically, the aims are to:

1) Investigate the association between sleep disturbances in the well-characterized CAIDE Study and the Betula Study (N=500+). In these longitudinal studies, available outcomes are various forms of brain imaging. Structural MRI includes: gray matter volume, white matter lesions, cortical thickness, hippocampal volume); Diffusion Tensor Imaging (DTI) white matter integrity; fMRI diffusion-weighted data (using the University of Oxford's Center for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library).

2) Examine the association between sleep disturbances and neuroimaging in a study from the Karolinska University Hospital memory clinic (Co-STAR, N=200+). MRI markers include: gray matter volume, white matter lesions, cortical thickness, hippocampal volume, medial temporal lobe atrophy.

3) Evaluate the associations between sleep and neuroimaging markers within multidomain lifestyle interventions to prevent dementia and cognitive impairment. These clinical trials (FINGER, N=1260 and MIND-AD, N=150 non-pharmacological lifestyle intervention studies) include diet, physical and cognitive training, and vascular risk management. In these trials we will investigate the association between sleep disturbances and MRI, MEG, and PiB-PET, and CSF AD biomarkers (beta-amyloid and tau).

All studies will examine the relationship between sleep and cognition, and the role of lifestyle (e.g. smoking, alcohol).

Taken together, this project provides a unique opportunity to study individuals across the spectrum of cognitive status from healthy individuals to patients with AD in clinical settings. This project takes place in a unique existing infrastructure, with interdisciplinary collaborations among world-leading experts on sleep and cognitive aging. The project will also transfer and implement the results in the new e-health tools that are being developed by the research group. Overall, in addition to generating valuable knowledge about the importance of sleep disturbances, the project will facilitate the development of tailored interventions to be used both in research contexts and in developing health programs for the general public.

Research group

Nordic Brain Network: An interdisciplinary team focusing on the risk and protective factors for dementia and Alzheimer's disease. The team also conducts multidomain lifestyle interventions and engage in implementation initiatives. Their research also investigates novel biomarkers underlying risk factors and dementia.

Supplementary information

Key words

Sleep, neuroimaging, dementia, Alzheimer's disease, aging

#77 Investigation of non-coding RNAs in skin inflammation

Type of recruitment
Doctoral student, 4 years
Postdoc, 24 months
Visiting researcher, 12 months

Project title
Investigation of non-coding RNAs in skin inflammation

Supervisor
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Qualifications of applicant
Required qualifications for a PhD student:

The applicant should have an MS degree in molecular biology, medicine or equivalent.

We are looking for a highly motivated student with a strong, genuine interest in medical research and a deep understanding of molecular biology. The student should speak excellent English and should be able to work in a team.

Experience with molecular biology and immunology techniques, non-coding RNA research, and/or in bioinformatics is an advantage.

Required qualifications for a postdoc:

We are looking for a highly motivated scientist with a strong background, deep understanding and proven expertise in molecular biology. The applicant should have a PhD degree within the area of biomedical research and have strong interest in medical and biological problems.

Hands-on experience with disease models of inflammation, competence in molecular biology and immunology techniques, non-coding RNA research, and/or in bioinformatics including analysis of global gene expression data, is an advantage.

Experience in supervising students and working with method development are meritorious.

The applicant should demonstrate ability to work in a team, to manage simultaneous projects and to interact well with others in the research group. Excellent English knowledge is a requirement.

Background

In the human genome, a large part of the transcriptional output is constituted of RNAs that lack protein-coding capacity . Genome-wide approaches such as the ENCODE project led to the understanding that more than 10,000 human genetic loci express non-coding RNAs and this number is constantly increasing. Intensive research in the past decades demonstrated that these non-coding transcripts function as important regulators of cellular physiology and pathology. Non-coding RNAs can be divided into several groups including small non-coding RNAs (e.g. microRNAs), and long non-coding RNAs (lncRNAs), RNAs longer than 200 nt, which are devoid of evident open reading frames. Non-coding RNAs have been implicated in various human diseases, and their modulation may become a novel therapeutic strategy.

Chronic skin inflammatory diseases such as psoriasis and atopic dermatitis belong to the most common inflammatory diseases and affect patients' quality of life significantly. These diseases can also serve as model diseases for understanding general mechanisms of inflammation. In 2007, we showed or the first time deregulation of miRNAs in psoriasis and atopic dermatitis, and our subsequent functional studies have demonstrated that a set of these miRNAs can contribute to the disease by regulating cell proliferation, differentiation and/or inflammatory pathways.

Research project description

The aim of the planned project is to explore the function and therapeutic potential of non-coding RNAs (ncRNAs) in chronic inflammatory skin disorders, such as psoriasis and atopic dermatitis. While in the past decades our understanding of the molecular/immunological mechanisms underlying these diseases has led to development of novel therapies, there is a need for new, efficient therapies with favorable safety profiles.

We have previously performed transcriptomic analyses in chronic inflammatory skin diseases and identified roles for ncRNAs, such as microRNAs and long non-coding RNAs in the regulation of tissue homeostasis and inflammatory responses in skin. In this project, the role of ncRNAs will be characterized in keratinocytes, the major cellular constituent of the skin epithelium. The therapeutic potential of their modulation will also be investigated, using in vitro and in vivo disease models.

The candidate will have the opportunity to join this exciting ongoing research. The candidate will analyze the cellular/subcellular localization of non-coding RNAs using single molecule in situ hybridization (RNAScope) and explore the regulation and function of selected non-coding RNAs. To this end, he/she will use both in conventional cell culture systems and reconstructed there-dimensional epidermal models, which are established in the Sonkoly-laboratory. To address the role of specific ncRNAs in the inflammatory response of skin cells, the candidate will modulate the expression of ncRNAs, e.g. by using mimics/inhibitors or using CRISPR-based gene activation/knockout). The candidate will evaluate the effect on ncRNA-overexpression/inhibition/knockout on cell proliferation, differentiation, cytokine/chemokine production of keratinocytes. Moreover, the effect of ncRNA-modulation on epidermal differentiation and barrier function will be analyzed in 3D epidermal model systems. The function of non-coding RNAs in vivo will be explored using mouse models of skin inflammation using genetically modified animals, and/or by inducing skin inflammation in conjunction with non-coding RNA modulation. The methods included in the project are well established in the laboratory, and the doctoral student/postdoc will have the opportunity to learn these techniques.

Identification of the role of non-coding RNAs in chronic inflammatory skin diseases and characterization of their function will add new layers of complexity to our understanding of chronic skin inflammation and also to the better understanding of skin biology. Findings of the project may also identify novel targets for RNA-based therapies for inflammatory diseases.

Research group

The Sonkoly group focuses on exploring the roles of non-coding RNAs in skin inflammation, and to explore their potential as biomarkers and therapeutic targets. The group has 14 years of experience in non-coding RNA research. The research activities are located at the Center for Molecular Medicine (CMM), where several dermatology research groups are located and collaborate closely. CMM is at the Karolinska Hospital area, in proximity to the New Karolinska Hospital, which allows a close interaction. The research group belongs to the Dermatology and Venereology Section which is an independent section within the Department of Medicine, Solna, Karolinska Institutet, where a broad range of experimental and clinical dermatological research is conducted. Extension of the current research group is planned during 2021 with an additional postdoctoral researcher and a PhD student.

Supplementary information

Key words

non-coding RNA, miRNA, inflammation, skin, keratinocyte, gene regulation, dermatology, 3D models, in vivo studies, translational

#78 Human adipose tissue senescence

Type of recruitment
Doctoral student, 4 years
Postdoc, 24 months
Visiting researcher, 12 months

Project title
Human adipose tissue senescence

Supervisor
Kirsty Spalding, Principal Investigator
Department of Cell and Molecular Biology

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Qualifications of applicant
The student is expected to have a background in the biomedical sciences (at a masters level), with previous laboratory research experience. Basic molecular biology techniques and confocal microscopy are an advantage, as is programming or bioinformatic experience (although not required).

The language of the group is English. It is necessary that the student be proficient in English and comfortable to converse, write and socialise in English.

Background
Senescent cells are cells that have permanently exited cell cycle and can no longer proliferate. Senescence is not a passive or dormant state, but rather a state whereby cells alter their phenotype and secrete factors that cause inflammation and tissue dysfunction. The abundance of senescent cells in tissues and organs increases during aging and obesity, although it is not known whether this represents an accumulation of senescent cells over time (i.e. poor clearance) or an increased rate of cellular senescence.

It has been proposed that senescence in obesity and type 2 diabetes has a positive function of limiting a fibrotic response (by inducing senescence in the damaged cells and activated fibroblasts) and triggering an immune response to clear

damaged cells. In this way, cellular senescence may act as a process whereby unwanted/dysfunctional cells can be eliminated and tissue remodelling induced. The pathology of senescence might therefore not be the incidence of senescence per se, but rather the failure of senescent cells to be cleared, which then go on to accumulate and contribute to tissue dysfunction. It is therefore of great therapeutic importance to understand whether an impaired immune response and altered senescence clearance results in the accumulation and pathology of senescent cells, or whether senescent cells are generated at a greater rate in pathology.

Research project description

The proposed project will determine the prevalence and kinetic clearance of senescent cells in human adipose tissue.

Investigating rates of cell clearance, and cell turnover in general in humans, has traditionally been difficult, with most of our knowledge inferred from animal studies (which often are not a good model for the human situation). To overcome these limitations, we developed a method for retrospectively determining the age of human cells, by analysing the integration of 14C derived from nuclear bomb-tests in genomic DNA. We will use radiocarbon dating to determine the age, and thus turnover, of senescent and non-senescent cells in human adipose tissue. Such information will provide first information on whether increased senescence in human adipose tissue results from an accumulation of senescent cells with impaired clearance, or whether adipose pathology associates with an increased rate of adipose tissue senescence.

Methods: The radiocarbon dating methodology relies on the worldwide exposure of humans to increased levels of 14C in the atmosphere derived from nuclear bomb tests in the 1960s. We are all readily integrating carbon from the environment into our bodies and it is the integration of these increased amounts of 14C, in particular into the stable genomic DNA of cells, that provides a read-out of the date a cell was formed. 14C levels in the atmosphere have remained relatively stable (with respect to all carbon) for the last several thousand years. However, atmospheric detonations of nuclear weapons during the period of the cold war (1955-1963) doubled the concentration of 14C/12C in the atmosphere. The Spalding research group, in collaboration with physicists from Uppsala University, are experts in biological 14C dating and accelerator mass spectrometry (AMS).

Senescent cells will be identified using either cellular or nuclear based labelling and sorting strategies. DNA isolation and downstream AMS analysis will be performed as described elsewhere (for protocols see Spalding et al., Cell 2005; Spalding et al., Nature 2008; Spalding et al., Nature 2013). Modelling of 14C data is done in collaboration with mathematician Professor Samuel Bernard, University of Lyon, France

Results from this project will provide first information as to the turnover kinetics of senescent cells in human tissues and provide important insights into the pathophysiology underlying increased senescent cell burden in tissues in disease and aging.

Skills obtained working in this project include handling of human adipose tissue (isolating adipocytes and stromal vascular fraction cells), nuclear isolation, immunocytochemistry, confocal microscopy, FACS (analysis and sorting), DNA isolation and purity assessment, AMS and scientific writing. The selected candidate will also have access to single cell mRNA sequencing datasets, so a background in computational biology or programming is an advantage.

Research group

The Spalding group consists of 1 postdoctoral fellow, 3 doctoral students, one senior lab manager and one lab technician (plus one or more masters students). The research interests of the group centre around aspects of human adipose tissue biology, with particular interest in how adipocytes respond to obesity and contribute to metabolic disease.

The group is located at Biomedicum, a large interdisciplinary centre that covers many aspects of biomedical research. The group also has an extensive network of collaborators in the fields of mathematics and physics as well as clinical collaborators, ensuring excellent access to the relevant expertise and human tissue.

Supplementary information

Key words

obesity, adipose tissue, adipocytes, hyperinsulinemia, senescence, radiocarbon dating

#79 A global perspective on the immune system for improved identification of biomarkers and resistance mechanisms in TB disease progression

Type of recruitment
Doctoral student, 4 years

Project title
A global perspective on the immune system for improved identification of biomarkers and resistance mechanisms in TB disease progression

Supervisor
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Qualifications of applicant
The student should have completed a university degree at a master of science level in a relevant topic, including experience with working in a laboratory. It is highly meriting if the student has experience with relevant methods, such as in vitro cell culture, cell isolation and sorting, cell-based immunoassays, flow cytometry, bioinformatics (experience with using R), and/or transcriptomic analysis.

The candidate is expected to be organised and able to work independently. The project is pursued in an interdisciplinary environment with collaboration with several research groups, and good collaborative skills are a necessary requirement. Fluency in English is mandatory.

Background

Research project description
Tuberculosis (TB) is characterised by a complex interplay between the immune system and the pathogen. However, we commonly study cells or molecules in isolation, trying to determine their role in a given disease. This limits our understanding of the interplay between different immune compartments during infection. By taking a global (or systems) perspective on the immune response and generating extensive datasets on several aspects of different diseases, e.g. the

plasma profile, cell phenotype, response to stimulation and/or transcriptome, followed by data integration we can now obtain a more complete understanding of how different immune compartments are affected during infection, which in turn could help identify promising diagnostic or therapeutic targets.

Over the last few years, we have built the capacity and know-how to generate and analyse large datasets based on cellular, proteomic, transcriptomic, serological, and clinical datasets. Within our team and through close collaborations we also have access to well-defined clinical samples from national and international TB cohorts. In this proposal these cohorts will be investigated using a systems approach to discern unique immunological features of the individual diseases. We will then further investigate how these differences are explained by functions in the immune response at a mechanistic level and also pinpoint potential markers that can be used to predict disease progression.

This research proposal is divided into three main aims:

Aim 1. Investigate the global immune profile during recent and remote latent TB and active TB to distinguish patterns associated with disease progression.

Aim 2. Investigate the immune response to Mycobacterium tuberculosis (Mtb) glycolipid stimulation to identify markers associated with TB disease progression.

Aim 3. Investigate mechanisms behind differential immune responses following stimulation with Mtb glycolipids.

The interaction between the host immune system and Mtb, the causative pathogen for TB, is multi-layered, resulting in a complex pattern of cellular and molecular responses during infection. We hypothesise that a broad characterisation of the immune response at a systems level will enable us to isolate unique immunological features associated with TB disease progression. This information can then contribute to improved diagnostic tests and guide studies into clinical interventions.

Research group

Team Sundling is part of the larger Anna Färnert research group at the Department of Medicine, Solna. We are composed of both clinical and experimental researchers and are located in modern laboratories at BioClinicum on the Karolinska University Hospital Solna campus. Within the group our main research focus is toward infectious diseases in humans, with projects including malaria, tropical fevers, COVID, and tuberculosis.

Team Sundling currently includes one research assistant doing mechanistic B cell studies and one PhD student using a systems immunology approach to malaria, with another one to be recruited shortly. Our focus is towards understanding how the immune system is engaged during infection. This information will help in identifying how protective immune responses develop and could potentially be used for more optimal vaccine design. Identifying unique immunological signatures can also potentially be used for development of novel diagnostic tools for infectious diseases.

Supplementary information

Key words

Tuberculosis, Systems immunology, B cells, antibodies, glycolipids, innate immunity

#80 Multi-omics analysis of the developing human spinal cord in vivo and in vitro

Type of recruitment
Postdoc, 24 months

Project title
Multi-omics analysis of the developing human spinal cord in vivo and in vitro

Supervisor
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Qualifications of applicant
We are interested in engaging postdocs for 1–2 years with documented experience in: neural development, spinal cord anatomy, organoids/3D cultures, RNA-sequencing, integrating different expression analyses/multi-omics, bioinformatics.

Background
The Human Cell Atlas is a world-wide international initiative to apply definitions of cells based on gene expression patterns, to identify all cell types in the human organism. Single cell RNA sequencing (scRNAseq) are used to determine global gene expression patterns in large numbers of cells, and identify cell types by unbiased cluster analysis. The data is combined with spatial analysis for unbiased identification.

Defining cell types during development is even more challenging since change is a key feature. Some cell populations only exist transiently as cells enter and exit different cell states during differentiation. Due to the difficulties in sampling of tissues at all continuously developing timepoints, recently published scRNAseq data indicate that these transient cell states may not be well defined, but rather constitute a continuum.

Studies on human tissue is severely limited with respect to experimental manipulation. To circumvent this, it is possible to use organoid cultures. These 3D cultures can mimic major features of developing tissue. Spinal cord organoids have been developed, applying morphogens to direct pluripotent stem cells towards dorsal and ventral spinal identities. Organoid cultures allow for genetic modifications, knock-in and knock-out methods, reporting-genes, tracing of cells,

and pharmacological treatments to block receptors and enzymes; tools to discern the role of key signaling pathways during early development.

Research project description

In our Human Developmental Cell Atlas (HDCA) project we determine the spatial expression patterns by microarray-based Spatial Transcriptomics, and combine these data to deconvolve them into cell types and clusters with bioinformatic tools. We then identify combinations of genes as specific markers for each cell type, and map these marker sets at cellular resolution in 3D by in situ sequencing. Finally, to validate expression data we use multiplex immunofluorescence, primarily the CODEX platform to map the spatiotemporal distribution of proteins, focusing on proteins not yet found in adult tissues. The first part of the project is focused on the development of the human spinal cord. We have so far sequenced approximately 50,000 cells in spinal cords from 5 to 14 weeks post-conception.

In the second part we will establish human spinal cord organoids derived from human embryonic stem cells to model the normal development. We use known morphogens to control spatial identity of the organoids. To validate the organoids, we use the same combination of scRNAseq and spatial methods to correlate with our human spinal cord data. Once organoid cultures have been established, the initial studies will concern.

Key topics and issues we will address in the project are:

- Using the experimental layout above, create a comprehensive data resource for gene expression during spinal cord development at single cell level.

- Define what the different subpopulations of spinal stem and progenitor cells represent with respect to fate specification, with a focus on transition states vs differentiation continuum, and previously unidentified subpopulations of progenitors.

- Determine if there are increasing quiescence among subpopulations of neural stem cells, the mechanisms regulating such quiescence and the consequences for in vitro isolation of neural stem cells.

- Use human spinal organoids to determine to what extent the developmental process can be mimicked in such cultures, analyze key pathways for fate specifications, and study the integration as assembloids with supraspinal organoids.

Research group

Our research group includes six persons at present, with the spinal cord as our prime interest. After a long-term commitment to research on spinal cord injury and

cell therapy, we are now focusing on human spinal cord development, to better understand the basis for spinal regenerative treatments. Together with four groups at the KTH Royal Institute of Technology and Stockholm University, we constitute the core of the Human Developmental Cell Atlas (HDCA) consortium within the Human Cell Atlas. Our goal is to identify all cell types during the human prenatal development. The source of the research material is the Karolinska Institutet Developmental Tissue Bank, a core facility that is run by our research group. The prenatal tissue is retrieved from clinical routine abortions in local hospitals.

Supplementary information

Key words

Development, Spinal cord, Transcriptome, Bioinformatics, Organoid

#81 Identification and clinical validation of novel pathways linked to the atheroprotective effects of high density lipoproteins

Type of recruitment
Postdoc, 24 months

Project title
Identification and clinical validation of novel pathways linked to the atheroprotective effects of high density lipoproteins

Supervisor
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Qualifications of applicant
We are looking for a highly motivated, structured, enthusiastic, and scientifically driven postdoc interested in exploring the molecular basis of atherosclerotic cardiovascular disease in relation to clinical outcomes. The person should exhibit a high degree of independence but on the other hand also value a collaborative approach to science and enjoy working in a team. Good proficiency in English, both oral and written is required. The postdoc should have a background in biomedical sciences, ideally covering molecular biology, experience with genetic screens and bioinformatics, combined with an interest regarding the work with preclinical models. Prior knowledge in cholesterol metabolism, macrophage or endothelial cell biology, cell culture or work with the CRISPR/Cas9 system is an asset.

Background
Circulating levels of HDL cholesterol (HDL-C) are inversely associated with atherosclerotic cardiovascular disease (CVD) risk in large general population studies, which resulted in the widespread clinical use of HDL-C as a biomarker in CVD risk prediction. However, outcomes of pharmacological intervention trials aiming to increase plasma HDL-C using cholesteryl ester transfer protein inhibitors or niacin have been disappointing and largely negative, since substantial increases in HDL-C did not translate into a reduction in incident CVD events. Further, genetic studies also showed that lifelong low or high levels of HDL-C do not relate as anticipated to a respective increased or decreased CVD event risk. Such data caused a shift in research focus from mass HDL-C levels as static biomarker towards

the dynamic measurement of HDL function metrics. HDL particles protect against atherosclerosis by eliciting cholesterol efflux from macrophage foam cells, decreasing endothelial inflammation and inhibiting oxidative modification of LDL particles among others. However, the clinical utility of HDL function assays is still only at the beginning to be explored and insufficient knowledge exists with respect to molecular pathways corresponding to HDL-related signal transduction.

Research project description

The aims of the project are (i) to provide novel insights into molecular signalling pathways triggered by HDL and (ii) to delineate the clinical value of these. Within this framework, first, using CRISPR-Cas9 knockout screens different HDL-related signalling pathways will be interrogated in cell culture. This strategy will conceivably lead to the identification of novel molecular targets central to the biological effects of HDL particles, which will be further mechanistically validated. In a parallel approach genome wide changes in gene expression in response to HDL will be determined using RNA sequencing in the setting of the in vitro HDL function assays, which we have previously established and characterized. For the pathways on which (ideally) the results of these parallel approaches converge we will determine which component of the complex HDL particle is responsible for the observed signalling events. Next the pathophysiological meaning of the obtained results will be investigated taking a multi-modality approach. (1) The predictive value of that specific HDL function for incident cardiovascular outcomes is determined in one or more of the suitable large, well-characterized prospective patient/general population cohorts available to us. (2) The predictive value of the identified specific component of HDL particles underlying the biological effect is characterized using mass spectrometry in clinical cohorts as under (1). (3) The impact of modulating expression of the identified target pathway (knockout/overexpression) on experimental atherosclerosis is investigated in suitable mouse models. (4) The effect of genetic variation at the locus of the identified molecular key player on incident cardiovascular events is delineated with the help of collaborators. Combined, this project is tailored to provide novel insights into key events in the process of atherogenesis from an in vitro discovery setting over preclinical models to clinical validation. The mentioned assays are established in the group, material from several clinical cohorts, a mass spectrometry platform and expertise in working with pre-clinical models are available.

Research group

The research group is embedded in the Div. of Clinical Chemistry, Dept. of Laboratory Medicine at Karolinska Institutet, specifically in the “Lipo-Group Research Constellation (LGRC)” led by three senior researchers: Prof. Paolo Parini, Prof. Mats Eriksson and me. The aim of our collaborative research activity is the discovery of biomarkers and therapeutic targets for the diagnosis and treatment of cardiometabolic disease. LGRC combines the background and expertise of different medical and basic research disciplines, consists of international researchers from all academic levels and includes technical and administrative support.

Supplementary information

Key words

HDL, cholesterol, atherosclerosis, inflammation, CRISPR, in vitro, in vivo, mass spectrometry, mouse models, personalized medicine, outcome, cohort

#82 Advanced 3D Imaging Analysis of Intact Tumor Volumes

Type of recruitment
Doctoral student, 4 years
Postdoc, 24 months

Project title
Advanced 3D Imaging Analysis of Intact Tumor Volumes

Supervisor
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Qualifications of applicant
Given that the research project contains both experimental and computational aspects, we are looking for highly motivated candidates with a research profile / interest that includes cell and molecular biology, biochemistry, and bioinformatics. Thus, an educational background in biomedicine is appropriate.

The applicant must be able to communicate well in English, both orally and in text.

Background
We have previously reported that 3D microscopic imaging can diagnose and stage tumors more accurately than current 2D microscopy methods used in hospitals (Nature Biomed Eng 2017). Using immunohistochemistry and tissue clearing, we stained the vascular system in intact tumor volumes and characterized its intricate architecture in three dimensions (3D). The analysis revealed the tumor malignancy with great accuracy. We recently published an improved 3D imaging method that, in addition to labeling proteins, could also perform transcription analysis of intact tissues (Nature Biomed Eng 2020). By labeling both RNAs and proteins, we discovered cancer stem cell niches deep inside of malignant breast cancer tumors. In the project described here, we will both develop 3D imaging methods and explore intra-tumoral heterogeneity in clinical samples. By developing new strategies for improved multiplexed staining and automated image processing algorithms, we can efficiently explore complex spatial RNA and protein expression patterns that critically contribute to intra-tumoral heterogeneity. Understanding intra-tumoral heterogeneity is the key to efficiently diagnosing and treating patients with cancer.

Research project description

This project can be divided into two parts, one of which focuses on method development, and the other focuses on exploring intra-tumoral heterogeneity. Detailed studies of the complex internal landscape of tumors require state-of-the-art tissue preparation and labeling methods as well as imaging and computing techniques. We strive to develop faster, simpler, and more sensitive multiplexed and multimodal imaging methods. Thus, this project extends over many different research areas such as biochemistry, cell and molecular biology, imaging, bioinformatics, and cancer medicine. The list below contains some examples of methods and issues we will explore:

Sample preparation:

- Apply small probe reagents such as nanobody and aptamer for detecting targets
- Develop gel embedding methods to cross-link and protect biomolecules
- Develop new tissue clearing, expansion microscopy, and multi-round methods
- Develop DNA barcode tags to distinguish antibodies and/or DNA probes for multiplexed and multi-round imaging
- Design DNA hairpins for hybridization chain reaction to orthogonal amplification of fluorescent signals

Imaging and data analysis:

- Develop efficient multi-round imaging pipelines using light-sheet microscopy or other high-throughput microscopy techniques
- Develop accurate image-stitching and -merging algorithms for multi-channel 3D images
- Develop fast and robust image segmentation algorithms using e.g., machine learning
- Develop data analysis algorithms for multiplexed data e.g., cluster analysis

Intra-tumoral heterogeneity:

- Study the association between tumor malignancy and abnormal blood and/or lymphatic vasculature
- Explore how the intra-tumoral heterogeneity affect treatment resistance and relapse
- Investigate cancer stem cell niches and their role for tumor stage
- Assess the connection between epithelial-to-mesenchymal transition (EMT) and Intra-tumoral heterogeneity

References

Tanaka N, Kanatani S, Kaczynska D, Fukumoto K, Louhivuori L, Mizutani T, Kopper O, Kronqvist P, Robertson S, Lindh C, Kis L, Pronk R, Niwa N, Matsumoto K, Oya M, Miyakawa A, Falk A, Hartman J, Sahlgren C, Clevers H, Uhlén P‡ "Three-dimensional single-cell imaging for the analysis of RNA and protein expression in intact tumour biopsies"

Nature Biomedical Engineering Sep;4(9):875-888 (2020)

Tanaka N, Kanatani S, Tomer R, Sahlgren C, Kronqvist P, Kaczynska D, Louhivuori L, Kis L, Lindh C, Mitura P, Stepulak A, Corvigno S, Hartman J, Micke P, Mezheyeuski A, Strell C, Carlsson JW, Moro CF, Dahlstrand H, Östman A, Matsumoto K, Wiklund P, Oya M, Miyakawa A, Deisseroth K, Uhlén P‡ "Whole-tissue biopsy phenotyping of three-dimensional tumours reveals patterns of cancer heterogeneity"

Nature Biomedical Engineering Oct;1(10):796-806 (2017)

Research group

The Uhlen research team consists of 2 PhD students, 2 post docs, and 2 senior scientists. The group has an interdisciplinary profile that covers cell and molecular biology, computer science, physics and mathematics, and tackles both cancer and neuroscience related issues. We strive to conduct research that will ultimately benefit patients.

Supplementary information

Key words

Three-dimensional imaging, Intra-tumoral heterogeneity, Image processing, Tissue clearing, Cancer stem cells, Machine learning, Bioinformatics, Epithelial-to-mesenchymal transition, Light-sheet microscopy, Immunohistopathology, In situ hybridization, Tumo

#83 Functional consequences of TET2 mutation in chronic myelomonocytic leukemia, CMML

Type of recruitment
Postdoc, 12 months

Project title
Functional consequences of TET2 mutation in chronic myelomonocytic leukemia, CMML

Supervisor
Johanna Ungerstedt, MD, PhD, Associate professor, specialist in Hematology
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Qualifications of applicant
PhD degree, good understanding of cell and molecular biology, proficiency in written and spoken English, Communication skills and interpersonal Communication and collaboration skills, experience in cell Culture of mammalian cells/primary human patient cells, at least basic knowledge and experience of flow cytometry, experience with next generation sequencing analysis (RNAseq/DNAmethylation/ChIP seq) and bioinformatic processing of data output.

Background
Chronic myelomonocytic leukemia (CMML) is hematological malignancy with heterogenous clinical phenotype, frequently displaying autoimmune disease and inflammation. The hallmark of CMML is peripheral blood monocytosis, and upon inflammation/infection there is often an extreme expansion of monocytes as well as other myeloid cells in peripheral blood. TET2 loss of function mutation occurs in 60% of CMML patients. TET2 protein is involved in DNA demethylation and also in resolving inflammation, however it is not known what functional consequences TET2 mutation has in the CMML disease driving monocytes and especially in the CD14+ CD16- monocytes that are expanded in CMML compared to healthy, nor in the early hematopoietic progenitors. This project aims at understanding the effects of TET2 mutation in monocyte subsets and in CD34+ early progenitors, on transcription, DNA methylation and hydroxymethylation, and Surface cytokine receptor expression in TET2 mutated CMML patients, and to understand if it is the healthy or TET2 mutated cell populations that expand upon infection/inflammation.

Research project description

As there are no good cell lines of CMML, we will use primary human cells for this project. This includes TET2 mutated CMML patients, age matched healthy Controls, and cells from TET2 mutated healthy individuals with clonal hematopoiesis but no overt disease (CHIP clonal hematopoiesis of indetermined potential).

From these Three groups, we will sort cell populations of CD34+ progenitors and monocytes, and assess DNA methylation and hydroxymethylation, as well as transcriptional output by RNA seq), to understand how TET2 mutated monocytes and progenitors drive disease, and the transcriptional difference between normal unmutated, TET2 mutated but with no disease, and TET2 mutated CMML monocytes. Using peripheral blood from the same patients, we will compare the transcriptome of classical and nonclassical monocytes by single cell RNA seq. In addition, in a collected material of peripheral blood at the time of infection/inflammation and high leukocyte Count, we will sort cell populations and determine whether the expansion upon infection/inflammation consists of healthy hematopoiesis or TET2 mutated cells. We will also characterise the cytokine receptor profile in the different monocyte subsets, compared to normal, to understand how the TET2 mutated monocytes drive the CMML Clinical phenotype.

Research group

Johanna Ungerstedt PI. Clinical Hematologist, Translational researcher, 50% position as Clinical Cancer Researcher funded by Cancerfonden. Kajsa Ax lab manager, responsible for Mastocytosis Biobank,

Stina Söderlund MD, specialist in Hematology, post doc, Matilda Kjellander MD, PhD student, Ebba Lundin, resident doctor in Hematology, PhD student, Wouter van Midden Master's student, Linda Forsell project student.

Supplementary information

Key words

CMML, TET2, DNA methylation, epigenetics, leukemogenesis

#84 CRISPR-based studies of pathogenic neutrophil biology

Type of recruitment
Doctoral student, 4 years

Project title
CRISPR-based studies of pathogenic neutrophil biology

Supervisor
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Qualifications of applicant
We´re looking for a highly motivated student with a background in biomedicine or medicine. The project is due to the clinical nature of the research unit, also suitable for applicants with clinical experience, but also for students with a more basic research background.

Prior research experience (e.g. immunology, molecular biology and bioinformatics) is highly valued. Organisational and communication skills are also highly valued.

Background
Neutrophils are the most abundant immune cell in our body, and they are rapidly recruited to sites of inflammation. Neutrophils can release a variety of potent effector molecules, including reactive oxygen species and proteolytic enzymes. In the acute setting, neutrophils are important for combating infectious agents. However, during sterile inflammation, like in patients with autoimmune disease, they contribute to excessive tissue damage and the release of antigens activating adaptive immune cells.

Neutrophils are challenging to study due to their short life span and general sensitivity. As a consequence, we have a limited understanding of how neutrophils are regulated in different settings and how to target them therapeutically. We have addressed this technical bottleneck by developing methods where we expand hematopoietic stem cells, use CRISPR to manipulate them, and then differentiate them into mature cells in vitro or in vivo. This approach enables us to rapidly identify genes central to neutrophil behavior.

We use patient material, and experimental systems aiming to (i) describe mechanisms that can be targeted to suppress neutrophil activation and migration to inflammatory sites, such as the joints of patients with rheumatoid arthritis, and (ii) develop CRISPR-based tools to study neutrophil behavior. This research is important as it addresses an understudied fundamental topic, aiming to develop basic understanding and identify drug targets linked to neutrophils.

Research project description

My research group has developed several tools related to neutrophils, joint inflammation and CRISPR (See https://wermelinglab.com/ for links and examples):

Example of our studies related to neutrophils and/or joint inflammation:

Anthony et al, Nature, 2011

Wermeling et al, PNAS, 2013

Lloyd KA et al, Front Immunol, 2019

Schulz A et al, Cell Rep, 2019

Panda et al, PNAS, 2020

Example of how we work with CRISPR as a discovery tool:

Panda et al, Bioinformatics, 2017

Wermeling, Addgene blog, 2017

Iyer et al, Comput Struct Biotechnol J, 2020

In the doctoral program, experimental in vivo animal models and in vitro model systems will be used to study neutrophil behavior with relation to joint inflammation. In parallel, clinical material from patients with Rheumatoid Arthritis (RA) will be studied; to validate findings from experimental systems, but also for discovery.

A major emphasis of the doctoral program relates to further develop CRISPR-based methods to study neutrophils. This includes the successful student getting experience with molecular biology, different OMICS approaches, and bioinformatics. See e.g. Iyer et al, Comput Struct Biotechnol J, 2020 for examples of the current direction of the research in my group.

A central hypothesis of my lab is that neutrophils contribute to autoimmune and inflammatory diseases, like RA, by (i) acting like an amplification loop of the local inflammation, and (ii) by depositing modified (citrullinated) antigens activating the adaptive arm of the immune system. Limiting neutrophil activation and migration to the inflammatory site could thus serve as a novel therapeutic approach for these patients.

The broad aims of the proposed program are:

- Identify ways to suppress neutrophil migration into inflamed joints.
- Develop methods to perform neutrophil CRISPR screens with patient material, as well as with in vivo animal models.

Research group

My research group (three PhD students, one senior postdoc and one lab manger) is part of the division of Rheumatology, at the Karolinska Institutet. This is a large and very active clinical research division with a broad International network within academia and the biotech industry.

The projects of my lab are related to using molecular biology tools, with an emphasis on CRISPR and CRISPR screens, to study clinically relevant research questions.

Co-supervisor in the project is Dr. Lars Klareskog, who has been the Secretary of the Nobel committee, as well as several other honorable positions, including being the head for several large scale international consortia related to Rheumatology research.

Supplementary information

Key words

CRISPR, immunology, autoimmunity

#85 Metabolism in skin

Type of recruitment
Doctoral student, 4 years

Project title
Metabolism in skin

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Qualifications of applicant
We are looking for a highly motivated candidate with a strong background in molecular biology. The applicant should have a M.Sci. Experience in bioinformatics or metabolism is an advantage. The candidate should be able to work independently but also be a good team player and be able to collaborate with others. High level English is an absolute requirement as the group's working language is English.

Background
Recent years have seen a tremendous surge in metabolism research in fields such as cancer and obesity, however little effort has been invested into researching metabolism in the body's largest organ – the skin. Metabolism is expected to be involved both in normal skin physiology as well as in disease pathophysiology.

Research project description
OBJECTIVES

The overall objective of this project is to examine cellular metabolism and its importance in the main skin cell types that occur during aging and skin diseases such as psoriasis and chronic leg ulcers.

WORK PLAN

The first part of the project will be based on a series of unique human patient samples that will be harvested from healthy and diseased human volunteers. The biopsies will be examined by omics techniques including RNAseq and metabolomics and the data analyzed with advanced bioinformatic approaches. This will give a

broad overview of skin metabolism. The second part of the project will involve in vitro experiments in which the findings from the biopsies will be modeled, both for skin aging as well as for skin disease. This modeling will allow us to understand the relevance of the molecular biopsy metabolism findings. The techniques that will be used includes basic methods such as cell culture and RT-qPCR as well as advanced laser confocal laser microscopy and respirometry. The third part of the project is likely to include in vivo mouse experiments in which we target specific mechanisms identified in the biopsy and in vitro studies. Thus, overall this novel project has excellent learning opportunities for a motivated doctoral student as well as promising publication prospects.

Research group

The research group is led by Dr Jakob Wikström, dermatology physician and basic researcher, and includes several postdocs and doctoral students. The current research interests include common skin conditions such as impaired wound healing as well as rare genetic skin diseases. The group belongs to a larger constellation of dermatology focused research groups and is situated at the Centre for Molecular Medicine on the Karolinska University Hospital Solna Campus in central Stockholm.

Supplementary information

Key words

skin, dermatology, metabolism, human disease, cell biology, molecular biology, aging

#86 Computational and statistical models to discover driver alterations in cancer

Type of recruitment

Visiting doctoral student, 12 months
Postdoc, 24 months
Visiting researcher, 12 months

Project title

Computational and statistical models to discover driver alterations in cancer

Supervisor

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Qualifications of applicant

The applicant is expected to have a background in bioinformatics, biostatistics or computer science. Programming skills at least one of the languages R/Python/C++ are required. Experiences in data analysis of next-generation-sequencing data are advantageous.

Background

Identifying driver alterations is a key step in precision medicine for individualized cancer therapy, since these genetic alterations play a primary role in tumour progression, hence potentially the best drug targets. However, due to the complexity of cancer, this task is still challenging and requires integrative analyses from different types of omics data. Tumour heterogeneity is generally divided into 1) inter-patient heterogeneity, which indicates genotype variations between patients and 2) intra-tumour heterogeneity, which implies the variability between cells in a tumour. Both can hinder the cancer clinical prognosis and therapeutic targeting of tumour.

Research project description

The overall aim of this project is to develop novel and robust statistical and computational methods to integrate genomics features from both tissue- and single-cell- data to discover and prioritise driver alterations of individual patients for precision medicine in cancer.

We will discover genomic features at tissue-level for analysis of inter-patient heterogeneity using bulk-cell sequencing data. This consists of discovery and

quantification of genomic information including mRNAs, non-coding RNAs including gene fusion and circular RNA and somatic mutations. We will also characterise intra-tumour heterogeneity to obtain single-cell specific genomic features from single-cell data. The analysis includes cell-level mutation detection, characterisation of isoform preference at single-cell level and their associations with cellular subgroups. Finally we will propose a methodology to integrate these genomic features discovered from multiple –omics data of both tissues and single cells, functional data and clinical data to predict and prioritise driver alterations in cancer.

We shall apply the methodologies in a project on precision medicine in AML with collaborators from the Karolinska Institutet. The data contain multiple omics data of 400 Acute Myeloid Leukemia (AML) patients. Each AML patient consists of multiple omics data including whole transcriptome sequencing (bulk-cell RNA-seq), low-pass whole genome sequencing (WGS) (0.5 X) and deep-DNA-sequencing of a panel of 600 cancer genes. Single-cell RNA-sequencing data and whole exome sequencing (WES) data are expected to be available by the end of 2020. Available public datasets such as BeatAML (PMID: 30333627) and TCGA-LAML (PMID: 23634996) are used for validation.

Research group

At Department of Medical Epidemiology and Biostatistics (MEB) of Karolinska Institutet (KI), we carry out epidemiologic research in a wide range of medical areas, including cancer, psychiatry, neurological diseases, etc. Our projects aim to increase knowledge about causes of diseases and to translate the knowledge towards clinical application. MEB has the largest critical mass of academic biostatisticians in Sweden and is one of the largest among Nordic countries. This project is under supervision of Assistant Professor Trung Nghia Vu experienced in developments and applications of statistical and computational methods for cancer large-scale omics data and co-supervised by Professor Yudi Pawitan with strong expertise in biostatistics, bioinformatics and high-throughput molecular data modeling. Our group currently has one professor, two assistant professors, two PhD students and two research assistants. A new PhD student will start in November 2020.

Supplementary information

Key words

Bioinformatics, biostatistics, omics data, Next Generation Sequencing, Acute Myeloid Leukemia

#87 Telomerase activation by TERT promoter mutations in carcinogenesis and implications in precision oncology

Type of recruitment
Doctoral student, 4 years

Project title
Telomerase activation by TERT promoter mutations in carcinogenesis and implications in precision oncology

Supervisor
Dawei Xu, Docent
Department of Medicine, Solna

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Home page:

Qualifications of applicant
The applicants should have a master degree before or by June 2021, with strong background in cellular and molecular biology (both theoretical and methodological). They should also show good capacities in English communications (e.g. IELTS≥6.5).

Background
Telomerase is repressed in most human somatic cells while activated in 90% of human malignancies, which is required for multi-cancer hallmarks. The mechanistic insight into cancer-specific telomerase activation is of both biological and clinical importance.

Research project description
Telomerase is an RNA-dependent DNA polymerase with its catalytic unit TERT (telomerase reverse transcriptase) as a key component. It is well established that TERT induction/telomerase activation is essential to malignant transformation and immortalization by lengthening telomere. Moreover, many studies revealed multiple activities of TERT independently of its telomere-lengthening function in cancer cells, which strongly suggests TERT/telomerase as a master regulator of cancer hallmarks. Given the key role of telomerase in carcinogenesis, great efforts have been made to define the mechanism underlying telomerase activation in human cancer during last decades, and more recently, the hotspot TERT promoter mutation has been identified as a novel strategy for cancer cells to activate telomerase. My research is focused on this area with special emphasis on the

following issues: (1) How the mutated TERT promoter is regulated in cancer cells, or which factors activate the TERT gene transcription under this setting; (2) Whether the mutated TERT promoter can serve as a diagnostic and prognostic marker for cancer patients. The obtained results from the present study are expected to gain insights into cancer-specific telomerase activation and to contribute to precision oncology.

Research group

The research group is located at Bioclinicum, New Karolinska Hospital and includes 2 post-doctoral fellows and 3 PhD students.

Supplementary information

Key words

Cancer; Telomerase; TERT

#88 Investigation the role of regulatory RNAs in human skin wound healing

Type of recruitment
Visiting doctoral student, 12 months
Postdoc, 24 months
Visiting researcher, 12 months

Project title
Investigation the role of regulatory RNAs in human skin wound healing

Supervisor
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Qualifications of applicant
The candidate should have obtained a Ph.D. or master degree within the area of molecular or cell biology and have a deep interest in medical and biological problems. The applicant is preferred to have documented the previous experience with RNA research or skin biology. Previous experience with tissue culture, molecular, and biochemical techniques is desired. A high level of English, spoken and written, is a requirement.

We are also looking for a postdoc or visiting researcher who will develop and implement bioinformatics approaches to analyze data generated with various high-throughput technologies. Required skills for a successful candidate include: (1) A Ph.D./master degree in Bioinformatics, Computational Biology, Biostatistics, or a related discipline including where sufficient bioinformatics expertise is demonstrated in life sciences. (2) Firm knowledge in Unix/Linux, R, and at least one scripting language such as Perl or Python. (3) Experience in the analysis of next-generation sequencing data or big data management or genomics data mining and visualization. (4) Knowledge of relevant biological areas (chromatin and gene expression, genetics, and epigenetics).

Background
The chronic non-healing wound is a common and severe medical problem with unclear pathophysiology, which severely hampers the development of efficient wound treatment. Although constituting the majority of the transcriptional output of the human genome, the functional importance of non-protein-coding RNA (ncRNAs) has only recently been recognized. Compared to protein-coding genes, not only the expression but also the function of ncRNAs are more tissue- and cell

type-specific, underscoring their great potential as precise therapeutic and diagnostic entities.

Research project description

The objectives of our research are to reveal the expression and functional signatures of ncRNAs in human skin wound healing, and to identify ncRNAs that may be targeted in wound therapy. In particular, we aim:

1. To establish a gene expression map of human acute and chronic wounds with single-cell resolution, which will significantly advance current knowledge about cell composition and gene expression in human normal and chronic wounds, providing a basis for the development of new diagnosis and treatment.

2. To identify the functions of wound-related ncRNAs: We expect to identify the significant ncRNA regulators for each cellular process impaired in chronic wounds; therefore, combination therapy targeting multiple 'master regulators' may be designed.

3. To decipher the targets and signaling networks regulated by the wound-related ncRNAs, which will extend our knowledge on regulatory pathways involved in wound healing, and may lead to the identification of additional therapeutic targets than ncRNAs.

4. To evaluate the therapeutic potential of targeting wound-related ncRNAs. This proof-of-concept study, if successful, will be the first step towards a novel therapeutic approach for chronic wounds.

The immense economic and social impact of chronic wound calls for attention and allocation of resources to develop more effective therapies, which are essentially lacking to date. Investigation of the role of ncRNAs represents an emerging concept and constitutes a promising area for pharmaceutical intervention. The proposed study will, from a new angle, add to our understanding of wound healing biology, but also to the pathogenesis of chronic wounds, which will open new avenues for disease stratification and highlight novel drug targets for clinical studies.

Research group

The wound healing research group consists of:
Associate Prof. Ning Xu Landén, Ph.D., group leader
Assistant Prof. Dongqing Li, Ph.D. in skin immunology in 2014.
Postdoc fellow Zhuang Liu, Ph.D. in bioinformatics in 2019.
Postdoc fellow Minna Piipponen, Ph.D. in molecular medicine in 2019.
Ph.D. student Letian Zhang, Master in Pharmacology, registered in 2018.
Ph.D. student Maria Toma, Master in Pharmacology, registered in 2017.
Visiting Ph.D. student Qizhang Wang (2021-2022)
Ph.D. student Xiaowei Bian, M.Surg., registered in 2020.
Lab manager Dr. Amit Laskar (15% of full time)

Supplementary information

Key words

Wound healing, skin, dermatology, RNA, gene regulation, epigenetics, bioinformatics

#89 Circular RNAs in cancer development

Type of recruitment
Postdoc, 24 months

Project title
Circular RNAs in cancer development

Supervisor
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Qualifications of applicant
The successful applicant will be a motivated researcher, who recently obtained a Ph.D. degree in Molecular Biology or related field. She/he should enjoy the process of obtaining new knowledge via experimental skills at the laboratory bench.

Experience in current molecular biology techniques is required and knowledge of strategies for the analysis of large sets of data, e.g. RNA-seq results, will be a plus.

Additionally, the applicant should have good social and communication skills, and characterized by the willingness to effectively integrate in the research group.

Background
The pediatric cancer of medulloblastoma is the most common childhood tumor in the brain. Treatment options include resection, chemotherapy, and craniospinal radiation. Approximately 1/3 of patients eventually die from this disease, while survivors suffer from long-term side effects by the implemented therapeutic approaches. To improve the current levels of survival a better understanding of the biology of medulloblastoma development is needed. In this direction, the current

research proposal addresses the role of a new class of biomolecules, circular RNAs, in the context of medulloblastoma development.

Circular RNAs in eukaryotes were discovered more than twenty years ago, with our Department pioneering in these early studies. Initially, RNA circles were thought as rare by-products of the splicing machinery. However, the advent of next generation sequencing has provided compelling evidence that circular RNAs can be quite abundant, exceeding the expression of mRNAs originating from the same gene. Circular RNAs have been demonstrated not only to regulate brain development but also act as oncogenes or tumor suppressor genes for an increasing number of cancers, e.g. hepatic, prostate, bladder. However, very little is known on how circular RNAs impact medulloblastoma development. In order to fill this gap, the expression of RNA circles in a large collection of human medulloblastoma samples is interrogated and their functional implications in tumor development is addressed.

Research project description

- Current state of the project

We have determined the circular RNA transcriptome of the Daoy medulloblastoma cell line, which belongs to the Sonic Hedgehog subgroup of this cerebellar tumor. Moreover, we have addressed how Hedgehog signaling activation impacts circular RNA expression in Daoy cells. Additionally, using a limited number of samples, we have identified 7 circular RNAs down-regulated in medulloblastoma compared to normal cerebellum, while their corresponding linear mRNAs remain unchanged. Furthermore, depletion of some of these circles inpacts on the growth rate of medulloblastoma, suggesting functional roles of these RNA circles in disease development.

- Future directions

We plan to expand the RNAseq analysis for circular RNAs using a large collection of human medulloblastoma samples provided by Swedish and international sources. Currently we have received over 25 medulloblastoma samples of the Sonic Hedgehog subgroup, which are being subjected to next generation sequencing, followed by specific software analysis to detect back-spliced junctions, the marker

of RNA circles. Additionally, over 55 medulloblastoma samples of the remaining three subgroups, the WNT (Wingless), Group 3 and Group 4, will be received from The Children's Brain Tumor Tissue Consortium (https://cbttc.org) and subjected to RNAseq analysis.

We also aim to address the mechanism of action of circular RNAs de-regulated in medulloblastoma. One functional mechanism of circular RNAs, which relates to their increased stability due to the lack of 5´and 3´ends, is their capacity to interact with microRNAs and sequester them. Consequently, the availability of microRNAs to down-regulate target mRNAs is reduced, and this can affect tumor growth depending on whether the target mRNAs act as oncogenes or tumor suppressor genes. However, this is not the only mechanism of action of circular RNAs, as an increasing body of evidence suggests that RNA circles may also interact with proteins and even encode peptides via internal ribosome entry sites.

- Significance

This proposal represents, to our knowledge, the first effort not only in Sweden but also worldwide to systematically identify de-regulated circular RNAs in medulloblastoma and address their mechanism of action.

It is very likely that RNA circles, which impact on tumor development, will be identified in medulloblastoma, as this has been the case in other cancers where the role of circular RNAs in tumor growth was systematically addressed.

It is therefore anticipated that the outcomes of these studies will contribute to a better understanding of the biology of medulloblastoma development and possibly provide clues for novel therapeutic approaches that may be implemented in the treatment of this tumor.

Finally, circular RNAs can be detected in blood and urine, reflecting their increased stability, providing possibilities for their use as effective biomarkers for the early detection of cancer disease.

Research group

- Ani Azatyan, Postdoc, initiated the project with RNA sequencing of Daoy medulloblastoma cells to detect circular RNAs.

- Ting Wang, Postdoc, contributed to the analysis of selected circular RNAs.

- David Brodin, Bioinformatician, performed the identification of back-spliced exon junctions, the marker of circular RNAs, in the raw Illumina data, within the Bioinformatic and Expression Analysis core facility (http://www.bea.ki.se).

Collaborators:

- Anna Darabi, Ass. Professor, Department of Neurosurgery, University of Lund

- Peter Siesjö, Ass. Professor, Department of Neurosurgery, University of Lund

- Helena Carén, Ass. Professor, Sahlgrenska Cancer Center, University of Gothenburg

These co-workers have provided precious medulloblastoma samples.

Supplementary information

Key words

Medulloblastoma, cerebellar tumor, paediatric cancer, back-splicing, RNA circle, gene expression

#90 Prescribed drug use in pregnancy: register-studies of safety and effectiveness

Type of recruitment
Postdoc, 24 months

Project title
Prescribed drug use in pregnancy: register-studies of safety and effectiveness

Supervisor
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Qualifications of applicant
We seek a candidate with formal training (PhD) in Epidemiology and/or Biostatistics, thus expecting a solid understanding of causal inference and broad knowledge in statistical methods. Experience with handling of large data and/or reproductive topics is a strong plus but not a requirement.

Proficiency in written English is essential and should be documented through first authorship of at least two publications in international peer-review journals. Previous academic experience abroad is valued but not strictly necessary.

Finally, in addition to a demonstrated interest in the subject-matter, a background in medicine or pharmacology would be considered most beneficial to the project overall.

Background
Generally, both the efficacy and most common adverse effects of medications are identified in clinical trials conducted before the medication is approved. For pregnancy safety, however, the situation is reversed: since pregnant women are excluded from clinical trials, we learn about most maternal and fetal toxicities only after a specific drug has been approved, and of course also after it has been used by pregnant women. For comprehensive monitoring in the post-marketing setting, health care utilization records offer prospectively collected data for large populations and allow study of multiple outcomes. When collected in national registers, the ability to consider the entire population can generate enough statistical power to examine rare outcomes and important subgroups. While studies lack the benefits of randomization, careful design and analysis can produce

valid and informative results, under the critical assumption that all systematic differences between the exposed and unexposed which could lead to a difference in the outcome(s) have been considered. Using Swedish registers, we have sought to address such confounding by considering extensive measures of plausible confounding factors across several domains and comparison groups that share similarities with the exposed, with exploratory studies looking into use of antidepressants, opioid analgesics and antiepileptics. Through this proposal we seek to expand and refine our investigations of these and other drugs.

Research project description

The overall goal of the project is to understand the extent and consequences of prescribed drug use in pregnancy, by pursuing the following aims in Swedish population register-data:

1. Map and characterize prescribed drug use in pregnancy

To understand the extent that specific prescribed drugs are used by pregnant women, and under what conditions, we will identify use of specific medications in and around the time of pregnancy, and examine patterns in patient and prescriber characteristics, temporal and regional trends, concurrent use of other medications etc.

2. Investigate the safety of prescribed drug use in pregnancy

To determine drug safety from observational data we will assess the risk of adverse events in mother and child following exposure to specific medications in etiologically relevant periods of pregnancy, using a rigorous approach to address confounding from systematic differences in underlying risk factors between the exposed and unexposed. This includes considering extensive measured confounders across many domains and selecting relevant comparison groups (e.g., women exposed prior to but not during pregnancy, or using another type of medication for the same indication).

3. Evaluate the effectiveness of prescribed drug use in pregnancy

To understand if discontinuation of specific medications increases the risk of adverse events in pregnant women, and evaluate the effectiveness of specific prescribed drugs in reducing such risks in the later phase of pregnancy, we will compare indices of disease complications (e.g., hospitalization) in those who continue versus discontinue treatment in pregnancy.

The importance of these aims applies to any medication used in pregnancy. Among our primary targets of interest are psychoactive medications (e.g., analgesics, antidepressants, antipsychotics, antiepileptics, anxiolytics, stimulants), but also specific drugs used in the management of different chronic conditions (e.g. autoimmune disease and hypertension).

We seek a postdoc candidate to contribute to this broader project. Which drug(s) to target, and how, will be discussed with the candidate, whose interests and potential a priori ideas may influence the specific direction of the final research project performed.

Maternal medication use in pregnancy will be evaluated using two sources of information; the woman's own reported use of medications at enrolment in antenatal care (available in the Medical Birth Register from mid 1994) and all dispensed prescriptions outside of hospital (available through the Prescribed Drug Register from mid 2005). The possible study population will thus principally concern all women giving birth in Sweden from 1995, their children, and the children's fathers.

We are currently in the process of obtaining ethical approval for a new register-linkage to allow fully up-to-date analysis of prescribed drug use among Swedish women, which we expect to have in place during the spring of 2020.

Research group

This project is made in collaboration with Professor Brian D'Onofrio at Indiana University, and involves at least two PhD students in his group. The collaboration also includes my intra-departmental colleague Zheng Chang and one of his PhD students, who are helping us refine the extraction of information from the Prescribed Drug Register. The postdoc candidate would primarily be working with me at the Department of Medical Epidemiology and Biostatistics, with frequent interactions with the aforementioned team.

Supplementary information

Key words

Epidemiology, Register-based research, Prescribed Drug Use, Pregnancy,

ausal inference