

Wallenberg Centre for Molecular Medicine Research School

Interfaces between Systems

2019/2020



LUND
UNIVERSITY

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Faculty of Medicine

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Wallenberg Centre for Molecular Medicine
FACULTY OF MEDICINE | LUND UNIVERSITY

*Knut and Alice
Wallenberg
Foundation*



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Welcome to the Wallenberg Centre for Molecular Medicine at Lund University



Our research center – the Wallenberg Centre for Molecular Medicine at Lund University – is part of a national plan to position Sweden in a world-leading position for biomedical research. This initiative is jointly supported by the Knut and Alice Wallenberg Foundation, Lund University and Region Skåne.

Vart forskningscentrumet – Lund University Wallenberg Centre for Molecular Medicine – ingår i en nationell plan för att åter ta Sverige till världsledande position inom biomedicinsk forskning. Bakom centrumet står Knut och Alice Wallbergars Stiftelse tillsammans med Lunds universitet och Region Skåne.

Our Centre

In the Wallenberg Centre for Molecular Medicine at Lund University, we bundle expertise in different areas of biomedical research, regenerative medicine and imaging, and provide an excellent basis for translational medicine through clinical experts with different specializations.

The following specific areas are currently represented at our centre:

Cardiovascular System – Anja Meissner & Gustav Smith

Respiratory System – Darcy Wagner & Sandra Lindstedt-Ingemansson

Nervous System – Iben Lundgaard & Gesine Paul-Visse

Hematopoiesis – Filipe Pereira, Cornelius-Jan Pronk & Markus Hansson

Diabetes – Joao Duarte & Martin Magnusson

Musculoskeletal System – Paul Bourgine & Robin Kahn

Cancer – Vinay Swaminathan & Anders Wittrup

Medical Imaging – Einar Heiberg & Elin Trägårdh

Nervous System with Emphasis on Plasticity and Function – Niklas Mattsson & Anders Björkman

Advanced Therapy for Medical Products – Agneta Kirkeby & Karin Tran Lundmark



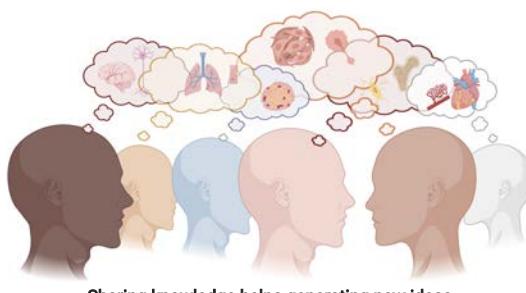
Our Research School and its mission to cross borders



#WCMM_ResearchSchool

Many diseases are only studied in the context of a single organ in isolation, but we know that patients often suffer from a number of co-morbidities, indicating more systemic diseases that act in multiple organs. The complexity of interactions between different biological systems makes cross-disciplinary collaborations and integrated research approaches mandatory for understanding mechanisms underlying diseases or co-morbidities. The formation of interdisciplinary research teams that are able to produce novel and outstanding scientific achievements has been limited, but is of strategic importance to pre-clinical and clinical scientists of all fields. However, cross-disciplinary communication is difficult. To improve this, it is necessary to train a new generation of scientists with fundamental skills for successful cross-disciplinary research endeavors. This can only be achieved by systematic exposure to different research fields, approaches and methods – a challenge that we are successfully tackling within the *WCMM Research School*.

Our school brings together PhD students and Postdocs from various backgrounds with the aim to foster critical thinking, scientific exchange between disciplines and thinking outside the box. With our program, we promote understanding of multidisciplinary research in regeneration, replacement and repair, and provide training in cutting-edge translational research to train the next generation of scientist.



Sharing knowledge helps generating new ideas

Greetings from the Coordinators

We are proud to have gathered a wonderful group of young scientists as trainees for the 2019/20 term of the *WCMM Research School*. Our trainees originate from a variety of scientific backgrounds and work in biomedical labs with either a clinical or preclinical focus. At this school, we have departed from our individual research differences and have directed the spot light onto the translational bridge in Molecular Medicine. This is the bridge that we will all need to cross for advancing the current biomedical knowledge, and then use it for the benefit of patients. We are striving for excellence in scientific education while preparing future research leaders. By bringing together Ph.D. students and Postdocs from different research fields we work towards this one goal: support our trainees to develop into scientists with a high level of curiosity and motivation to cross borders and enter yet unexplored paths with their research. We hope that, in this booklet, you enjoy learning about the research projects from the eyes of our *WCMM Research School* trainees.

The image shows two handwritten signatures side-by-side. The signature on the left appears to be "Anja Meissner" and the signature on the right appears to be "João Duarte". Both signatures are written in blue ink.

Anja Meissner & João Duarte

Our trainees

For the term 2019/2020, 18 trainees were enrolled in our program from different disciplines. Each of them works on their independent projects in their respective research groups within or outside the Wallenberg Centre for Molecular Medicine Lund.

This booklet compiles research summaries from the trainees, and was put together as part of the communication module in the *WCMM Research School* curriculum. One of the ground pillars of our program is science communication: communication to scientists both within and outside our own research areas, clinicians, patients and the general public. As part of their public outreach training, our trainees prepared a lecture to present in conjunction with the NMT days at Lund University. As topic they chose to discuss the importance of different communication routes within our bodies, such as the nervous system, or the endocrine (hormone) system. During *The Communicating Body* lecture you will learn how these routes connect the various organs and function in unison to respond to and interact with our environment.

The communicating body

In a healthy body, cells and organs communicate with each other in different ways. As an example, when bacteria enter the body, communication between cells is very important: immune cells, that protect us from disease, will send signals to other cells throughout the body to work together to destroy the bacteria. Communication between organs is also important. For instance, our brain needs to receive nutrients via the blood. Therefore, the heart and the blood vessels have to work together to transport enough blood with nutrients to the brain. If this communication does not work well, the brain does not get enough food and cannot work the right way. The brain also communicates to the body when more nutrients are needed by sending out substances called hormones, which for example make you feel hungry after an exam. When you are sick, some of these communication channels break down. In this lecture, we will help you understand some communication systems in our body and how they change when you are sick.

Den kommunicerande kroppen

För att en kropp ska vara frisk måste celler och organ kommunicera med varandra på olika nivåer. På en cell-nivå kan exempelvis kroppens försvarsceller skicka signaler till varandra så kallade cytokiner, för att fler försvarsceller ska komma dit och förstöra det okända, exempelvis en bakterie. På organnivå är till exempel hjärnan beroende av ständig tillförsel av näringssämnen för att fungera och därfor behövs det alltid ett blodflöde till hjärnan. Om denna kommunikationen inte fungerar kommer inte hjärnan få tillräckligt med näring och kommer därfor inte fungera. Skulle det inte finnas tillräckligt med näringssämnen i blodet kommer hjärnan kommunicera med hormoner till resten av kroppen samt få dig att känna känsla av hunger. I en kropp som av någon anledning är sjuk kommer någon kommunikation att misslyckas och därfor kommer funktioner som kanske skulle behövt inte fungera. Vi kommer under detta seminariet ge en inblick i hur kroppen kommunicerar eller inte, i hälsa och i sjukdom.

Our Research

Our trainees are engaged in research projects which cover multiple disciplines and topics of important relevance in current medicine. Each and every single researcher strives to finding new strategies to help reducing disease burden not only for the Swedish society but also for patients all over Europe and the world.

In the following pages, you will find a summary of each of our trainees' research projects, which have been written for the general public.

Could pericytes regulate the outcome of stroke?

Andreas Enström

PhD student

Translational Neurology Group



Approximately every 20 seconds someone in the world gets a stroke. This occurs when the blood to the brain is somehow compromised causing lack of oxygen and swelling of the brain which ultimately could have severe complications for the affected patients. Today one third of the world's population that suffer stroke do not survive and one third are permanently disabled.

Pericytes are cells found on the smallest of vessels, called capillaries. The total length of brain capillaries alone is approximately 643 km, which is roughly the distance from Lund to Stockholm and keeping them intact and fully functional is vital. Pericytes together with other cell types form what we call the blood-brain barrier (BBB). The BBB acts as a selective barrier that regulates what molecules are able to travel from the blood to the brain and vice versa. Pericytes are strategically placed at the intersection between the blood and brain and therefore have close contact and communication with several other cell types to maintain the integrity of the vessels and to exclude any toxic molecules entering the brain. Recent research show that pericytes respond early to stroke by sending out an abundance of signalling molecules to their surroundings including microvesicles. Microvesicles are small membrane particles which can contain complex signalling information and have the ability to travel over long distances to other recipient cells. Because of pericytes strategic position and their secretory capabilities they make an interesting candidate to study under stroke. We see that the signals pericytes are sending out during stroke can initiate the formation of new vessels, be protective to the precious neurons of the brain and also regulate the immune response.

Studying this can give us new insights in the cellular communication under stroke and hopefully lead to an understanding of how we can slow down or even prevent the detrimental outcomes.

In this project, I am doing a cell culture model of the BBB under low oxygen exposure, much like you would observe under stroke. In addition, we are using an enzyme that is able to label the secreted molecules from pericytes so that the origin can be determined. We hope that this will lead to new insights on how pericytes communicate under stroke and possibly be a new target for therapeutic intervention.

How does diabetes affect the brain?

Cecilia Skoug

PhD student

Diabetes and Brain Function



Our brain could be considered as our most important organ. To be able to function it needs energy in the form of sugar. In the rest of the body, our cells need a signal called Insulin to be able to take up the glucose so we can use what we eat as energy. We are studying the communication between the brain and the rest of the body metabolism, and why people with diabetes type 2 have a higher risk of getting memory problems (dementia).

Type 2 diabetes is one of the biggest diseases in the world, it is calculated that 1 in every 11 people is affected and it is type 2 diabetes that is affecting the most people. A big factor why this is affecting so many people is due to our lifestyle and our choice of diet. When people get obese this could develop into type 2 diabetes. The disease is based on that insulin does not really work for different reasons; this leads to that the cells can't use the glucose.

However, in our brain we don't need insulin for the brain cells to take up glucose, the brain uses another system to take up glucose. So, if our brains don't use insulin to fuel the cells, why is the brain affected by diabetes? Other researchers have shown that in animals with conditions similar to diabetes, the brain cells have a hard time communicating with each other and this could lead to dementia. We want to answer the question why diabetes is affecting the brain even if the brain cells do not use insulin to get fuel and also why diabetes can lead to dementia.

My research focus on molecules called endocannabinoids (EC), these are molecules that are formed when fat is broken down. The ECs are important in our normal body function as they regulate many things such as inflammation, how hungry we should feel or how the brain cells communicate with each other. In my project we investigate how the EC function in type 2 diabetes and if we can manipulate them to protect the brain.

Analysing the link between heart failure and lung diseases: How do they interact?

Franziska Uhl

Postdoc

Vascular Biology



Long lasting (=chronic) heart and lung diseases are amongst the main causes of death worldwide. 20 million people die from chronic heart and lung diseases according to the World Health Organization each year. Unfortunately, there are no good medications available to cure either of them. Therefore, patients with heart or lung diseases usually have no other options than heart or lung transplantation. Researchers have found hints that often, both diseases go hand in hand. This makes their treatment even more complicated. Often medications for one disease worsen the other. A better understanding of how these two diseases are connected to each other will therefore help us make better medications to treat both together.

In our research, we try to understand the biological processes that connect the heart and the lung during disease. We found that the balance of two components called S1P and CFTR is not normal in one of the most severe heart conditions called heart failure and multiple chronic lung diseases like chronic obstructive pulmonary disease (COPD) and fibrosis. We believe that the misbalance between those components in heart failure and chronic lung disease patients is bad for the respective other organ and over time leads to their failure. A treatment that can correct the amount of those two components may therefore prevent heart failure patients from developing problems with breathing and lung disease patients from developing heart problems.

To investigate this, we model heart failure and COPD in mouse models. We study how the misbalance of the two identified components affects

heart and lung function and the development of problems in both organs. We want to bring S1P and CFTR back into balance and will test specific medications that correct their relative amounts. Some of the medications that we are going to test are already used for treatment of a specific lung disease. We will try to show that these medications can also help heart failure patients to not develop breathing problems and prevent COPD patients from heart problems. If we are successful, these medications could in the future be tested in humans in a clinical trial and hopefully help people with heart failure and COPD.

Fighting cancer with the human body defense system

Ines Nascimento Caiado

PhD student

Cell Reprogramming in
Hematopoiesis and Immunity



In the same way that cities have police forces to defend us from threats, our human body also has a defense system- the immune system- that protect us from threats like bacteria and virus. The immune system can also defend us from cancer by detecting and killing cancer cells. To do this, cancer cells must have at their surface specific detection molecules that activate the immune system. Unfortunately, cancer cells can decrease the presence of these detection molecules and thereby become invisible to the immune system. There are already some therapies that use the immune system- Immunotherapy- to treat people with cancer. However, if cancer cells hide from the immune surveillance by decreasing their detection molecules the treatment is less likely to work.

In my project, I aim to make the cancer cells detectable again to the immune system. To do it, I am using cell reprogramming. This is the transformation of one cell type into another, for instance a cell from the skin can be transformed into a blood cell. Our bodies contain one cell type- so-called Dendritic Cells- that have in their surface high amounts of the detection molecules that are needed for the identification of cancer cells by the immune system. I aim to transform cancer cells into a Dendritic cell. In this way, I will force cancer cells to present in high amount the specific detection molecules so that they will become visible to the immune system again. Thus, cancer cells will be detected and killed by the immune system. In the future, I want to use this strategy to develop a cancer therapy for multiple cancer types.

Haplo-identical Hematopoietic Cell Transplant: *in-vivo* model

Isabel Hidalgo

Postdoc

Hematopoietic and Immune
Development Group



Hematopoietic stem cells (HSC) are cells that live inside our bones. They are extremely important since they are producing all the blood cells that we need during our lives. Blood cells have many important functions. They are in charge of the delivery of oxygen and food to our whole body and of the transport of immune cells (our natural “army”) when we are getting sick or having an injury.

But sometimes, certain types of blood cells can escape to the body’s control and present an undesired behavior like overgrowth. That generates a blood cancer type that we know as leukemia. Nowadays, advances in the treatment of some leukemia types have become so good that in the case of acute lymphoid leukemia (a specific type) for example, a 90% of the children can recover from it by applying chemotherapy. The problem is that these treatments sometimes do not kill all cancer cells and that they are so aggressive that also healthy cells are destroyed. The children therefore need a new source of HSC to re-produce their blood cells.

What can we do in those cases? Hematopoietic cells transplantation (HCT): that is to take some healthy HSC often from other person after the mentioned treatment and put them into the patients to regenerate their blood cells. Sounds easy, but we face then another big problem: there is a high risk that immune cells recognize these new HSC as strangers and attack them, causing rejection. When that happens, the new cells are not able to settle down and restore the function of producing blood cells. For that reason, we need the new HSC cells to be as similar as possible to the patient so they are not being noticed as strange and therefore not attacked.

All humans are different, so to find 100% compatible donors is often difficult and takes a long time to search among all the worldwide available donors.



The good news is that all of us have a 50% compatibility with any of your parents, and in the majority of the pediatric cases the parent's cells are very close and available, so wouldn't it be great if we could use those cells? That modality is called Haplo-identical HCT (Haplo-HCT). What if we could also train these parent cells to "attack" the cancer cells that sometimes are able to escape the treatment? To study this idea, we are using mice that are in a similar situation as these patients. We try to answer the questions above and some others and find out what works so that we can use it for leukemia patients.

Investigating Insulin-Dependent Regulation of Brain Energy Metabolism

João Vieira

PhD student

Diabetes and Brain Function



Did you know that 422 million people in the world have diabetes? Researchers think that this is because people get older, are less active and eat unhealthy food (e.g., food rich in fat and sugar). Patients with diabetes have a lot of problems in different organs of their body, including their brains. It was shown that there is a dramatic increase in the number of patients with both type 2 Diabetes Mellitus and Alzheimer's disease. These diseases not only affect the life of the patients but also their families and the whole society. It is important to ensure healthy ageing and promote well-being in the elderly. But to do this, we first need to understand the reasons why so many diabetes patients develop brain problems.

In my project, I want to understand how the fueling of the brain is affected by insulin, which is a hormone that is responsible for making the cells able to use glucose. Insulin is very important to control energy metabolism in the different brain cells. Metabolism is the sum of chemical reactions, known as pathways, that take place within each cell of a living organism and that provide energy for vital processes. In the brain, it is necessary to have well-functioning energy metabolism to make sure that our brain functions properly. It's known that cells from type 2 diabetic patients are not sensitive to the effect of insulin any longer. I will test the chemical reactions in the brain that are controlled by insulin and how these can be modified to prevent brain damage in patients with type 2 diabetes.

What drives me to do all this? I want to find a way to help patients with type 2 diabetes to grow old with a high life quality.

The protective effects of immunobiotics on human airway epithelium in asthma

Juan Jose

Postdoc

Respiratory Immunopharmacology Group led by Dr. Lena Uller

The world health organization (WHO) defines probiotics as "*living microorganisms that, when supplied in adequate quantities, promote health benefits of the host organism.*" Many people take probiotics or eat food that is rich on probiotics, like some yogurts. These living microorganisms are useful because they restore the intestinal flora and therefore improve your defenses against infections. The intestinal flora impedes the use of nutrients (Figure A) by bacteria or virus that are responsible for diseases, prevent that those organisms adhere to your intestines (Figure B), stimulate your immune system (Figure 1C), or kill these damaging organisms (Figure 1D). For example, you will probably have heard about or even taken probiotics when you had to take antibiotics. The antibiotics kill the bacteria that cause diseases but also kill these

bacteria that are part of the intestinal flora. Therefore, what you do when you take the probiotics is to restore this loss of helpful intestinal bacteria.

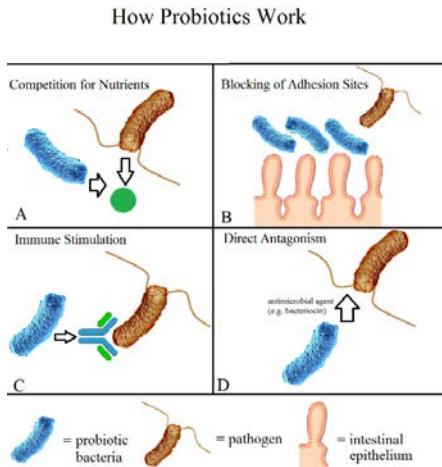


Figure 1. Scheme of the different mechanisms of action of probiotics. This figure represents the different protecting mechanisms of probiotics, including A) competition for nutrients with pathogens, B) blocking the adhesion sites of the pathogens, C) stimulating immune system, or D) directly antagonizing pathogens.

You should know that there is not only normal bacterial flora in the intestinal tract, but also in your lungs. However, this has been known for a short time and was very little studied. In addition, it has been seen that these microorganisms in the lung could be help our body against colds, flu or for chronic diseases such as asthma. I intend to study these helpful microorganisms and develop probiotics that serve for the treatment of patients with asthma or viral infections. In my studies, I am going to use both asthmatic patient cells from lung but also a mouse model of asthma. With these studies I try to find a combination of bacteria that you could take when you have asthma which protect you from a worsening of the disease and getting a viral infection.

Peer pressure can promote cancer

Julia Petersson

PhD student

Myeloma Research Group



Have you ever done something that you didn't really want to do, but you still did it just because people close to you wanted you to do it? As you might know, this is called peer pressure and can be a quite harmful thing – especially when it happens to cells inside your body.

Cancer cells can have a negative effect on the cells that are in close contact to them. By sending out different signals, they can make other cells do things that they normally would not do in a healthy body. Cancer cells can in other words expose surrounding cells to a kind of peer pressure, and this peer pressure can help the cancer cells survive.

In my research, I study how this “peer pressure” occurs in a cancer type called Myeloma, which is a type of bone marrow cancer. The myeloma cancer cells grow inside the bone marrow, which is the body's factory of blood cells. In Sweden, 600 people are diagnosed with the disease each year. Unfortunately, even if the survival of myeloma patients has increased the past years, myeloma is still an incurable disease. When the myeloma cancer cells take over the bone marrow, they start to make molecules that break down the bones, and this is why many patients suffer from skeletal pain. The myeloma cancer cells also affect the immune system, the body's defense against virus and bacteria, and make it less functional. How the myeloma cancer cells affect other cells is still not clear, and it could be an important key for a future cure of the disease. Therefore, I study how the peer pressure from myeloma cancer cells affects cells of the immune system. Hopefully, this will lead to a cure for myeloma patients in the future.

Breast cancer: what makes the cancer cells move?

Linn Engström

PhD student

Cell and Molecular Mechanobiology



The cells in our body are able to feel and respond to the environment surrounding them and the way it changes. The cells can for example feel how hard or soft the tissue surrounding them are and act different depending on this. In our research, we focus on understanding these so-called mechanical signals, and how they alter processes in our body. These mechanical signals can change the way the cells grow, develop and move, which is why it is extremely important to understand these.

In my project, I am investigating how mechanical signals work in breast cancer cells that are moving and forming metastases. Breast cancer is one of the most common disease diagnoses given today and many people still die from it each year. When cancer cells start to grow, they do so at one specific “starting”-site in the breast tissue in the body. These cancer cells can then start moving from the breast tissue out into the body – this is called cell migration. When the migrating breast cancer cells attach and stick to another place in the body and start forming a new tumour this is called metastasis. The ability of the tumour cells to migrate and form metastatic tumours is the main cause of death in cancer patients of all types of cancer. Cancer cells can move either alone, as single cells, or in groups of many cells held together, this is called collective cancer cell migration. How cells move together depending on how their surroundings change is not really understood. We are researching how mechanical signals are involved when breast cancer cells start to migrate collectively, hoping to understand what drives the metastasis process.

Treating brain damage in heart failure patients

Lotte Vanherle
PhD student
Vascular Biology



Heart failure describes a disease where the heart is too weak to pump enough blood through our body. Worldwide, over 23 million people have heart failure. Because the world's population ages, it is possible that many more people will develop this disease. Health care has become better and better over the years and helped heart failure patients to live longer. Sadly, heart failure often causes problems in organs other than the heart itself. Our brain for example, needs the heart to nonstop carry blood with oxygen and nutrients to our brain cells because they can only store very little energy themselves. If the brain's "food" supply is low, brain cells become smaller or can die. In healthy people, the brain can deal with short periods of lower blood flow, but the brains of heart failure patients cannot handle these changes. At the moment, there is no medicine that helps to protect our brain during heart failure.

In our research, we showed that the blood vessels in the brains of mice with heart failure do not function normally and cannot supply the brain with enough blood. By repairing the blood vessels and with it the delivery of "food" to the brain cells, we showed that fewer brain cells were damaged. One important task of one type of brain cells, also called nerve cells, is to help remember things. Mice with heart failure and unhealthy blood vessels had a bad memory, but when we repaired the function of the blood vessels the memory also became better. This "blood vessel repairing" treatment could be a medication to stop the damage in the brains of heart failure patients from becoming worse.

In the future, we would like to study if we can foresee these changes in the brain. We want to look for early changes that happen in the body, for example in the blood or different organs before damage in the brain occurs. If we find a sign of damage earlier, we can treat the patients sooner. The earlier we can treat, the less problems the patients will have.

A new treatment for high blood pressure?

Nicholas Don-Doncow

Postdoc

Vascular Biology



Over 30% of the world's population suffers from high blood pressure. High blood pressure harms our blood vessels and can lead to heart failure, stroke and damage many organs. It is also linked to increased activation of our immune system. Normally the immune system is our self-defense against dangerous bacteria and other diseases. But during high blood pressure the immune system activation is unhealthy. This activation can lead to damage to the blood vessels and the brain. Despite a lot of research, the connection between the immune system and high blood pressure is still not understood.

Our group, as well as others, has found that the molecule S1P plays an important role in blood pressure control. S1P can also guide our immune cells into the blood. We have found that as blood pressure rises, so does the amount of S1P in our blood. These increases go hand in hand with immune cell activation in the blood. Our group was able to show that animals missing a part responsible for making S1P did not have increases in blood pressure. These mice also did not have increased immune system activation.

Now, we are testing a drug that blocks the production of S1P. We hope that this drug will lower blood pressure and block the immune cell activation and entrance into the blood. The overall goal of our project is to find a new, more effective, drug for high blood pressure that targets the immune system.

A better life for extreme premature infants

Niklas Ortenlöf

PhD student

Neonatology-neuroprotection headed by David Ley



You should not be in a hurry. Please, take your time when doing something. Timing is everything in everyday life. Your lunch time, bedtime, different times of routines. The first schedule of your life could be the most important. A normal pregnancy takes about 40 weeks. If you are in a hurry to the world you will face problems. 15 million infants are born early or very early (called preterm infants) in the world annually. Being a preterm infant is the most common death of all under the age of five. In Sweden, most of the preterm infants, around 80 %, especially the extreme preterm (EPT) infants (you are born before 26 weeks of pregnancy) survive. Unfortunately, 62 % of the EPT infants born in Sweden develop serious damage and disease of the brain and lungs.

I work in the neonatology-neuroprotection group which focuses on the brain development of EPT infants. We have shown that EPT infants are low on different growth factors in their blood in comparison to infants that were born after a normal length pregnancy. Growth factors are molecules that are responsible for cells to grow and are very important for the brain's development. We investigate how this lack of growth factors affects EPT infants brain development.

Growth factors are very important for the communication of the body. I investigate how growth factors affect the communication in the brain via the release of extra cellular vehicles (EVs) from certain brain cells. EVs are very small versions of cells that different cells use to communicate and share nutrients with each other. The brain is very specific of what can enter from the blood to the brain. Some cells act like gatekeepers, they check

molecules from the blood and see if they have the right “documents” to enter the brain. These gatekeeper cells let growth factors connect with them and afterwards, the gatekeeper cells produce and release EVs to the surrounding environment to give information to the nearby and far away brain cells. The lack of growth factors in EPT infants could make for a non-healthy communication in the brain because not enough EVs are made from the gatekeeper cells.

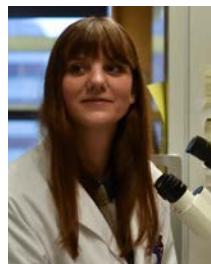
Being born prematurely means that you missed your first schedule in life. But it was not your fault. I hope that my research about growth factors, gatekeeper cells and EVs will help to lower the risks to develop problems in the brains of preterm children.

Towards better clinical tools for rheumatic children

Sabine Arve

PhD student

Center of Pediatric Rheumatology



Did you know that your immune system may go berserk and start attacking your own body? This is what happens when you have an autoimmune disease. The immune system mistakes something in the body for an invading microorganism and initiates a targeted attack and starts to produce antibodies towards this “something”.

Antibodies can be described as super specific flags, telling the rest of the immune system where it should attack. Depending on where the attack is there will be a different disease. As an example, antibodies targeting insulin-producing cells are connected with diabetes type I while antibodies targeting red blood cells cause autoimmune anemia. Therefore, the health care can use information about presence or absence of a certain antibody as a tool in setting a diagnosis or predicting the disease course.

The disease my research group is working on is a rheumatic autoimmune disease affecting children, called juvenile idiopathic arthritis (JIA). Many children with JIA have antibodies directed to material present in cell nuclei, called ANA. Unfortunately, these are not very helpful in diagnosing or predicting the disease in JIA. Partly because ANA are present in several diseases, but primarily because very many things can be found in a cell nucleus and no one knows exactly what the ANA in JIA are targeting.

In our research, we try to identify the specific molecules that ANA are targeting in JIA. I believe that antibodies towards certain molecules are more dangerous to have (associated with severe disease) while antibodies towards other molecules might be harmless (not associated with anything

in particular). When we know which antibodies that are dangerous and not, this is when we know which antibodies that will be important to screen for and what their presence can tell us about the disease.

In the end, I hope that my research on antibodies and the molecules they target will give rise to an easy test. A test which can be used in the clinic to facilitate diagnosing, predicting disease progression and the choice of correct medication for children with JIA.

På väg mot bättre kliniska verktyg för barn med reumatism

Visste du att immunförsvaret kan löpa amok och börja attackera din egen kropp? Det är vad som händer vid en autoimmun sjukdom. Immunförsvaret misstar något i kroppen för en infekterande mikroorganism och vips startas en riktad attack och det produceras antikroppar mot detta ”något”.

Antikroppar kan beskrivas som målsökande flaggor, som berättar för resten av immunförsvaret var det ska göra sin attack. Beroende på vad som attackeras får man olika sjukdom. Till exempel är antikroppar mot insulinproducerande celler associerat med typ I diabetes medan antikroppar mot röda blodkroppar ger autoimmun anemi (blodbrist). Därför kan sjukvården använda information om närväro eller frånvaro av vissa specifika antikroppar som hjälp vid diagnostik eller för att förutspå hur en sjukdom kommer att utvecklas.

Sjukdomen vår grupp forskar om är en reumatisk autoimmun sjukdom som drabbar barn, juvenil idopatisk artrit (JIA). Många barn med JIA har antikroppar som är riktade mot saker som finns i kärnor i kroppens celler, dessa antikroppar kallas ANA. Tyvärr är ANA ganska dåliga för att sätta diagnos eller förutspå sjukdomsutveckling i JIA. Delvis beror det på att många sjukdomar kan ha ANA, men främst beror det på att det finns oerhört många saker i en cellkärna och ingen vet exakt vilka av dem som antikropparna är riktade mot i JIA.

I vår forskning försöker vi identifiera de specifika molekyler som ANA i JIA är riktade emot. Jag tror att det kommer visa sig att antikroppar mot vissa molekyler är farliga att ha (t.ex. associerade med svår sjukdom)

medan andra är ofarliga (inte associerade med något särskilt). När vi vet vilka antikroppar som är farliga och inte, det är då vi vet vilka antikroppar som det är viktigt att testa för och vad de kan säga om sjukdomen.

Jag hoppas att min forskning om antikroppar och molekylerna de flaggar i framtiden kan leda till ett enkelt test. Ett test som kan användas i kliniken för att underlätta diagnostik, förutspå sjukdomsutveckling och göra så att barn med JIA snabbt kan få rätt medicin.

Characterize and recreate the bone marrow *in vitro*

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The bone marrow is a unique tissue located in the inner part of the longest bones of the human body (hip, femurs ...). It constitutes the birth place of all the cells that flows into your veins and is therefore necessary for the proper function of all the other organs of the human body. Being so important, the bone marrow is naturally protected by the difficult-to-penetrated bone tissue, making the study of this tissue in human very difficult as it is not easy to get bone marrow samples. Therefore, the vast majority of what we know about the bone marrow is come from studies of animal models, mice in particular. However, the more we know about how the cells within the bone marrow function, interact and develop, the more we realize that mouse and human are quite different even with the limited data we have for humans. This is a problem for scientist trying to develop new weapons to kill cancer affecting the bone marrow, as what is working for mice cancer does not necessarily work the same way in humans.

This is why, in my PhD, I am aiming to reconstitute parts of the bone marrow *in vitro* (without the use of animals). To do so, I am using a device called a perfusion bioreactor that mimics a blood circulation, combined with a support for the cells to attach. I seed particular cells called ‘nurse cells’ in this bioreactor to feed and home the cells (blood stem cells) that give rise to of all the blood cells. Of course, the scaffold and the cells are all from human origin.

To establish this new *in vitro* system, I will have to provide a functional analysis of the bioreactor. To put it in other terms: I will have to determine if the blood stem cells behave in a similar way as they do inside

your bone. One added bonus is that I can fully control the nurse cells by making them produce particular molecules that can help the blood progenitors to make more red blood cells or more immune cells or just stay asleep. This ‘customization’ of the bone marrow *in vitro* will help to understand the mechanism by which the nurse cells and the blood stem cells interact in a human context. The more we understand about the biology of the human bone marrow the better we can develop therapies.

Is it possible to generate bones in the lab?

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Bone is a unique organ. It gives stability to our body and protects the organs. It helps in blood formation and stores minerals and fat. It is one of the strongest parts in our body. They could heal without producing scars, when they get broken. But in extreme cases, like accidents or diseases, our body cannot completely restore the broken bones. There are several possible treatments available. One of them is to replace the defective bone using surgery (bone grafting) using bone taken from the same person (auto graft) or from other people (allograft). But it involves multiple surgeries and finding a suitable donor is challenging. Another option would be to use artificial bone materials (synthetic graft), but they cannot function like natural bones during its repair. To overcome the disadvantages in the options above, Bone tissue engineering has been emerged as a promising alternative.

Our research group uses bone tissue engineering to generate new grafts in the laboratory that are capable of inducing bone regeneration. The aim of my project is to study and understand how the cells which protects our body – the immune cells, helps in regenerating bone. We study and compare the bone growth in both normal mice and mice lacking immune system and try to understand how these immune cells help in bone remodeling. Understanding this process could help to generate a new graft which could be useful for treating humans in the future.

Children with arthritis – not just an age associated disease

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When someone hears the words joint pain and arthritis, the first thing that often comes to mind are old people. However, children can also develop arthritis, and it is more common than you think. Arthritis, or inflammation of the joints, is as common as several childhood related cancers. The peak age of getting arthritis as a child, is two years of age. It can be a horrible disease, leading to pain, movement difficulties and even very severe complications, such as amputations. The disease is chronic and unfortunately there is no available cure.

In our lab, the goal is to understand how and why these children develop arthritis. To achieve this, we are looking at the local site of disease – the joint, and the immune cells that are present. Like a country needs the military for defense, our bodies depend on its military defense against viruses and bacteria – the immune system. In arthritis, the immune system mistakes the joint for an intruder – and tries to do what the immune system does best – fight the threat. We are determining which cells of the immune system that end up in the joint.

To understand how these cells give rise to arthritis, we analyze samples from patients – joint fluid (the lubricating fluid that makes your joints flexible and easy to move) and tissue (biopsies from the joint). By using patient samples, we can then use various methods to look at cells present in the joint and how they behave. For example, we look at how these cells talk with one another – what signaling molecules they produce. When the immune system stumbles across an intruder, they call out to the rest of the immune system by sending out signaling molecules. These molecules are

also produced by immune cells in arthritis. We are trying to understand which molecules are being produced, by which cells and if we can stop the production. With this information, we hope to be able to develop new drugs that target specific immune cells. We hope to answer the important question of the patients – why did I get this, and will I ever be healthy again?

The role of tumor environment mechanics in regulating cell metabolism and migration in cancer

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Cancer metastasis is the spread of cancer from the primary tumor to other organs and it is a major cause of death in cancer patients. Cancer metastasis has two main features: 1) the cells from the primary tumor gain the ability to move to other places, and 2) the cells adapt their energy levels to support moving and tumor growth at the new location. Both of these processes are regulated by chemical and mechanical signals from the tumor environment. Recent research has shown that the cells can understand and react to the mechanical characteristics of their environment both in health and disease. For example, every healthy person has stem cells, cells that have the potential to produce many cell types in the body. Stem cells make different cell types when grown on soft or hard substrate. In a disease like cancer, the risk of breast cancer is higher in women with harder breast tissue and metastasis is higher in harder tumors. It is clear that cells require energy to survive, grow, divide and move. Cancer cells use the usual energy production pathways of the cell in a different manner to increase tumor growth or cell movement. In this project, we aim to investigate how the cells understand the physical and mechanical changes in their environment and modify their energy production and movement accordingly.

