Master Thesis Catalogue 2022

Department of Pharmacy
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preface</td>
<td>3</td>
</tr>
<tr>
<td>CNS Drug Delivery and Barrier Modelling</td>
<td>4</td>
</tr>
<tr>
<td>Copenhagen Centre for Regulatory Science</td>
<td>6</td>
</tr>
<tr>
<td>Drug Delivery and Biophysics of Biopharmaceuticals</td>
<td>9</td>
</tr>
<tr>
<td>LEO Foundation Center for Cutaneous Drug Delivery</td>
<td>17</td>
</tr>
<tr>
<td>Manufacturing and Materials</td>
<td>21</td>
</tr>
<tr>
<td>Microscale Analytical Systems</td>
<td>27</td>
</tr>
<tr>
<td>Pharmaceutical Physical and Analytical Chemistry</td>
<td>30</td>
</tr>
<tr>
<td>Physiological Pharmaceutics</td>
<td>38</td>
</tr>
<tr>
<td>Protein Analysis</td>
<td>44</td>
</tr>
<tr>
<td>Social and Clinical Pharmacy Group</td>
<td>47</td>
</tr>
<tr>
<td>Solid State Pharmaceutics</td>
<td>49</td>
</tr>
<tr>
<td>Surface and Colloid Chemistry Group</td>
<td>53</td>
</tr>
<tr>
<td>Toxicology and Drug Metabolism</td>
<td>55</td>
</tr>
<tr>
<td>Vaccine Design and Delivery</td>
<td>61</td>
</tr>
</tbody>
</table>
Preface

This thesis catalogue is intended to inspire you and help you complete the thesis that suits you best. In the next pages, you will find a description of each research group, together with examples of project titles and research areas.

As you will not be writing your thesis until next year, these descriptions should be viewed as tentative only, as future research results may alter the projects. Therefore, the final projects will be defined in agreement with the students immediately before the projects start.

What might not be written in the catalogue is that in addition to the projects performed in the facilities of the University of Copenhagen, most supervisors offer projects in collaboration with other institutions/industries in Denmark or abroad. Therefore, if you find an interesting project area, feel free ask for options as to where such a project can take place.

To make sure you have a positive experience, there might be expectations as to existing knowledge or grades, depending on the project placement, but please remember that grades are not everything, and that a good attitude will get you just as far as good grades.

NOTE: Groups do not all use the same procedure to recruit Master students. Look carefully at the section "Application procedure and dates" at the end of each group's presentation so as not to miss any deadline.

Good advice when contacting your potential thesis supervisor:
1. Study the research conducted in your potential supervisor’s lab before you ask for a meeting
2. Don’t send out generic emails – tailor your emails for each potential supervisor you contact
3. Tell your potential future supervisor why you find their specific area of research interesting
4. Tell something about yourself in the email – your academic background and your interests
5. Remember to be ready to answer questions about details about your study program, the timing of your thesis work, how many ECTS points, and remember to ask if the supervisor recommends any elective courses

Good luck, and we hope to see many of you at the Department of Pharmacy in the near future.
We investigate how we can overcome the barrier tissues in the body and deliver drug compounds at the site of action. The major focus is on transport of compounds through the blood-brain barrier, but we also have projects on intestinal absorption and efflux of drug compounds.

The practical work includes design of novel peptide drug compounds, physicochemical studies of drug compounds, prodrugs and model drug compounds, ADME studies in cell models and in vivo and characterization of relevant membrane transport proteins. Special focus is on peptides. A number of peptide drugs for the treatment of brain diseases are available. However, to reach their target site of action, they must pass the blood-brain barrier (BBB). The capillary endothelium comprises the major physical barrier of the BBB and allows only passive permeation of molecules <400 Da. Brain delivery of the larger biopharmaceuticals, which today includes an increasing number of novel peptide-drug entities, is therefore restricted; both due to their large molecular size and hydrophilic nature. Thus, the development of peptide-drugs for the treatment of brain specific diseases requires a delivery strategy for overcoming the endothelial BBB in order to reach its final target within the brain.

The group consists of one professor, two assistant professors, one research scientist, as well as technicians, PhD-students and Masters students. We work in a cross-disciplinary fashion, have a large international network and an exciting work environment.

Potential thesis supervisors

<table>
<thead>
<tr>
<th>Mie Kristensen</th>
<th>Lasse Saaby</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assistant Professor</td>
<td>Research Scientist</td>
</tr>
<tr>
<td><a href="mailto:mie.kristensen@sund.ku.dk">mie.kristensen@sund.ku.dk</a></td>
<td><a href="mailto:lasse.saaby@sund.ku.dk">lasse.saaby@sund.ku.dk</a></td>
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Potential thesis supervisors

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<tr>
<th>Birger Brodin</th>
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<tr>
<td>Professor</td>
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<tr>
<td><a href="mailto:birger.brodin@sund.ku.dk">birger.brodin@sund.ku.dk</a></td>
</tr>
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Potential thesis supervisors
Examples of projects

**Cell models for screening of CNS drug compounds**
Industrial screening of CNS drug compound candidates involve the use of cell culture models. The project concerns characterization of drug transport in cell culture models developed by the group and investigation of their use in predicting blood-brain barrier permeability. The overall aim of the project is to generate predictive tools for CNS drug development.

**Supervisors:** Lasse Saaby & Birger Brodin. Max no of students: 3

**Stability of cell-penetrating peptide conjugated therapeutic peptides in biological matrices and their adsorption to plasma proteins**
The cell-penetrating peptides (CPPs) comprise a promising tool to facilitate delivery of macromolecular drug entities not only into cells but also across biological barriers, such as the BBB. However, due to their peptide nature they are prone to enzymatic degradation. In addition, cationic CPPs have been demonstrated to adsorb to plasma proteins, thus potentially hindering their cellular uptake.

With the present project, the CPP stability in relevant matrices (physiological buffer, cell culture media, plasma) as well as during incubation with brain endothelial cells (e.g. bEND3 cell line and a primary blood-brain barrier model) will be evaluated using e.g. HPLC, LC-MS, SDS-PAGE, and thin layer chromatography. In addition, CPP interaction with plasma proteins and its effect on uptake into brain endothelial cells will be evaluated via e.g. cell uptake studies and confocal microscopy.

**Supervisors:** Mie Kristensen. Max no of students: 3

**Glycocalyx characterization on in vitro blood-brain barrier models**
The cell-penetrating peptides (CPPs) comprise a promising tool to facilitate delivery of macromolecular drug entities not only into cells but also across biological barriers, such as the BBB. The mechanism by which CPPs translocate across cell membranes is widely discussed and both direct membrane translocation and endocytic uptake has been demonstrated. In addition, a number of studies suggest importance of CPP interactions with cell surface glycosaminoglycans (GAGs) prior endocytic uptake. GAGs are polysaccharide chains attached to a core protein unit making up the proteoglycans within the cell surface glycocalyx.

In order to obtain detailed knowledge on the potential involvement of GAGs for CPP membrane translocation, the glycocalyx layer on the cell culture model used for mechanistic studies must be well characterized. Furthermore, some studies question the presence of glycocalyx in endothelial cell culture.

With the present study we will characterize the glycocalyx surface lining primary mouse brain endothelial cells cultured as monoculture on permeable filters or in co-culture with mouse astrocytes. Employing antibodies and lectins we will identify the GAG composition and protein anchors as well as sugar moieties using confocal microscopy and Eastern blotting. In addition, electron microscopy may be applied to visualize the Glycocalyx morphology.

**Supervisors:** Mie Kristensen. Max no of students: 3

**Application procedure and dates**
If you are interested in writing your thesis with CNS Drug Delivery and Barrier Modelling, please write an email to one of the supervisors with more information about you. There is no deadline.
Medicines are important for our society, both to improve public health, but also for economic growth. At the same time, medicines are one of the most regulated products in our society.

Regulation is set in place to protect public health, while still fostering innovation that ensures that Europe continues to benefit from new medicines. However, regulating medicines is an increasingly complex issue. The structures of drug regulation that exist today have evolved over time, in an attempt to respond to an increasingly sophisticated pharmaceutical development, safety crises and needs and demands of the society.

The field of Regulatory Science seeks to study, evaluate and optimize drug regulatory systems in terms of their ability to ensure patient safety, enhance public health and stimulate innovation. This also includes the development of new methods, tools and instruments to assess the safety, effectiveness, quality, public health impact, or performance of medicines, thereby facilitating regulatory decision-making.

Through improvement of the drug regulatory system, we aim to contribute to an improvement of the health of the society. Furthermore, we carry out research that produces evidence to be used in drug regulatory decision-making.
Potential thesis supervisor

Christine E. Hallgreen
Associate professor
cors@sund.ku.dk

Researcher Profile
Christine Erikstrup Hallgreen is an associate professor at the Copenhagen Centre for Regulatory Science. She has a background in engineering physics, and a PhD from Department of Physics at the Technical University of Denmark. In her professional career, she has been previously employed in the pharmaceutical industry (Novo Nordisk) and academia (Imperial College London). Christine has also conducted research at the National Institute of Health, Maryland, USA. In her research, she utilizes her quantitative and methodological training in the development and evaluation of drug regulatory tools and systems. Her research is motivated by a desire to describe and understand the functioning of the regulatory system and thereby optimize and improve the systems and regulatory tools set in place to promote public health. Her research includes development and evaluation of formal qualitative and quantitative methods to assess benefit-risk of pharmaceutical products, probabilistic methods to assess the effect of uncertainty in outcome data, and methods to collect preference values to support benefit-risk decisions.

Examples of projects

**How best to protect public health: a comparative analysis of regulatory safety warnings on medicines in Australia, Canada the European Union and the United States.**

Medicines have important health benefits but can also lead to harm. When new safety concerns arise, national regulatory agencies issue warnings to health professionals and the public. These warnings differ between countries, but no research has compared the effectiveness of different approaches. This study compares safety advisories on medicines in Australia, Canada, the United States, and the European Union in order to identify how to best protect public health. Within the project several working groups will focus on different aspects: discordances in safety communication, regulatory policy analysis, qualitative analyses on HCP and patient perspectives, media analyses and pharmacoepidemiology to estimate health effects.

**Factors ensuring effective Direct to Healthcare Professional Communication of Risk Minimization**

Every day general practitioners receive all kinds of new information about new medicines and new research. But what do they need in their everyday practice in front of their patients? How can we secure that they receive vital information about newly discovered medicine risk? Normally physicians and HCPs receive this kind of information in a letter. But that mode of communication is not very beneficial to physicians nor patients. For those reasons this project sets out to understand how general practitioners prefer receiving this information and what is important for them to know about medicine. With this knowledge future communications may better support the decisions they make when prescribing medicine.
The Impact of Paediatric Regulations on Drug Development in a Trans-Atlantic Perspective

The objective of this PhD project is to provide insights into the effectiveness of the EU and US paediatric regulations to promote access to medicines for children as well identifying potential barriers of the paediatric regulations to innovative drug development in general. Ultimately, these analyses should serve to provide recommendations for improvements to the global regulatory frameworks for paediatric medicines development with a focus on the US and the EU.

You can find examples of previous Master thesis projects at CORS on our website: www.cors.ku.dk/education/

Application procedure and dates

If you want to learn more about writing a thesis at CORS, please join the Master thesis webinar organised by the Social and Clinical Pharmacy group on Tuesday, December 8 at 12am.

Join the webinar by clicking on the link: Master thesis webinar in the SCP group 2020.

If you are interested in writing your thesis with CORS, please write an email christine.hallgreen@sund.ku.dk with a short motivation (250 words) describing why you are interested in Regulatory Science (deadline December 10, 2020).
Drug Delivery and Biophysics of Biopharmaceuticals

www.pharmacy.ku.dk/research/drug-delivery-biophysics-biopharmaceuticals/

Our research focus is the design and development of optimal drug formulations with a focus on biopharmaceuticals, specifically peptides and proteins, used for e.g. metabolic diseases or infections. Our research spans from physico-chemical analysis of stability, and biomembrane interactions via design of advanced drug delivery systems, to assessment of the efficacy in cell culture models and animals. We aim to gain detailed, fundamental, and mechanistic understanding of the challenges associated with these molecules when administered via injectable and non-injectable routes.

Please note, that the below described projects serves as examples. We are always open for suggestions and discussions to design a project based on your scientific interest.

**Potential thesis supervisors**

**Hanne Mørck Nielsen**  
Professor  
hanne.morck@sund.ku.dk  
Research focus: Drug delivery of peptides and proteins (biopharmaceuticals) and antimicrobial drugs. Oral peptide delivery, drug delivery systems, nanogels, cell-penetrating peptides, biomembrane interactions, mucus, cell uptake and cell transport

**Urs Häfeli**  
Professor  
Urs.hafeli@sund.ku.dk / urs.hafeli@ubc.ca  
Research focus: Drug delivery of peptides and proteins (biopharmaceuticals), radiopharmaceuticals for diagnostic and therapeutic applications, nanomedicines for cancer and inflammatory diseases, SPECT/PET/CT as well as IVIS imaging.

**Marco van de Weert**  
Associate Professor  
marco.vandeweert@sund.ku.dk  
Research focus: Peptide and protein formulation; analytical chemistry

**Vito Foderà**  
Associate Professor  
vito.fodera@sund.ku.dk  
Research focus: Protein science; neurodegenerative diseases; nanomaterials for drug delivery; X-ray and neutron science, microscopy and optical and IR spectroscopy. If you want to look at my research focus, please visit: www.vitofodera.com/
Research focus: Nanoparticles-based pulmonary drug delivery to combat chronic and persistent respiratory bacterial infections (e.g., biofilm induced infections). Meanwhile, we attempt to obtain a fundamental understanding of Bio-nano interactions under pathological conditions to achieve the rational design of the nanoparticles and prompt the transition from lab research to clinical application.

Examples of projects

**Novel dosage forms with permeation enhancers for oral delivery of peptides and proteins**

Oral delivery of biopharmaceuticals is considered the Holy Grail of drug delivery. We will investigate new approaches to enhance uptake of biopharmaceuticals across oral mucosa by co-formulating the drug with permeation enhancers in novel solid dosage forms (e.g., micro-tablets, micro-containers, adhesive electrospun nanofiber patches, or expandable films). We will develop, characterize, and investigate *in vitro*, *ex vivo* and potentially *in vivo* how these increase oral peptide delivery.

**Supervisors:** Hanne Marck Nielsen, PhD student, and Jukka Rantanen, Stine Harloff-Helleberg or Mai Bay Stie
**Overcoming biobarrier challenges in drug delivery by functional excipients in nanosystems**

When studying drug delivery across epithelial barriers, e.g. the oromucosal or intestinal barrier, one of the key properties is the tightness of the epithelium due to the presence of epithelial cells as well as the tight junctions between the cells. This epithelial integrity is crucial for the normal function of the tissue, and tailored drug delivery systems are needed to enhance drug delivery.

In this project, we investigate the mechanisms of how tailored formulation can lead to improved drug delivery. Specific junction-modulating compounds or other permeation enhancers like cell-penetrating peptides will be formulated together with therapeutic peptides or proteins in nanoparticulate delivery system such as nanogels or polyelectrolyte complexes and thoroughly characterized. The drug delivery systems will evaluated biophysically to understand the intermolecular interactions and biobarrier dynamics *in vitro* in cell culture models.

**Supervisors:** Hanne Mørck Nielsen, Sylvia Klodzinska and PhD student

**Antimicrobial peptide (AMPs) and antibiotics formulation design**

Combatting infections is a highly challenging task because antimicrobial drugs have difficulties in reaching intracellular or biofilm encapsulated bacteria in sufficient amounts. We formulate AMPs in for example novel polymeric delivery systems, characterize and evaluate their effect in killing bacteria and removing bacterial biofilm produced by e.g. *Staphylococcus aureus*.

**Supervisor:** Sylvia Klodzinska and Hanne Mørck Nielsen

**Biomimetic cell membranes: design, fabrication and characterization**

Oral delivery of biopharmaceuticals is considered the Holy Grail of drug delivery. We will investigate new approaches to enhance uptake of biopharmaceuticals across oral mucosa by co-formulating the drug with permeation enhancers in novel solid dosage forms (e.g. micro-tablets, micro-containers, adhesive electrospun nanofiber patches, or expandable films). We will develop, characterize, and investigate *in vitro*, *ex vivo* and potentially *in vivo* how these increase oral peptide delivery.

**Supervisor:** Post doc Ada-Ioana Bunea (DTU Nanolab) and Hanne Mørck Nielsen

**Characterizing ligand binding to proteins**

The pharmacological effect of drugs usually depends on their binding to a target protein and to plasma proteins. Protein binding can also be used to stabilize therapeutic proteins. It is therefore important to characterize this so-called ligand binding to proteins using a set of analytical methods. To do this characterization properly can be a challenge, however. In this project you will use several advanced analytical methods to characterize binding of model ligands to model proteins, and test different published approaches to analyze the data. You will thereby get a solid understanding of the advantages and limitations of various methods and learn how to critically assess the literature on this topic.

**Supervisors:** Marco van de Weert
### Interaction of protein aggregates with the innate immune system (provisional)

The presence of protein aggregates is known to be a risk factor in the development of unwanted immunogenicity to protein therapeutics. As yet poorly investigated is the role of the innate immune system in this immune response. Under condition we get our funding proposal awarded, we intend to investigate this by studying the potential activation of the complement system by specific protein aggregates.

In this project you will prepare different type of protein aggregates, study their stability in blood, and be involved in the studies on complement system activation. This involves a broad array of biophysical methods to characterize the aggregates, as well as clinical chemical methods to study complement activation.

**Supervisors:** Marco van de Weert + PhD student

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<th>Physical instability of peptides</th>
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| Therapeutic peptides offer many advantages, but their instability is often a major formulation challenge. Many peptides tend to aggregate into long fibrillar structures. Preventing this fibrillation is a major challenge. Within this area you can go into some fundamental aspects of peptide (or protein!) fibrillation, and study how the fibrillation process is changed by using heavy water (D₂O).

A second, more practically oriented project is to study the impact of various excipients on the instability of some model compounds. This project may be performed at, or in collaboration with, a local company.

**Supervisors:** Marco van de Weert + Vito Foderà or company supervisor

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<th>Role of protein-protein interactions in the formation of protein superstructures</th>
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<td>Protein-protein interactions are regulated by the physico chemical properties of the solution. Co-solvents (e.g. alcohols), pH and mechanical stress strongly affect such interactions having as a final result the modification of the aggregation reaction. With this project we want to investigate what is the effect of different parameters on both the kinetics of formation and the structure of superstructures.</td>
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**Supervisors:** Vito Foderà and Marco van de Weert

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<th>Amyloidogenic protein interaction with cell membranes</th>
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<td>The formation of amyloid fibrils is considered to play a key role in the development of pathologies such as Parkinson’s and Alzheimer’s diseases. New view supports the concept that the interactions of amyloidogenic proteins with cell membranes are a key factor in regulating related toxicity mechanisms. Aim of this project is to directly observe the progression of amyloid fibril formation in the presence of membranes both in synthetic model systems and in living cells.</td>
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**Supervisor:** Vito Foderà and Jijo Vallooran
### Green and sustainable protein materials for drug delivery

A new frontier in protein self-assembly is represented by the analysis of protein structures in terms of their mechanical/structural properties. This is pivotal for the use of protein aggregates as sustainable materials for drug delivery. Aim of this project is to produce protein nano- and micro- materials via electrospinning techniques, bulk methods and microfluidic chips and use them for the delivery of active compounds in *in vitro* and *in vivo* models.

**Supervisors:** Vito Foderà, Jijo Vallooran and PhD student Kleopatra Kalouta

### Protein stability in pharmaceutical formulations

The presence of protein aggregates in protein drug products is a major concern in pharmaceutical industry. These particles may alter the efficacy of the product. As a consequence, it is of great relevance to isolate and characterize each of these types of particles and evaluate their risk profile. Aim of this project is to produce and analyze homogeneous populations of protein aggregates originated from insulin formulations.

**Supervisor:** Vito Foderà and Marco van de Weert+ company supervisor

### Elucidating the impact of surfactants on biophysical interaction of PLGA nanoparticles with mucin using QCM-D and AFM

In the project, we hypothesize that the intrinsic properties and the amount (density) of the applied surfactants would play important roles in determining the mucin-nanoparticle interaction. The main purpose of the study is to elucidate the potential influence of surfactants applied for the preparation of PLGA nanoparticles on the mucin-nanoparticle interactions by using the quartz crystal microbalance with dissipation (QCM-D) technique, thus, providing the scientific rationale for rational selection of surfactants. The surface-modified PLGA nanoparticles will be prepared by using microfluidic approaches. Size and zeta potential of the resulted nanoparticles will be characterized by using dynamic light scattering. Morphology of the resulted nanoparticles will be characterized by using transmission electron microscopy. The mucin-nanoparticle interactions will be investigated by using QCM-D and AFM described in our previous studies.

**Supervisors:** Feng Wan and Hanne Mørck Nielsen
### Lipid layer-coated polymeric nanoparticles for combating respiratory bacterial infections

In the project, we hypothesize that lipid composition would play a critical role in determining the mucus-penetrating and bacteria-interacting properties of the nanoparticles. The main purpose of the study is to optimize the composition and nanostructure of the lipid layer in terms of mucus-penetrating and bacteria-interacting properties of the nanoparticles. The Lipid layer-coated polymeric nanoparticles will be prepared by using microfluidic approaches. The physicochemical properties of the resulting nanoparticles will be characterized by using dynamic light scattering, transmission electron microscopy, fluorescence Quenching, and HPLC. The mucus-penetrating and bacteria-interacting properties will be investigated using particle tracking technique described in our previous studies. Can be optimized by rational selection of the lipid composition.

**Supervisors:** Feng Wan and Hanne Mørck Nielsen

### Biophysical characterization of mucosal cross-talk: biopharmaceuticals and their excipients

This proposed project aims to uncover the interaction between delivery system encapsulating a biopharmaceutical and mucus at molecular level allowing for novel and innovative biomedical approaches to overcome the challenges of mucosal drug delivery. Relevant techniques would be X-ray, rheology, calorimetry (DSC & ITC), microscopy (CLSM; SEM; PLM) and spectroscopy. Moreover, *in vitro* models could be included to evaluate the effect of the developed delivery systems on permeability and cell integrity.

**Supervisor:** Stine Harloff-Helleberg

Master thesis projects can be carried out both at Department of Pharmacy, in collaboration with researchers at e.g. DTU or SCIENCE or internationally.

### Understanding mucosal barrier interactions in vivo

Exploring orally administered biopharmaceuticals such as insulin *in vivo*. Depending on your interest, the project could focus on optimization of delivery system or excipients and the effect hereof on bioavailability, intestinal integrity and mucosal interaction. Please note that this project requires 60 ECTS credits and elective course in Laboratory Animal Science (SVEK17001U).

**Supervisors:** PhD student, Stine Harloff-Helleberg & Hanne Mørck Nielsen

Master thesis projects can be carried out both at Department of Pharmacy, in collaboration with researchers at e.g. DTU or SCIENCE or internationally.

### Mucosal interaction studied using *in situ* ellipsometry and atomic force microscopy

This project aims to develop a model to explore molecular interaction and surface morphology alterations between excipients (used in drug delivery systems intended for oral administration of biopharmaceuticals) and mucin (the main component of mucus) using *in situ* ellipsometry and atomic force microscopy. Please note that this project requires laboratory work both at Malmö University and University of Copenhagen.

**Supervisors:** Stine Harloff-Helleberg & Professor Marité Cárdenas (Malmö University)

Master thesis projects can be carried out both at Department of Pharmacy, in collaboration with researchers at e.g. DTU or SCIENCE or internationally.
## Improving biopharmaceutical stability using Lipids

Formation of aggregates in biopharmaceutical formulation continues to be one of the major quality concerns in biotherapeutics development. The presence of large quantities of aggregates is believed to be one of the causes of unwanted immunogenic responses. Protein particulates can form in a wide range of sizes and shapes. Lipids can generally bind on proteins and peptides, which could lead to improved stability. Aim of this project is to inhibit the protein aggregation in presence of medium-chain fatty acids and lipids.

**Supervisors:** Jijo Vallooran, Marco van de Weert and Vito Foderà

## Enzyme-like activity of protein amyloid superstructures

Protein aggregation and fibrillation are associated with numerous neurodegenerative diseases such as Alzheimer’s and Parkinson’s. In addition to their pathological role, these amyloid materials have also been identified as functional biological materials in vivo and in many technological applications. Therefore, It is crucial to investigate the biological activities of amyloid materials. Aim of the project will be to study the enzyme activity in amyloid superstructures of the model protein lysozyme and investigate whether the morphology and conformation affect the antibacterial activity.

**Supervisors:** Jijo Vallooran, Hanne Merck Nielsen and Vito Foderà

## Drug delivery via polymer-based nanocarriers for the treatment of blood disorders

When treating blood disorders is important to be able to finely tune the drug formulation to avoid important adverse effects. Therefore, we aim to use a polymer as a nanocarrier for the delivery of blood modifiers, i.e., coagulants and anti-coagulants. The grade of polymer modification with the drug of interest can be controlled and adjusted in order to obtain a formulation that can maintain the drug efficacy in vivo, while improving its safety.

**Supervisor:** PhD student Marta Bergamo and Urs Häfeli

Master thesis projects will be carried at the Faculty of Pharmaceutical Sciences of the University of British Columbia in Vancouver, Canada, in collaboration with researchers at the Department of Pharmacy at KU. The described projects are examples and will be adjusted according to the MSc student’s scientific interest.

## Effect of cell penetrating peptides and excipients on the bioavailability of orally delivered drugs

Using a novel platform for oral delivery, studying the efficacy of cell penetrating peptides (CPP) and excipients to improve delivery of different cargo materials. Absorption of drugs across intestinal membrane will be tested with bioanalytical techniques and cell culture models. Validation of *in vitro* data will be performed in a mouse or rat model using SPECT/CT imaging.

**Supervisor:** PhD student Tanya Saxena and Urs Häfeli

Master thesis projects will be carried at the Faculty of Pharmaceutical Sciences of the University of British Columbia in Vancouver, Canada, in collaboration with researchers at the Department of Pharmacy at KU. The described projects are examples and will be adjusted according to the MSc student’s scientific interest.
**Drug delivery to the lungs and tumors with embolizing microspheres**

Intravenously injected microspheres of 12 µm will reach the lungs and then get stuck in the capillaries, where they can release drugs (e.g., antimicrobial drugs, anticancer drugs) while slowly degrading. This project is about making drug releasing microspheres of the appropriate size, measuring the release kinetics, and quantifying the drug that reach the target area and induce a treatment response.

**Supervisor:** Research Associate Kathy Saatchi and Urs Häfeli

Master thesis projects will be carried at the Faculty of Pharmaceutical Sciences of the University of British Columbia in Vancouver, Canada, in collaboration with researchers at the Department of Pharmacy at KU. The described projects are examples and will be adjusted according to the MSc student’s scientific interest.

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**Pharmacokinetics and -dynamics of radiolabeled biopharmaceuticals measured by SPECT and PET**

Evaluation of drug exposure (pharmacokinetics, PK) and response (pharmacodynamics, PD) is critical to select appropriate molecules, assess safety and efficacy of drug candidates, and design optimal dosing strategies. PK for biopharmaceuticals can be determined by imaging techniques like PET and SPECT, and yields fully quantitative biodistribution and kinetic data. Biopharmaceuticals in this project can include antibodies, peptides, metal-binding small molecules and nanoparticles.

**Supervisor:** Research Associate Cristina Rodriguez and Urs Häfeli

Master thesis projects will be carried at the Faculty of Pharmaceutical Sciences of the University of British Columbia in Vancouver, Canada, in collaboration with researchers at the Department of Pharmacy at KU. The described projects are examples and will be adjusted according to the MSc student’s scientific interest.

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**Application procedure and dates**

If you are interested in writing your thesis with Drug Delivery and Biophysics of Biopharmaceuticals, please contact us for more details on our projects and possibilities.
The aim of the center is to contribute to an integrating knowledge on skin as a barrier for drug absorption, and key properties of drugs and excipients for cutaneous drug delivery. Based on a predominantly physicochemical approach, we aim to develop methods for the rational development of novel drug delivery systems for cutaneous and transcutaneous delivery of both small and large molecules, ranging from wounds to intact skin.

Potential thesis supervisors

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<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Email</th>
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<tbody>
<tr>
<td>Martin Malmsten</td>
<td>Professor</td>
<td><a href="mailto:Martin.malmsten@sund.ku.dk">Martin.malmsten@sund.ku.dk</a></td>
</tr>
<tr>
<td>Kathryn Browning</td>
<td>Assistant Professor</td>
<td><a href="mailto:Kathryn.browning@sund.ku.dk">Kathryn.browning@sund.ku.dk</a></td>
</tr>
<tr>
<td>Andrea Heinz</td>
<td>Associate Professor</td>
<td><a href="mailto:Andrea.Heinz@sund.ku.dk">Andrea.Heinz@sund.ku.dk</a></td>
</tr>
<tr>
<td>Mariena van der Plas</td>
<td>Associate Professor</td>
<td><a href="mailto:mariena.van_der_plas@sund.ku.dk">mariena.van_der_plas@sund.ku.dk</a></td>
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Research focus:
- **Martin Malmsten**: Microgels, nanoparticles for drug delivery, and host defence peptides for combatting infection and inflammation
- **Kathryn Browning**: Neutron reflectivity, skin lipid organization, lipid membrane interactions with nanomaterials and antimicrobial peptides
- **Andrea Heinz**: Drug delivery, electrospinning, wound healing
- **Mariena van der Plas**: Wound healing, peptidomimetics, host defence peptides

Examples of projects

**Oxidative stress on lipid membranes as a new tool for developing new antimicrobial agents**

Inorganic nanoparticles are very attractive as antimicrobial agents ('nanobiotics'), notably due to the increasing resistance development against conventional antibiotics. Apart from scalability and versatility, such materials offer advantages related to responsiveness of antimicrobial and anti-inflammatory effects and the possibility of controlling them by a range of triggering factors. For instance, oxidative stress is known to be behind the antimicrobial activities of TiO₂ nanoparticles when activated by UV light. However, studies on the mechanisms underlying these activities remain scarce. Based on previous work done by our group on the oxidative destabilization of lipid membranes, and using different biophysical and surface-chemical techniques such as fluorescence spectroscopy, QCM-D, FTIR-ATR, and DLS, the present project will focus on the effects of TiO₂ nanoparticle-induced oxidation of lipid membranes, lipid degradation, and their consequences for membrane structure and stability. Any potential membrane selectivity that could allow more efficient antimicrobial activities along with reduced side effects will be also explored.
for instance the combination with cationic peptide coatings. In a wider perspective, this project will contribute to the mechanistic foundation for the use of photocatalytic nanomaterials as triggerable antimicrobial agents.

**Supervisor:** Martin Malmsten & Elisa Parra-Ortiz.

### In vitro modelling of the skin barrier for cutaneous drug delivery

The stratum corneum, the outermost layer of the skin, is the main barrier between the body and its external environment protecting against water loss, and incoming pathogens and/or allergens. It is formed of a complex mixture of dead cells (corneocytes) imbedded in a lipid matrix. Drugs applied topically must pass through this barrier to reach the target; therefore, modelling human skin allows us to predict and understand the ADME properties of topical drugs and design more efficient transport vehicles. Furthermore, skin diseases such as atopic dermatitis and psoriasis are known to affect the lipids present in the stratum corneum, making the barrier leakier and the patient more prone to infection. By understanding drug interactions with both healthy and diseased stratum corneum we can better design drugs and formulations to cross the stratum corneum.

In this project, you will be isolating stratum corneum from pig ears, and testing the barrier properties of whole stratum corneum and extracted stratum corneum lipids with and without corneocytes. In this line of research, we use physical chemistry and surface science methods to investigate the molecular structure and interactions between the stratum corneum, drugs and formulations. Techniques such as ATR-FTIR, SAXS and neutron reflection will be coupled with more traditional pharmaceutical transport experiments using Franz cells. Using these techniques, we are able to study skin interactions with a wide range of molecules of interest, for example, common topical drugs, dermal penetration enhancers, excipients, formulations, skin irritants and allergens. This project provides an excellent opportunity for you to take control of your studies and steer the project in the direction you find to be the most interesting. It may also be possible to be involved in a neutron reflection experiment at a large-scale neutron scattering facility in the UK or France.

**Supervisors:** Kathryn Browning

### Development of peptide-based electrospun wound dressings

Wound healing is a major burden to healthcare systems worldwide, and there is a clinical need for dressings that can be used to treat partial thickness burn wounds that affect the epidermal and dermal layers of the skin. Requirements for ideal wound dressings include the ability to prevent infection and maintain skin hydration. The wound dressing should further be non-toxic, non-immunogenic and should enhance tissue regeneration. Peptide-based electrospun wound dressings fulfill these criteria.

This project focuses on the development of an electrospinning method to produce peptide-based wound dressings. The peptide will either be electrospun in a mixture with a polymer or co-axially electrospun (peptide core surrounded by polymer mantle). The electrospun fibers will then be comprehensively characterized by a range of analytical techniques, including scanning electron microscopy, X-ray powder diffraction and differential scanning calorimetry. The release of the peptide from the fibers will also be determined.

**Supervisor:** Andrea Heinz
**Development of peptide-based nano- and microgels for the treatment of Ichthyosis vulgaris**

Ichthyosis vulgaris (IV) is a relatively common skin condition that causes dry skin and strongly increases the risk of atopic dermatitis (AD). Individuals with IV have a flaky and dry skin and increased occurrence of hair follicle plugging on the upper arms and shoulders. As the disorder is caused by a loss-of-function mutation in the filaggrin (FLG) gene, replacement of the protein FLG shows great potential for relieving symptoms of IV and significantly improving the quality of life of IV patients.

This project will develop nanogel formulations containing FLG peptides for the treatment of IV and AD. The nanogel formulations contain a novel class of polyethylene glycol-based excipients. Systematic investigation of the physicochemical properties of the nanogel formulations with and without peptides will allow optimizing the systems with respect to their (a) physical stability during storage and sterilization, (b) protein release, (c) biocompatibility and (d) pharmaceutical performance with respect to treatment of IV.

**Supervisor:** Andrea Heinz

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**2D and 3D skin models for atopic dermatitis**

The goal of this project is to develop skin infection models for studying drug delivery systems in atopic dermatitis. The work will consist mostly of techniques within the fields of immunology and microbiology, including cell and bacterial cultures, analysis of inflammatory markers and signalling pathways, cytotoxicity, and histology.

**Supervisors:** Mariena van der Plas

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**Membrane vesicles for targeted drug delivery**

Antibiotic resistance development is one of the biggest challenges of our time. Antimicrobial host defence peptides are promising alternatives to antibiotics, as they kill a broad spectrum of microbes, including multi-resistant strains. Given the importance of membrane vesicles in microbe-microbe and microbe-host interactions, the purpose of this project is to investigate the potential of membrane vesicles for targeted delivery of antimicrobial peptides.

The work will include techniques within the fields of microbiology, cell biology, molecular biology, physical chemistry and drug formulation.

**Supervisors:** Mariena van der Plas
**Peptide-based drug delivery systems for atopic dermatitis skin infections**

Atopic dermatitis (AD) is a multifactorial relapsing inflammatory skin disease affecting 1 out of 5 Danish children. As decreased levels of antimicrobial peptides are a popular explanation for the observed increased susceptibility to infection in these patients, antimicrobial and immunosuppressing peptides have great therapeutic potential in AD.

The goal of this project is the development of potent and safe peptide delivery systems for treatment of AD lesions.

The work will comprise optimisation of drug formulation, *in vitro* antimicrobial and biofilm assays and, if time allows, *in vitro* immunological assays as well. As we have various peptides to be tested, several students can perform this project independently.

**Supervisor:** Mariena van der Plas & Martin Malmsten

**Application procedure and dates**

If you are interested in writing your thesis with the LEO Foundation Center for Cutaneous Drug Delivery, please write an email to one of the supervisors with more information about you. There is no deadline.
The Manufacturing and Materials group is focusing on processing and material sciences around solid state and semisolid pharmaceuticals. This international group has over 20 PhD students, postdocs and associate professors. The section is aiming for understanding the chemical and physical properties of the active pharmaceutical ingredients, both small molecules and bio-macromolecules, and excipients in relation to their processing behaviour. Further, the group aims to optimize stability and bioavailability of the final dosage form. The research is focusing on facilitating the future implementation of Quality by Design (QbD) principles for drug development processes, as well as implementation of process analytical technologies (PAT) for industrially relevant applications. We focus on processing of small-molecule and protein/peptide-based medicinal products. Our goal is to understand the properties of active pharmaceutical ingredients and excipients in relation to their processing behaviour, and further, in relation to the optimal bioavailability of the final dosage form.

**Potential thesis supervisors**

<table>
<thead>
<tr>
<th>Lene Jørgensen</th>
<th>Natalja Genina</th>
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<td>Associate Professor</td>
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<td><a href="mailto:lene.jorgensen@sund.ku.dk">lene.jorgensen@sund.ku.dk</a></td>
<td><a href="mailto:natalja.genina@sund.ku.dk">natalja.genina@sund.ku.dk</a></td>
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**Research focus:**
- **Lene Jørgensen:** Protein stability, protein formulation, adsorption to surfaces, manufacturing and processing of protein pharmaceuticals, excipients design and requirements, quality of pharmaceutical products, regulatory aspects of manufacturing pharmaceuticals.
- **Natalja Genina:** 2D printing/inkjet printing, 3D printing/additive manufacturing, personalized medicine, physicochemical characterization of innovative product, innovative manufacturing, spectroscopy.
Examples of projects

**Hot melt processing of biopharmaceuticals**

In this project, the amorphous environment created by various polymers in a hot melt process will be studied to see whether it is sufficient to prevent the degradation caused by heat, and therefore would enable protein formulations to be produced by hot melt processing. This will be investigated by monitoring structural changes in both the solid and the liquid state. Several process and formulation variables form a good basis for the application of Design of experiments (DoE).

**Supervisors:** Lene Jørgensen and Johan Peter Bøtker

**Physical stability of proteins**

Maintaining the physical stability of proteins is crucial in both formulation and manufacturing, since the biological activity may otherwise be reduced. We will expose a protein to various types of stresses, formulation components, processing and use advanced techniques to characterize the changes that we observed. In this project, you will gain knowledge of basic protein formulation, effect from various types processing and excipients and you will get experience with techniques to study protein stability and structure.

**Supervisor:** Lene Jørgensen
**Master project in industry or abroad**

You could also do your project in the pharmaceutical industry, Medico industry or at a University abroad (e.g. University of Otago, School of Pharmacy, Dunedin, New Zealand). This requires planning, so short notice project are often not possible. You need to plan 6 months-1 year ahead. You will be asked to supply a copy of your grades, as you will need to work independently. The projects topics in industry are typically defined in detail 2-3 months before the actual start of the project.

**Supervisor:** Lene Jørgensen

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**Information-rich pharmaceutical products**

Data-enriched edible pharmaceuticals (DEEP) enable encapsulation of both the drug and the sensitive information in a single dosage unit. This can pave the way against counterfeiting of medicine. The goal of the project is to explore the further possibilities of efficient and secure data storage within edible drug-containing dosage unit.

**Supervisors:** Natalja Genina and External from the Department of Computer Sciences

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**Feasibility of printed medicine**

Currently, there is only one commercially available 3D printed medicine. If the needs of the patients are identified, the situation can be different in the near future with more printed drugs coming to the market to provide more exact pharmaceutical treatment in society. The aim of the project is to explore the patients’ attitude towards the idea of getting personalized digital drug product by conducting interviews and showing the possibilities of 3D printing.

**Supervisors:** Natalja Genina and Sofia K. Sporrong

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**Development of personalized medicine by 2D and 3D printing**

Delivering an accurate dose of active pharmaceutical ingredients (API) and tailoring their release profile are the key factors to produce efficient pharmacotherapy. With current dosage forms, tunable dosing and tailoring multidrug products’ properties are difficult and perilous. The evident flexibility of the printing technology allows commercial on-demand fabrication of individualized dosage forms. The overall goal is to produce novel solid dosage forms with easily adjustable doses and release profiles.

**Supervisors:** Natalja Genina and Johan Bøtker
Image analysis of pharmaceuticals

In this project, image analysis of e.g. the tablet coating quality is investigated using MATLAB programming. The project will revolve around creating MATLAB scripts for segmenting objects in images and constructing and operating analytical scripts as well as artificial neural networks for classification purposes. This project will thus focus on optimizing both the process of obtaining the images and the programming needed to analyse the images.

**Supervisor:** Johan Peter Bøtker

Optimization of bulk properties of pharmaceuticals

Particle properties determine the successful manufacturing of solid dosage forms. Shape and size distributions are critical parameters affecting flow ability of materials. However, it is a huge scientific challenge to translate these particle characteristics into optimal final formulation. There are several new innovative approaches to investigate powder rheology together with solid form analysis, making a huge impact in commercial scale process and product optimization. This project will investigate powder rheology as a part of solid dosage form development, as well as implementation of process analytical technologies (PAT) in an industrial setting. The projects topics in industry are typically finalized in detail 2-3 months before the actual start of the project. This project can also be performed as an industrial project at AstraZeneca, LEO Pharma, Lundbeck or Novo Nordisk.

**Internal supervisors:** Jukka Rantanen

**External supervisors:** AstraZeneca, LEO Pharma, Lundbeck or Novo Nordisk

Pulmonary drug delivery

Lung diseases including chronic obstructive pulmonary disease (COPD), respiratory infections and lung cancer are leading cause of death world-wide. Inhaled drugs can directly reach the sites of the diseases, lower side effect, and improve pharmacological effect. The aim of this project is to utilize particle engineering technology to improve the efficacy of inhaled products by improve lung deposition, modulating dissolution rates and absorption of inhaled drugs. This project can be carried out at University of Sydney or Shenyang Pharmaceutical University, China.

**Supervisor:** Mingshi Yang
### Spray-dried protein formulations

The spray-drying process may be less expensive, but more efficient to process proteins or peptides as compared to other drying techniques. This technique has additional potentials in not only stabilization of the proteins but also engineering the protein formulations into dry particles for various pharmaceutical applications, e.g. inhalable, injectables, and oral administration. This project is intended to investigate the influence of formulation and process variables in the spray-drying process on particle characteristics and physicochemical stability of the protein formulations. This project can be carried out at Novo Nordisk.

**Supervisor:** Mingshi Yang

### Electrospraying/Electrospinning in pharmaceutical application

Electrospraying/Electrospinning are emerging technologies in the pharmaceutical filed to fabricate micro/nano-structured materials for drug delivery and tissue engineering. This project aim to explore the application of this technology and investigating to promote this technology in the pharmaceutical field for producing orodispersible films, wound dressing, and injectable depot microparticles.

**Supervisor:** Mingshi Yang

### Anhydrate-hydrate systems in pharmaceutical products

During production and storage of solid state dosage forms the role of hydrate formation cannot be underestimated. The transformation between hydrates and anhydrates occurs as a function of temperature and humidity, and severely affects the properties of the crystals.

The aim of this project is to understand how the water activity level and the temperature can influence the ratio of the anhydrate and hydrate forms of different model compounds, and how the properties of the bulk material changes as a consequence of these transformations.

**Supervisors:** Anders Ø. Madsen, Jukka Rantanen
Co-crystals for crossing the blood-brain barrier

It is notoriously difficult to treat disorders in the central nervous system, because most molecules cannot reach the brain due to the blood-brain barrier. In this project, you will work on designing, making and characterizing the properties of co-crystals consisting of several drugs that will work together to cross the barrier and maintain the drugs in the brain.

Supervisor: Anders Ø. Madsen

Application procedure and dates

If you are interested in writing your thesis with the Manufacturing and Materials group, please write an email to one of the supervisors with more information about you. There is no deadline.
Microscale Analytical Systems
www.pharmacy.ku.dk/research/microscale-analytical-systems/

Our research group develops analytical chemical tools for tackling many challenges in pharmaceutical and medical research, especially in situations where sample size is limited, where the molecules of interest are only present in small concentrations, or where a large number of samples needs to be processed in a short time frame. To enable this cutting-edge analysis we develop and apply technologies such as micro-nano engineering, microfluidics, and polymer science for next generation high-throughput workflows, e.g., in protein characterization, peptide analysis, drug transport studies, and drug delivery.

Main focal areas of the group are modern separation techniques (e.g. LC, CE) coupled to mass spectrometry, advanced sample preparation methods (e.g., µSPE, µEME), traditional spectroscopic techniques (e.g., NMR, IR, Raman) and a range of microfluidics-driven techniques (e.g., droplets, micro-nano particle fabrication); furthermore, we apply ex vivo models and develop microphysiological in vitro models (i.e., organ-on-a-chip) that are all intended to understand drug-target interactions, investigate drug metabolism, and getting insight into disease progression and therapeutic efficacies.

Potential thesis supervisor

**Jörg P. Kutter**
Professor
jorg.kutter@sund.ku.dk

**Claus Cornett**
Associate Professor
claus.cornett@sund.ku.dk

**Nickolaj J. Petersen**
Associate Professor
nickolaj.petersen@sund.ku.dk

**Stig Pedersen-Bjergaard**
Professor
stig.pedersen-bjergaard@farmasi.uio.no

Research focus: Microfluidic devices for bioanalytical challenges in pharmaceutical and related life sciences.

Research focus: Quantitative analysis of pharmaceutical compounds from plants; human metabolism and drug validation.

Research focus: Miniaturized analytical techniques, in particular separation methods coupled to mass spectrometry, for pharmaceutical analysis.

Research focus:
### Examples of projects

#### Lab-on-a-Chip for next-generation sample separation and analysis

The analysis of complex protein mixtures is of tremendous importance for pharmaceutical drug discovery. To identify potential drug targets, complex mixtures such as blood, cell cytoplasm or secretome have to be screened. High-throughput screenings involve large numbers of samples and compounds, which are, however, only available in small amounts. Therefore, the sample preparation has to be miniaturized, integrated and automated. Ideal platforms to meet these requirements are microfluidic devices, which allow the precise control of chemical reactions and the integration of other functional elements (so-called lab-on-a-chip). For instance, microchip liquid chromatography provides high separation efficiency, resolution, and sensitivity. During such a project, a microscale device capable of chromatographic separation will be further developed to enable direct coupling to highly sensitive analytical methods, such as mass spectrometry (MS).

**Supervisors:** Jörg P. Kutter, Nickolaj J. Petersen; **No of students:** 1-2

#### Advanced sample preparation methods on microfluidic chips

Analysis from complicated matrices (i.e., cell cultures) requires advanced sample preparation tools. This is particularly challenging when small sample volumes are involved. Here, we develop techniques such as electro-membrane extraction to, e.g., monitor drug transport through cell-based models of natural barriers (so-called organ-on-a-chip systems).

**Supervisors:** Jörg P. Kutter, Nickolaj J. Petersen, Stig Pedersen-Bjergaard; **No of students:** 1-2

#### Quality assurance and development of Plant medicine

Focus will be on characterizing plant based raw materials. Earlier and ongoing projects have been centered around Cannabis and Quinine, a current project (funded by DANIDA) is studying *Synadenium glaucescens* from Tanzania, and profiling industrial hemp, primarily via terpene profiles. BYOP (Bring Your Own Plant...), if You have a special interest in a plant medicine, and access to plant material, let’s negotiate.

Analytical methods used: HPLC-UV, HPLC-MS, GC-MS and NMR.

**Supervisors:** Nickolaj Petersen and Claus Cornett; **No of students:** 1-2
Streamlining the grasshopper in vitro model

Finding human drug metabolizing enzymes in other species, such as insects, can reduce the number of animal experiments in pre-clinical trials in drug discovery and development. Within this project, you will work with the grasshopper Schistocerca gregaria, to find relevant drug metabolizing enzymes in the grasshopper’s “blood” – the hemolymph. You will learn, how to inject drug compounds into the grasshopper and how to collect samples, and how to set up and run enzyme assays, and how to prepare these samples for instrumental analysis with LC-MS or UV detection. Finally, you will be able to evaluate drug metabolism in the grasshopper’s hemolymph and conclude on the relevance of your findings for the grasshopper model in early drug discovery and development.

Analytical methods used: HPLC-UV, HPLC-MS, GC-MS and NMR.

Supervisors: Nickolaj Petersen and Claus Cornett; No of students: 1-2

Grasshopper model for drug permeation and metabolisation studies in brain

Small animal models are a tool in early drug discovery to predict drug uptake and metabolism. Recently, the grasshopper Schistocerca gregaria has been introduced as a model to investigate drug uptake and metabolism in the grasshopper brain. In order to optimize throughput we will investigate the feasibility of using frozen grasshopper brains, as the excision of the brains is time consuming, so the possibility of using previously frozen brains would enable well-plate methods or microanalytical methods.

Analytical methods used: HPLC-UV, HPLC-MS

Supervisors: Nickolaj Petersen and Claus Cornett; No of students: 1-2

Capillary electrophoresis coupled to MS

Capillary electrophoresis (CE) provides great potential for a wide range of molecular formats, from small peptides to proteins, DNA and nucleotides. With CE-MS analysis, information about the degradation pathways, post-translational modifications and process-related impurities could be acquired which would otherwise be difficult to obtain with LC-MS. Samples from Novo Nordisk that have been stress tested for stability will be investigated to compare advantages and limitations compared to traditional LC-MS.

Analytical methods used: CE-MS, HPLC-MS

Supervisors: Nickolaj Petersen; No of students: 1

Application procedure and dates

If you are interested in writing your thesis with Microscale Analytical Systems, please write an email to one of the supervisors with more information about you. There is no deadline.
Pharmaceutical Physical and Analytical Chemistry

www.pharmacy.ku.dk/research/pharmaceutical-physical-analytical-chemistry/

The main purpose of the Pharmaceutical Physical and Analytical Chemistry (PPAC) Group is to develop novel approaches for physical chemical characterization of drugs and delivery systems. The work paves the way for design of effective novel medicines and a better understanding of the fate of drug substances and delivery systems through application of quantitative analytical methods.

The PPAC group applies physical chemical approaches in combination with advanced analytical techniques (ICP-MS, SAXS, UV-Imaging and Taylor dispersion analysis) to advance understanding of fundamental processes in drug design, development and characterization. Common to the activities is a focus on the interplay between basic physical chemical properties of drug substances and excipients, kinetics and transport processes in relation to both drug delivery and analytical methods.

**Keywords:** analytical chemistry, cubosomes/hexosomes, drug delivery, excipients, injectables, *in vitro* release, LC-ICP-MS, metallo-drugs, nanoparticles, preformulation, SAXS, Taylor dispersion analysis.

**Potential thesis supervisor**

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<thead>
<tr>
<th>Jesper Østergaard</th>
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<td>Professor</td>
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<tr>
<td><a href="mailto:jesper.ostergaard@sund.ku.dk">jesper.ostergaard@sund.ku.dk</a></td>
</tr>
<tr>
<td>Researcher Profile</td>
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Research focus: Physical chemical characterization of drug substances and delivery systems. Development of methods for physical chemical characterization, transport studies, *in vitro* release and dissolution testing (e.g., UV imaging, capillary electrophoresis (CE), Taylor dispersion analysis (TDA)). Molecular interactions. Study of non-covalent interactions of drugs substances and development of affinity methods based on affinity CE and TDA. Development of parenteral depot formulation principles (intra-articular and subcutaneous administration). Kinetics. In relation to drug transport processes as well as chemical kinetics and stability testing. Design of prodrugs.

<table>
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<th>Anan Yaghmur</th>
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<td>Associate Professor</td>
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<td><a href="mailto:anan.yaghmur@sund.ku.dk">anan.yaghmur@sund.ku.dk</a></td>
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<td>Researcher Profile</td>
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Research focus: 1) Design of soft drug nanocarriers based on cubosomes, hexosomes, and other related nanodispersions. 2) In situ formation of parenteral dosage forms with tunable liquid crystalline nanostructures. 3) Cancer cubosomal and hexosomal nanomedicines. It is also of my interest to design theranostic cubosomal and hexosomal nanomedicines. Development of methods for physical chemical characterization, transport studies, *in vitro* release and dissolution testing (e.g., UV imaging, capillary electrophoresis (CE), Taylor dispersion analysis (TDA)). Molecular interactions. Study of non-covalent interactions of drugs substances and development of affinity methods based on affinity CE and TDA. Development of parenteral depot formulation principles (intra-articular and subcutaneous administration). Kinetics. In relation to drug transport processes as well as chemical kinetics and stability testing. Design of prodrugs.
**Research focus**: Investigation and application of physicochemical approaches to improve understanding of processes in drug delivery including parenteral depot design, profiling of drugs and analytical approaches for *in vitro* release testing. Research projects are related to i) development of parenteral sustained release drug delivery systems including in situ suspension-forming injectables, in situ formed liquid crystalline nanostructures and prodrug approaches and ii) development and utility of *in vitro* release methods to predict *in vivo* performance of depot formulations for the subcutaneous and intra-articular route of administration.

**Research focus**: Our research aims at exploring the application potentials of functional excipients based on a better understanding of excipient effects on drug release and absorption, as well as interactions between excipients and drug molecules. We use both lipids and polymeric excipients, and are especially interested in lipid excipients due to their versatility and stability, as well as the potential in controlling drug release. The main research activities include designing and characterizing drug carriers such as microparticles, films and foams, optimizing formulations for specific applications, and developing *in vitro* models to evaluate formulations with sustained drug release properties.

**Research focus**: Analytical chemistry. Our general research interest is to develop and apply advanced analytical techniques for exploration of novel drug delivery systems and gain knowledge of the uptake, distribution, and metabolism of metal-based drugs, trace elements, peptides and proteins, and nanoparticles in biological systems. Selenium metabolism is a special interest. To pursue this interest we apply LC-ICPMS, CE-ICPMS, and LCMS.

**Research focus**: My research concern development and application of advanced analytical techniques for exploration of novel drug delivery systems to gain knowledge of the uptake, distribution, and metabolism of (bio)pharmaceuticals and applied drug delivery systems in biological systems. To pursue this interest I apply chromatographic separations and inductively coupled plasma mass spectrometry (LC-ICPMS, CE-ICPMS) and LC-MS.
### Research focus: Stefan Stürup

Our general research interest is to develop and apply advanced analytical techniques for exploration of novel drug delivery systems and gain knowledge of the uptake, distribution, and metabolism of inorganic and bioinorganic molecules and drugs in biological systems. To pursue this interest we apply LC-ICPMS, CE, and LCMS.

### Research focus: Henrik Jensen

My research is mainly focused on developing new analytical methodologies for characterization of drugs and drug formulations. The primary focus has been on miniaturization as well as automation of analytical protocols. We often rely on capillary based approaches, but recently we are further developing the methods into wearable sensors for monitoring drugs and their unwanted side effects. Most of my former master thesis students are employed in the pharmaceutical industry, amongst others in the spin-out company FIDA-Tech which is based on research in the group.

### Examples of projects

#### Characterization of nanoparticulate drug delivery systems

This project focuses on the development of new methods to characterize nanoparticulate drug delivery systems, e.g., liposomes, cubosomes, nanocrystals. New methods based on capillary electrophoresis, Taylor dispersion analysis and UV imaging will be developed. It is important that the methods require limited amount of sample as nanoparticulate drug delivery systems are usually only produced in small quantities. The methods will allow us to address critical parameters such as incorporation efficiency, release, non-covalent interactions, aggregation and adsorption.

**Supervisors:** Jesper Østergaard, Henrik Jensen and Bente Gammelgaard

#### Novel in vitro drug release models for predicting in vivo performance of injectables

The aim of the project is to develop novel in vitro release testing methods suited for predicting the in vivo fate of injectables. Such methods are of importance in the development of future drugs for subcutaneous, intramuscular or intra-articular injection. We intend to combine a understanding of the transport processes occurring at the injection site with efficient characterizing techniques for unravelling release mechanisms and predicting the biological fate. The ultimate validation will be establishment of an IVIVC.

**Supervisors:** Jesper Østergaard and Susan Weng Larsen

#### Compound screening in early drug development using real-time surface dissolution imaging

Surface dissolution imaging provides new opportunities for visualization and study of drug dissolution mechanisms. The aim of the project is to identify and establish best practices in UV imaging-based dissolution testing. The work will involve development of new methods for selected test compounds.

**Supervisors:** Jesper Østergaard (project may involve an internship at external partner)
**Characterization of monoclonal antibodies (mAbs) by Flow Induced Dispersion Analysis**
Characterization of therapeutic mAbs with respect to structure, aggregation and antigen binding using FIDA. Investigation of sensitivity to stress conditions (temperature and chemical denaturation).
**Supervisor:** Jesper Østergaard

**Thesis projects on pharmaceutical analysis with pharma industry or hospital pharmacy**
Ask for current possibilities.
**Supervisor:** Jesper Østergaard

**Cancer cubosomal and hexosomal nanomedicines**
Formation, characterization, and uses of cubosomal and hexosomal nanomedicines for delivery of anticancer drugs.
**Supervisor:** Anan Yaghmur

**Multifunctional cubosomal and hexosomal nanomedicines**
Formation, characterization, and uses of cubosomal and hexosomal nanomedicines for multifunctional drug delivery applications.
**Supervisor:** Anan Yaghmur

**Continuous production of monodispersed cubosomes & hexosomes**
Combining SAXS to a microfluidic device for the structural characterization of monodispersed drug nanocarriers.
**Supervisors:** Anan Yaghmur (co-supervisor NN)

**Design of sustained release injectable liquid crystalline formulations**
In situ formation of liquid crystalline depots with sustained drug release properties. Combination of biophysical investigations with drug release studies.
**Supervisors:** Anan Yaghmur & Susan Weng Larsen

**BRAIN-PENetrating cubosomal and hexosomal NANOcarriers for glioma-targeting delivery**
This project focuses on the formulation of immune-safe non-lamellar liquid crystalline nanocarriers for bioimaging of - and concomitant drug delivery to - cancerous brain tumors.
**Supervisor:** Anan Yaghmur
Local and sustained co-delivery of drugs to improve outcomes following joint replacement

To improve pain management and prevent infections related to joint replacement surgery, there is a need for efficient drug delivery systems (DDSs) that can maintain and sustain an optimal therapeutic level of multiple drugs at the surgical site. The current project focuses on rational design of parenteral in situ forming DDS based on lyotropic non-lamellar liquid crystalline phases for co-delivery of drugs. The drug substances are incorporated in lipids, which self-assemble upon contact with the tissue fluid to form well-ordered inverted type nanostructures (bi-continuous cubic and hexagonal phases). The aims of the project are to i) study incorporation of model drugs with different physicochemical properties in these systems and ii) investigate drug release characteristics from in situ formed liquid crystalline phases. Various in vitro release methods as well as the presence of biologically relevant fluid will be used to characterize events influencing the sustained release properties.

**Supervisors:** Susan Weng Larsen, Anan Yaghmur and Jesper Østergaard

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A novel prodrug principle to achieve localized and sustained NSAID action after joint injection

Orally administered NSAIDs are intensively used in the treatment of osteoarthritis for pain management and reduction of inflammation. However, oral NSAIDs may evoke severe side effects even after short term use which constitutes impediments to their use. Following direct injection into the injured joint, a high therapeutic NSAID concentration can be accomplished while minimizing systemic adverse effects. As NSAIDs disappear rapidly from the synovial space (half-lives of 0.5-6 h), depot strategies are needed. In the current project, a prodrug-based in situ suspension-forming system intended for localized and sustained NSAID action upon intra-articular injection will be investigated. The project relates to characterization of synthesized NSAID prodrugs and will include: (i) solubility in aqueous buffers and in synovial fluid, (ii) pH dependent stability, (iii) sensitivity to enzymatic cleavage (plasma and synovial fluid), (iv) affinity to proteins and (v) rate of NSAID release from prodrugs using an in vitro release model simulating the joint environment.

**Supervisors:** Susan Weng Larsen and Jesper Østergaard

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Design of in vitro drug release models for predicting in vivo performance of depot injectables

Development of in vitro release models for quality control as well as formulation design purposes is a critical activity in the characterization of parenteral depot formulations. Ideally, an in vitro-in vivo correlation should be established, however, it requires that the drug release mechanism is the same in vitro and in vivo. The project focuses on characterizing drug release from sustained release formulations for subcutaneous and/or intra-articular administration. The aim of the project is to develop in vitro release models to achieve in depth understanding of how formulation designs as well as physiological parameters influence drug release mechanism and rate and drug transport the blood capillaries.

**Supervisors:** Susan Weng Larsen, Jesper Østergaard and Henrik Jensen
**Functional excipients and drug delivery**

Excipients play an essential role in drug delivery. Lipid-based formulations can increase the bioavailability of lipophilic drugs by improving drug dissolution and permeation. Both solid lipid particles and polymeric particles are good carriers for sustained drug delivery, but the mechanism of drug release from those particles are different. Hybrid polymer-lipid particles provide better effect in sustained delivery of drugs due to synergistic effect of polymer and lipids. The project aims at evaluating effect of excipients and particle preparation methods on drug release kinetics in order to design efficient drug carriers for specific applications via different administration route.

**Supervisor:** Huiling Mu

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**In vitro models to evaluate formulations for sustained drug delivery**

Understanding the release kinetics of drugs from particles is a fundamental prerequisite for efficient design of drug carriers for drug delivery. However, there is no suitable method available to assess formulations with sustained drug release properties *in vitro*. The project aims at establishing bio-relevant *in vitro* models addressing *in vivo* conditions including pH, temperature, and matrix composition.

**Supervisor:** Huiling Mu

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**Bioadhesive formulations for local mucosal drug delivery**

Solid lipid formulations can be used for sustained drug delivery. Incorporation of functional excipients in the formulations may create extra application potentials and be used to improve local therapeutic effect by adhesion to the mucosal surfaces (e.g. mouth, eye). The project aims at investigating the potential of combining bioadhesive excipients in formulations and validating the bioadhesive *in vitro*. Nanoparticles, prepared by hot melting and probe sonication method, will be incorporated into thin films or hydrogels, drug encapsulation efficiency and drug release, as well as bioadhesion properties will be evaluated.

**Supervisor:** Huiling Mu

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**Characterization of metal nanoparticles in biological samples**

Metal nanoparticles like Ag, Au, Cu, Fe, Si, and Ti have shown great potential for various biomedical applications, but very few metal NP-based drugs have so far been approved for the pharmaceutical market. A key reason is inadequate characterization and quantitation of the NPs in biological systems. The most important characteristics are composition, concentration, size and size distribution, protein interaction, surface charge and release of ions from the metal. These characteristics are not easily determined in biological samples. This project will focus on determination of size, size distribution, composition, release of metal ions and quantitation of standard NPs in human plasma. A particle system will be chosen among Ag, Au, FeO, Se, Si, and TiO$_2$. The analytical methods applied will be single-particle (SP)-ICPMS, LC-ICPMS and/or CE-ICPMS. The projects will form basis for future research on the interaction of nanoparticles in biological systems.

**Supervisor:** Laura Hyrup Møller, Bente Gammelgaard, Stefan Stürup

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### Projects at Department of Forensic Medicine (External projects)

Examination of drugs and drugs of abuse in alternative matrix
Application of automated pipetting robots in forensic chemistry
Use of informatics and statistical methods for optimization and quality control in forensic chemistry

**Supervisor:** Bente Gammelgaard + external supervisor

### Projects at the National Research Center for the of Working Environment (External projects)

Method development of 2D-LC-MS-MS method for metabolites of organophosphate esters in urine
Dermal uptake of PCBs using an ex vivo skin model and GC-MS-MS analysis (collaboration w. SDU)
Method validation and analysis of pesticides on silicone wristbands from farmers in Uganda using GC-MS-MS

**Supervisor:** Bente Gammelgaard + external supervisor

### Metal nanoparticles for brain drug delivery

Metal nanoparticles have shown potential for drug delivery to the brain. However, several metal NPs including Ag and Au are associated with cytotoxicity and accumulation in tissues. In this project, blood-brain barrier (BBB) permeability of biocompatible selenium (Se) NPs will be investigated in order to elucidate on their potential for brain drug delivery. SeNPs will be prepared chemically in different sizes and with different surface modifications. Cell uptake, permeability, and transformation of SeNPs in a BBB cell model will be investigated using HPLC and ICP-MS analysis.

**Supervisor:** Laura Hyrup Møller

### Selenium labelled cell-penetrating peptides for quantitative information on brain delivery

Cell penetrating peptides (CPPs) can improve the bioavailability of drug compounds. Application of CPPs for drug delivery to the brain is currently investigated using in vitro blood brain barrier (BBB) models. In order to quantitate the very low amounts of CPP crossing the BBB, fluorophores are often applied as detection labels. However, attachment of a relatively large fluorophore to a relatively small CPP, changes the physicochemical properties and barrier permeability. We have suggested Se-labelling as an attractive alternative to commonly applied labelling methods. Se are incorporated as selenomethionine in the peptide sequence allowing for sensitive ICP-MS analysis. In this project, we will examine the stability, BBB-permeability and transformation of different Se-labelled CPPs and compare with fluorophore labelled peptides.

**Supervisor:** Laura Hyrup Møller and Mie Kristensen

### Determination of trace element impurities in drug products (External project)

This project entails development and validation of new ICP-OES based analytical methods to comply with Pharmacopeia requirements for elemental impurities. The project is a collaboration with Lundbeck Pharma A/S.

**Supervisors:** Stefan Stürup

### UHPLC-ESI-MS/MS for quantification of isotope labeled metabolites

Development and validation of a UHPLC-ESI-MS/MS method for quantifying of isotope labelled glucose metabolites such as citrate, succinate, glutamate and glutamine. The final method will be applied for determination of isotopologues in cell samples.

**Supervisors:** Stefan Stürup, Laura McNair (ILF), Blanca Garcia (ILF)
**FIDA: A new approach for biomarker quantification and immunogenicity assessment**

Protein based biomarkers may be used to determine the most optimal drug treatment as well as to monitor treatment status. Therapeutic monitoring of drug compounds is in many cases also beneficial for a successful treatment and recovery. In this project Flow Induced Dispersion Analysis (FIDA) will be investigated for biomarker and immunogenicity assessment. The project may involve internal as well as external collaborations.

**Supervisors:** Henrik Jensen and Jesper Østergaard

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**Stability assessment of protein based drugs**

In this project, the FIDA methodology (see project above) is utilized for stability assessment of protein based drugs. While protein based drugs have proven efficient for the treatment of a range of serious diseases, a number of challenges remains in developing and formulating these drug compounds. Notably, they are known to be structurally labile and efficient methods for assessing stability are currently suboptimal. In this project we take advantage of the fact that structural changes can be monitored as size changes, change in optical properties and altered function (binding ability).

**Supervisors:** Henrik Jensen and Jesper Østergaard

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**Application procedure and dates**

If you are interested in writing your thesis with Pharmaceutical Physical and Analytical Chemistry, please write an email to one of the supervisors with more information about you. There is no deadline.
Physiological Pharmaceutics

www.pharmacy.ku.dk/research/physiological-pharmaceutics/

In the Physiological Pharmaceutics group (PhysioPharm) we work with oral and mucosal drug delivery. We develop novel drug delivery systems (DDS) to improve drug bioavailability and/or to ensure the maximal therapeutic effect with fewest possible side-effects. We work with both poorly soluble drugs and peptides, and focus on lipid-based DDS and customized release. We develop DDS for special populations (e.g. children; the elderly and patients with hypochloridia or inflammatory bowel disease). We use in vitro models of the mouth, eye and the gastro-intestinal (GI) tract that we are continuously improving in order to make them as physiologically relevant, and predictive for bioadhesion, dissolution, release and permeation, as possible. In addition, we also use and develop in silico models to further understand the absorption and metabolism of the drug.

Note 1: As a general rule, a co-supervisor will be allocated to each master student, often a PhD student from the PhysioPharm Group, or a person from the industry or from other institutions.

Note 2: All of us have close contact to the industry and other universities – so come talk with us if you desire a master project in the industry – or abroad.

Potential thesis supervisors

Jette Jacobsen
Associate Professor
jette.jacobsen@sund.ku.dk

Research focus: Mucosal drug delivery, oromucosal (buccal, sublingual), ocular, bioadhesion, ex vivo permeation, liquid-semi solid- solid formulations, xerostomia.

Researcher profile

Daniel Bar-Shalom
Associate Professor
daniel.barshalom@sund.ku.dk

Research focus: Pediatric and geriatric formulations. Functional excipients. Implementing learnings from food science and material science into pharmaceutical science.

Researcher profile
# Physiological Pharmaceutics

**Ragna Berthelsen**  
Assistant Professor  
ragna.berthelsen@sund.ku.dk  

**Researcher profile**

**Research focus:** Human gastro-intestinal physiology. Design and development of predictive *in vitro* models, simulating the gastro-intestinal tract. Use of *in vitro* models to evaluate oral drug performance, and formulation design, as well as to study and to understand mechanisms of drug solubilization and absorption. Special focus on drug delivery to the pediatric population.

**Examples of projects**

**In vitro in vivo correlation of oromucosal lubrication and bioadhesiveness**

- of selected polymers with different physico-chemical properties (charge, molecular size, chemical structure, HLB) aiming at a platform for screening of oromucosal bioadhesiveness. Today, human *in vivo* studies of oromucosal bioadhesion are sparse. Examples of qualitative and quantitative *in vitro* bioadhesion methods to be validated in this project: Zeta potential, tissue-based tensile strength, rheology, tissue-based retention model, turbidity, contact angle. Initially, an application to authorities for study of human *in vivo* oromucosal bioadhesiveness must be written.

**Supervisor:** Jette Jacobsen

**Rule of ## for buccal and sublingual drug absorption to systemic delivery**

This project aims at elucidating the optimal physico-chemical properties of drugs for buccal or sublingual absorption. A series of drugs will be evaluated with regard to solubility in saliva and permeability (cell cultures or *ex vivo* animal mucosa in side-by-side diffusion cells (e.g. sublingual or buccal mucosa,)). The project may be planned in collaboration with pharmaceutical industrial partner.

**Supervisor:** Jette Jacobsen

**Safety and enhancement of oromucosal or ocular drug permeability**

These projects aim at evaluating excipients (e.g. absorption enhancers, bioadhesive polymer, co-solvents, buffering pH, surface active preservatives, flavours etc.) to gain a mechanistic knowledge of *in vitro* mucosal permeability of drugs with different physico-chemical properties by employing physiological relevant transport studies with cell cultures or *ex vivo* animal mucosa in side-by-side diffusion cells (e.g. sublingual or buccal mucosa, and cornea). Potential formulations are liquids (e.g. original product and generics), drugs printed on bioadhesive films (for individualized personal medicine) or solids. The projects may be planned in collaboration with pharmaceutical industrial partner and Chr. Janfelt to perform high-resolution MALDI mass spectrometry imaging of drugs and excipients.

**Supervisors:** Jette Jacobsen, Miriam Kolko (ILF), Susan Weng Larsen, Natalja Genina, Christian Janfelt
**Bioadhesive formulations for alleviation of xerostomia**

Xerostomia (dry mouth) can be a very disabling state of health. Xerostomia can be due to e.g. use of medicine or illness (Sjögrens syndrome, radiation therapy in cancer). We hypothesize that each, salivary proteins and lipids, contribute to maintain functions of saliva in bulk and at the mucosal surface. The projects will focus on formulation of a physiological relevant composition for daily care and as a drug delivery system. The work may comprise preparation and characterization of semisolid or liquid bioadhesive formulations with and without drugs, development of *in vitro* cell culture based methods for oromucosal spreadability/wettability (i.e. measurement of single-sided contact angle and surface tension) or friction of formulations, characterization of bioadhesiveness (retention time and force), and mucosal hydration rate. The projects are in collaboration with an external clinical specialist in oromucosal medicine and pathology.

**Supervisors:** Jette Jacobsen, Huiling Mu and Daniel Bar-Shalom

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**Development of “instant pudding” vehicles**

There are different scenarios requiring different solutions: (a) Individual, single dose commercial products to be produced by the industry, (b) Vehicles to be added to magisterial compounded products at the hospital or community pharmacy and (c) Vehicles for mass treatment in the developing world where a whole village is treated at once (for example, with anti-parasitic combinations) etc. The projects are usually carried out in collaboration with interested parties (pharmaceutical and food industry, raw materials suppliers, analytical instrumentation producers and academic partners. Many of those abroad)

**Supervisors:** Daniel Bar-Shalom, Ragna Berthelsen

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**Paediatric/Geriatric drug delivery**

Children and the elderly are special population groups from the oral drug delivery perspective. Their swallowing (in)abilities are different from those of the “average population” (those able to swallow tablets and capsules). The elderly and chronically sick children tend to take multiple drugs, thereby complicating the treatment. Our approach is to individually microencapsulate the drugs to eliminate the (bad) taste problem, to prevent unfortunate interactions between the drugs when in combination and to provide controlled release, if possible. The microencapsulates are mixed with dry, “instant pudding” formulations, and just before administration water is added, resulting in a pleasant, easy to swallow pudding/applesauce mass.

**Supervisor:** Daniel Bar-Shalom, Ragna Berthelsen

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**Development of the dispensing systems for Microencapsulate/Pudding products**

It is not sufficient to have the components of the product, a dispensing strategy and device are needed too. Project in this part involve collaboration with design experts.

**Supervisor:** Daniel Bar-Shalom, Ragna Berthelsen

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**Development of microencapsulated particles for children and elderly**

Different applications require different solutions. The drugs used at the hospital are a very heterogeneous group, those given in anti-parasitic treatments are notoriously water insoluble, in single doses and long-term stability is expected.

**Supervisor:** Daniel Bar-Shalom
**Oral controlled release of high dose, highly soluble drugs**

The problem of insoluble drugs is much researched all over the world, including people in our own department. The opposite problem has been largely ignored, but it is there and represents an interesting “niche”.

**Supervisor:** Daniel Bar-Shalom

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**Probiotics as therapeutic agents**

Our GastroIntestinal Tract, GIT is the home of a rich population of microorganisms, in fact, there are more microorganisms there than cells in the entire human body. The focus has been on the delivery of selected microorganisms to the lower GIT and on “fecal transplantation” (transferring feces from a healthy patient to another suffering from certain diseases. Getting the bacteria - alive! - to the target is a tricky problem, far from satisfactorily solved. Other areas, nose, mouth (which might or might not be considered a part of the GIT), vagina and skin are other areas where “flora manipulation” is being explored.

**Supervisor:** Daniel Bar-Shalom, Anette Müllertz

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**Development a combined gastrointestinal digestion and permeation in vitro model.**

In order to achieve a systemic response following oral administration, a given drug needs to dissolve (or be solubilized) in the gastrointestinal (GI) fluids and permeate the intestinal mucosa to reach the systemic circulation. As many poorly water soluble drugs are affected by the co-administration of food, or formulated in a lipid based drug delivery system to ensure GI drug solubilization, the GI digestion processes will affect the drug absorption. Therefore, two key parameters to evaluate in order to predict the in vivo performance of orally administrated poorly water soluble drugs are the drug solubilization during GI digestion and the permeation across the intestinal mucosa. As these two processes affect each other, a predictive in vitro model needs to mimic both processes simultaneously. The purpose of the present master’s thesis project is to develop and evaluate a combined GI digestion and permeation in vitro model.

**Supervisors:** Ragna Berthelsen, Mette Klitgaard (phd student) and Anette Müllertz

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**Lipid based drug delivery systems for the pediatric population**

As the pediatric population differs from the adult population in many aspects, the design of drug delivery systems (DDS) for the pediatric patient requires careful considerations. In oral administration, the physiological conditions of the gastro-intestinal tract is so complex that the rate and extent of drug absorption are influenced by many factors, especially when the drug solubility is low, it often causes incomplete absorption and low bioavailability, seriously affecting the drugs clinical efficacy and the treatment of the disease.

The project may involve: 1) construction of a pediatric lipid based DDS, and 2) In vitro evaluation of the designed DDS, studying drug solubilization capacity and mechanism, stability and drug release profiles using in vitro pediatric digestion model, and 3) studies of the permeation of poorly soluble drugs following administration of the designed DDS.

The study will be conducted in collaboration with hospital-pharmacists from Rigshospitalet.

**Supervisors:** Ragna Berthelsen
**Is intestinal mucus an important factor in solubilization and absorption of poorly soluble drugs?**

Efficient oral therapy is dependent on a good and reproducible drug absorption. However, many active drug candidates suffer from poor water solubility, which makes it difficult to formulate them into delivery systems with high and reproducible bioavailability. One important factor influencing this, is the poor understanding of the actual conditions in the gastrointestinal tract, and the factors that are limiting for the drug absorption. Therefore, the tools that are used in the development process are in many cases not predictive for the *in vivo* situation. One example is the media that are used for predicting the drug dissolution in the intestine, which often underestimates the *in vivo* dissolution. We hypothesize that the intestinal mucus layer has a larger solubilization capacity than the intestinal fluids and is therefore a major player in the absorption mechanism for poorly water soluble drugs. Thus, the mucus layer need to be included in *in vitro* models simulating drug dissolution and absorption.

This project aims to elucidate the impact of the intestinal mucus layer in dissolution, solubilization, diffusion and absorption of poorly water soluble drugs. The project will be directly linked with the current PhD project of Mette Klitgaard.

**Supervisors:** Mette Klitgaard (PhD student), Anette Müllertz, Jette Jacobsen, Ragna Berthelsen

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**Development of a targeted drug delivery system by use of micro-containers**

Inflammatory bowel disease (IBD) affects more than 50,000 people in Denmark. Current treatment options are not effective and are often associated with severe side effects due to systemic uptake of the drug. The aim is to develop a DDS that targets only inflamed areas of the gastrointestinal tract in IBD patients. This can be achieved e.g. by functionalizing the surface of the DDS. Newly developed DDS will be tested *in vitro*, and the promising DDS will be investigated *in vivo* in a preclinical IBD rodent model.

**Supervisors:** Anette Müllertz, Thomas Rades & Maja Nørgaard Kristensen (PhD student)

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**The effect of gastric transfer rate on supersaturation and precipitation of poorly water soluble weak bases**

A large solubility difference in the low pH stomach and neutral pH small intestine is a challenge for many new drugs. This solubility difference can lead to supersaturation and subsequent precipitation in the small intestine. This can lead to a large variability in pharmacokinetic studies. Supersaturation is an unstable system, where the concentration of a compound exceeds the (thermodynamic) solubility and over time will precipitate. The aim is to establish a novel two-step dissolution model with a gastric and an intestinal compartment to investigate the effect of gastric transfer rate on small intestinal supersaturation and precipitation of formulations of poorly water soluble weak bases.

**Supervisors:** Anette Müllertz & Jakob Plum (Post doc, Leo Pharma)
<table>
<thead>
<tr>
<th><strong>Functionalized self-emulsifying DDS (f-SEDDS) for oral delivery of peptides or proteins</strong></th>
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<tbody>
<tr>
<td>Self-emulsifying drug delivery systems (SEDDS) are solutions of oil, surfactant and co-surfactant spontaneously forming an oil/water emulsion upon mixing with an aqueous medium. SEDDS have shown great potential to improve the bioavailability of peptides by the advantages of mild preparation conditions, protection against enzymatic hydrolysis and build-in permeation enhancement. We will develop functionalized SEDDS (f-SEDDS) with e.g. mucoadhesive properties. F-SEDDS will be characterized by particle size, zeta-potential and in vitro digestion. The performance of the developed f-SEDDS will be evaluated by in vitro cell culture study and in vivo animal models.</td>
</tr>
<tr>
<td><strong>Supervisor:</strong> Anette Müllertz</td>
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<tr>
<th><strong>Assessing the relation between release profile and pharmacokinetics using PBPK models</strong></th>
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<tr>
<td>Physiologically based pharmacokinetic (PBPK) modelling is important in the drug development process to understand the relation between drug release, absorption and plasma profile. However, there is still shortcomings in the input (absorption) profiles in the PBPK models, e.g. the entire drug solubility profile in the GI tract is not considered. We want to apply PBPK models to different solubility and dissolution profiles, from selected formulations. We will use the softwares GastroPlus and SimCyp.</td>
</tr>
<tr>
<td><strong>Supervisors:</strong> Anette Müllertz, Ragna Berthelsen, Jakob Plum (Post doc, Leo Pharma)</td>
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<tr>
<th><strong>Simulating food effect on poorly soluble drugs</strong></th>
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<tr>
<td>Many poorly soluble drugs have positive food effect; they have a better bioavailability in the fed state. This is a problem for the reproducibility of the therapeutic effect and it is therefore desired to develop DDS that abolish the food effect. The aim is to develop in vitro models, simulating the fed state GI tract, and by use of this to develop formulations without food effect.</td>
</tr>
<tr>
<td><strong>Supervisor:</strong> Anette Müllertz</td>
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<tr>
<th><strong>Development of a predictive in vitro dissolution-, permeation model for evaluating amorphous solid dispersions</strong></th>
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<tr>
<td>Many drug molecules suffer from low aqueous solubility, which results in low oral bioavailability. Some of these drug molecules can benefit from the formulation principle of amorphous solid dispersion (ASD), in which the drug is molecularly dispersed in a polymer matrix. Dissolution of ASDs might result in a supersaturated solution of the drug, thereby increasing the absorbable drug amount in the gastrointestinal fluids. The aim of this project is to develop an in vitro model, predicting the in vivo performance of such ASD formulations.</td>
</tr>
<tr>
<td><strong>Supervisors:</strong> Anette Müllertz &amp; Jacob Rune Jørgensen (Postdoc)</td>
</tr>
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**Application procedure and dates**

If you are interested in writing your thesis with Physiological Pharmaceutics, please write an email to one of the supervisors with more information about you. There is no deadline.
Protein Analysis

www.pharmacy.ku.dk/research/protein-analysis-group/

The vast majority of drugs work by binding to and changing the function of proteins in the human body. Furthermore, many new drugs are themselves protein-based (so-called biopharmaceuticals) and these complex drugs account for the most rapidly growing drug in the pharmaceutical industry. Analysis of proteins is therefore at the core of pharmaceutical research.

Through the thesis projects below, you can get hands-on laboratory experience of how to work with proteins and learn state-of-the-art techniques for detailed analysis and characterization of protein-drug targets and biopharmaceuticals (protein chemistry, biophysics, liquid chromatography and mass spectrometry).
Our research centers around the use of mass spectrometry to provide the critical information concerning quantity, quality, structure and interactions of proteins - which is needed to guide and develop new and improved drugs. In particular, we have world-leading expertise with the HDX-MS technique, an incredibly sensitive method for studying the conformation, dynamics and interactions of proteins.

Examples of publications involving past master thesis projects:

Potential thesis supervisors

<table>
<thead>
<tr>
<th>Kasper D. Rand</th>
<th>Esben Trabjerg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Professor MSO.</strong></td>
<td><strong>Assistant Professor</strong></td>
</tr>
<tr>
<td><a href="mailto:kasper.rand@sund.ku.dk">kasper.rand@sund.ku.dk</a></td>
<td><a href="mailto:esben.trabjerg@sund.ku.dk">esben.trabjerg@sund.ku.dk</a></td>
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<tr>
<td><a href="#">Researcher Profile</a></td>
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<tr>
<td><strong>Research focus:</strong> Protein Analytical Chemistry, HDX-MS</td>
<td><strong>Research focus:</strong> Protein cross-linking mass spectrometry, HDX-MS</td>
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</table>

**Examples of projects**

### Structural analysis of biopharmaceuticals

Analysis of the primary and higher-order structure of protein-based drugs is critical for both understanding molecular action as well as monitoring and comparing drug product quality. In this suite of projects, you will apply a new powerful analytical technology that uses mass spectrometry to measure the hydrogen/deuterium exchange of proteins in solution (HDX-MS) and is thus capable of producing detailed information on the structure of biopharmaceuticals. You will use this technique to analyze and compare the structural properties of new potential protein drugs in development and thus help provide a critical molecular understanding of their pharmaceutical properties and function in the human body. Work will be done in close collaboration with researchers at UCPH or industrial collaborators such as Biogen Idec (USA), Roche (Germany) and Novo Nordisk (Denmark), depending on the project. There is typically also the possibility to perform parts of the project at the industrial collaborator.

**No. of students:** 1-2
### Understanding the binding of drugs to target proteins of the human body

HDX-MS is a very sensitive method to study the binding of small molecule ligands or large protein-based drugs to naturally occurring protein receptors in great detail. By using mass spectrometry, we measure the hydrogen/deuterium exchange (HDX-MS) of the protein receptor in the absence and presence of a single or a panel of potential ligands. We can thus map the binding site of ligands on the protein receptor and study the structural effects of binding. In this project, you will use HDX-MS to study both the binding of ligands (small molecule or large protein-based) to important new pharmacologically interesting protein receptors. Work will be conducted in collaboration with academic/industry collaborators.

No. of students: 1-2

### Coupling microfluidics and mass spectrometry for improved analysis of proteins

Analysis of protein drugs requires specialized sample treatment and advanced analytical techniques as they are large and complex and often contain modifications (e.g. glycosylations, disulfide bonds). In this suite of projects, we explore the use of microfluidic chips to perform rapid and automated preparation of protein samples (sample concentration, enzymatic reactions, chromatographic separation) for analysis by mass spectrometry. You will learn how to implement protein chemistry and liquid chromatography on a microfluidic device coupled to state-of-the-art protein analysis by mass spectrometry. The project will be done with co-supervision from Jorg Kutter of the Microscale Analytical Systems group.

No. of students: 1-2

### Application procedure and dates

If you are interested in writing your thesis with the Protein Analysis Group, please write an email to kasper.rand@sund.ku.dk with more information about you. There is no deadline.
Social and Clinical Pharmacy Group
www.pharmacy.ku.dk/research/social-clinical-pharmacy/

Social pharmacy seeks to have the broad view of medicines in society and focuses on how medicines are perceived, used, and managed by different stakeholders. Clinical pharmacy seeks to ensure the optimal and rational use of medicines for the benefit of patients and society through collaboration between pharmacists, other health professionals, and the patient. SCP’s research ultimately seeks to ensure the benefit of medicines for users, organizations, and society. SCP’s research is concerned with the three levels (the user, organization and society) and how they interact to ensure the optimal use of medicines.

Potential thesis supervisors

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>Researcher Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anna Birna Almarsdóttir</td>
<td>Professor</td>
<td></td>
</tr>
<tr>
<td>Lourdes Cantarero-Arévalo</td>
<td>Associate Professor</td>
<td></td>
</tr>
<tr>
<td>Lotte Stig Nørgaard</td>
<td>Associate Professor</td>
<td></td>
</tr>
<tr>
<td>Susanne Kaae</td>
<td>Professor</td>
<td></td>
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<tr>
<td>Charlotte Vermehren</td>
<td>Associate Professor</td>
<td></td>
</tr>
<tr>
<td>Ramune Jacobsen</td>
<td>Assistant Professor</td>
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</table>

In addition to these supervisors, SCP has contact to researchers off campus who are willing and able to supervise, eg. at hospital pharmacies, Pharmakon, Medicinrådet, regional research centers, etc. Each of these come with ideas that are important to them and can be used as basis for a master project under their supervision, but in close collaboration with the SCP supervisors.

Project ideas

Master thesis projects may be connected to existing research projects in the SCP Group, but other relevant ideas for master thesis projects within social and clinical pharmacy are also welcome. If you wish to know more about us and what kind of research we do you can have a look at our website and at our WHO collaborating center. Alternatively, you can use the “Find a Researcher” option for members of the research group on the website of the University of Copenhagen.

We expect that projects by master students can be within already established areas such as polypharmacy, communication over the counter, medicines use among adolescents, young people and vulnerable population, ethical dilemmas in medicine use among others. We also see new areas emerging that students can work on such as COVID-19 (which ethical and political issues will emerge from the pandemic related to medicines, vaccines and the pharmacists’ role).
The SCP master thesis system
We have a coordinated master thesis student system. We first accept students for the entire group, and we then allocate a supervisor to each student. The contacts regarding master theses are lou.cantarero@sund.ku.dk and anna.bima@sund.ku.dk. Please do not write to others in the SCP group with questions about thesis projects.

If you are interested in writing your thesis within Social and Clinical Pharmacy, please send your application via our website: www.pharmacy.ku.dk/research/social-clinical-pharmacy/master-thesis-application-form/
The deadline is 15 December, 2020.

On 8 December 2020 at 12am, we arrange our own webinar in the SCP group. You will be able to discuss with us about possibilities for master theses and our process for selecting students. Note that we do not arrange individual meetings with students. Therefore, if you want to know more, please join us at the webinar on 8 December 2020.
Students selected for master thesis writing in 2022 in our group will be notified in week 51.
Join the webinar by clicking on the link: Master thesis webinar in the SCP group 2020.
Solid State Pharmaceutics
www.pharmacy.ku.dk/research/solid-state-pharmaceutics/

The scientific staff consists currently of the three scientists Korbinian Löbmünn, Thomas Rades and Holger Grohganz, and a varying number of PhD students.

We develop drug delivery systems based on high-energy solids. The aims are improved stability of the formulations, and solubility enhancement of poorly water-soluble drugs. We furthermore aim to obtain a deeper understanding of the underlying mechanisms for amorphous stability and have a keen interest in novel formulations approaches and novel excipients.

Low solubility is the major challenge for many small-molecule drugs. By stabilizing a poorly water-soluble drug in its amorphous form, its bioavailability can be increased, due to a higher dissolution rate and apparent solubility. Understanding molecular interactions and thereby overcoming the inherent instability of amorphous drugs is one solution to the solubility problem. The amorphous drug can be stabilized with both polymers and small molecules. The amorphous formulation is characterized by a wide range of advanced analytical state-of-the-art methods.

For the production of amorphous formulations of both, small molecules and biomacromolecules, various production techniques, such as ball milling, spray-drying, freeze-drying, microwaves and hot melt processing are applied. Understanding the influence of process and formulation parameters on the solid state of both excipient and drug enables a rational choice of formulation.

Potential thesis supervisors

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Email</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holger Grohganz</td>
<td>Associate professor</td>
<td><a href="mailto:holger.grohganz@sund.ku.dk">holger.grohganz@sund.ku.dk</a></td>
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<tr>
<td>Thomas Rades</td>
<td>Professor</td>
<td><a href="mailto:thomas.rades@sund.ku.dk">thomas.rades@sund.ku.dk</a></td>
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Research focus: Development of solid dosage forms, including preformulation, formulation, processing and manufacturing together with the relevant solid-state characterization and multivariate analysis. This includes in particular the development co-amorphous systems as well as a deeper understanding of freeze-drying as production technique.

Research focus: Development of solid oral dosage forms, including preformulation, formulation, processing and manufacturing together with the relevant solid-state characterization and quality control. This includes in particular the development of amorphous and co-amorphous systems as well as amorphous solid dispersions.
Korbinian Löbmann
Associate Professor
korbinian.loebmann@sund.ku.dk
Researcher Profile

Research focus: Development of solid oral dosage forms, including preformulation, formulation, processing and manufacturing together with the relevant solid state characterization and quality control. This includes in particular the development of new enabling formulation strategies, such as microwave amorphization (in situ amorphization) as well as novel excipients, such as mesoporous silica or deep eutectic solvents.

Examples of projects

Quality by design (QbD) in the processing of biomacromolecules

The quality by design (QbD) principle can be expected to influence the way of pharmaceutical processing in the years to come towards the development of more rational processes. Although, freeze-drying and spray-drying are widely used in peptide and protein formulation, the interaction between various excipients and proteins is not fully understood. This project aims to obtain a deeper understanding of the influence of various composition and process parameters on the solid state form of both novel and established the excipients, and the macromolecule. The investigation of novel excipients to support improved freeze-drying is of especial interest. Analytical techniques may include X-Ray powder diffraction, dynamic mechanical analysis, NIR and Raman spectroscopy as well as the application of multivariate data analysis.

Supervisor: Holger Grohganz

Evaluation of preparation methods for co-amorphous formulations

Low drug solubility is the major challenge for future small molecule drugs. In order to overcome the problematic solubility of BCS class 2 drugs, small excipients are investigated to form co-amorphous formulations. Due to the low solubility, ball milling is used as preferred production process. Due to the low capacity of ball mills, other production procedures, such as freeze-drying, spray-drying and hot-melt processing should be evaluated.

Supervisor: Holger Grohganz
### Down-stream processing of co-amorphous formulations

In this project, co-amorphous systems intend to be moved from the powder formulation state towards a more applicable state, i.e. downstream-processing towards a final dosage form, including the investigation of critical processing and formulations parameters of the pharmaceutical performance. A comparison between the amorphous and crystalline forms with regard to downstream processing also needs to be investigated. The effect of various excipients on compactability and compressibility of co-amorphous systems will be connected with the results of pharmaceutical quality testing.

**Supervisors:** Joint project with Thomas Rades and Holger Grohganz

### On the role of water in amorphous systems

Water is generally seen as detrimental for the stability of amorphous drugs and solid dispersions. However, initial in-house work has shown that this may not necessarily be true for all systems especially at low water concentrations. The aim of this Masters project is to determine the water absorption and stability of a range of amorphous systems (pure drugs, amorphous solid dispersions with polymers and co-amorphous systems with amino acids) in the presence of different amounts of water. The student will learn preparative techniques, including ball milling and quench cooling as well as using a wide range of analytical techniques, including X-ray powder diffraction, FTIR spectroscopy, thermal analytical techniques, water determination and dissolution techniques.

**Supervisors:** Project in co-operation with Thomas Rades, Matthias Manne Knopp and Holger Grohganz.

### Electrospun amorphous solid dispersions of poorly water-soluble drugs.

The development of oral dosage forms from poorly water-soluble active pharmaceutical ingredients (APIs) remains a major challenge for the pharmaceutical industry. Preparing amorphous solid dispersions (ASDs) allows increasing the solubility and dissolution rate of an API, hence, increasing its bioavailability. The application of electrical energy during electrospinning can generate ASD nanofibers from drug-loaded solutions and melts. This project focuses on the development of an electrospinning method to produce ASDs. The electrospun fibers will be comprehensively characterized by a range of analytical techniques, including scanning electron microscopy, X-ray powder diffraction, differential scanning calorimetry and dynamic mechanical analysis. The dissolution rate advantage will also be determined.

**Supervisor:** Project in co-operation with Thomas Rades and Andrea Heinz
**In situ amorphization using lasers or microwave irradiation**

A major concern of amorphous formulations is their physical instability, which puts the gain in solubility at risk upon long time storage. Using lasers or microwaves, it is possible to transform a crystalline drug into its highly soluble amorphous counterpart within the final dosage form (tablet). The aim of the project is to develop new drug delivery systems that can be “activated” using lasers or microwaves and to understand in depth the mechanism behind the in situ amorphization process using microwave irradiation.

**Supervisor:** Korbinian Löbmann

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**Development of novel Dispersome® formulations**

The novel solubility enhancing Dispersomes® technology is based on the use of whey protein isolate as excipient for amorphous stabilization and solubility enhancement and is the basis of the KU spin-out company ZERION. The projects aim is to further understand the mechanisms behind the amorphous stabilization and solubility enhancement of a given drug when formulated as Dispersomes®. The project will partly be an industry project and is co-supervised by Zerion scientists.

**Supervisor:** Project in co-operation with Korbinian Löbmann and senior scientist Donglei Leng (ZERION ApS)

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**Tiny medicine sponges – Understanding drug adsorption and molecular mobility in mesoporous silica**

Mesoporous silica (MS) is an excipient that can stabilize the amorphous form of a drug via surface adsorption in a monolayer. One project aims to increase the mechanistic understanding of molecular interactions and mobility of adsorbed drug monolayers on MS surfaces. A second project aims to increase the understanding of the monolayer mobility and phase transition, which we recently were able to experimentally identify.

**Supervisor:** Project in co-operation with Korbinian Löbmann and senior scientist Matthias Manne Knopp (Bioneer:Farma).

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**Application procedure and dates**

If you are interested in writing your thesis with Solid State Pharmaceutics, please write an email to one of the supervisors with more information about you. There is no deadline.
The goals of the Surface and Colloid Chemistry Group are to advance the knowledge regarding the membrane interactions of antimicrobial peptides and different nanomaterials, particularly inorganic nanoparticles with potent antimicrobial activities or used as carriers for antimicrobial and anti-inflammatory agents. Both state-of-the-art techniques and innovative approaches are used in the group to evaluate the interactions between these agents and membrane components of cells and bacteria, including for instance fluorescence spectroscopy, DLS, QCM-D, FTIR-ATR, neutron and X-ray scattering. The overarching aim is to take fundamental research about physicochemical properties and mechanisms to a stage where it can be translated to further therapeutic development.

### Potential thesis supervisors

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<tr>
<th>Name</th>
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<tr>
<td>Martin Malmsten</td>
<td>Professor</td>
<td><a href="mailto:Martin.malmsten@sund.ku.dk">Martin.malmsten@sund.ku.dk</a></td>
</tr>
<tr>
<td>Elisa Parra Ortiz</td>
<td>Assistant Professor</td>
<td><a href="mailto:elisa.parra@sund.ku.dk">elisa.parra@sund.ku.dk</a></td>
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### Research focus
- **Martin Malmsten**: Microgels, nanoparticles for drug delivery, and host defence peptides for combatting infection and inflammation
- **Elisa Parra Ortiz**: Lipid membranes, lipid peroxidation, nanoparticles for drug delivery

### Examples of projects

#### Membrane interactions of structured silica nanoparticles as antimicrobial agents

In the wake of increasing bacterial resistance against conventional antibiotics, there is a growing interest in alternative approaches for reaching antimicrobial effects. Among those, nanoparticles are attracting considerable current interest due to the comparatively low cost, good scalability, and broad versatility of such materials, but also due to presently undeveloped bacterial resistance. Here, various nanomaterials offer opportunities for triggered functionalities to combat challenging infections. Although the performance in these diverse applications is governed by a complex interplay between the nanomaterial, the properties of included drugs (if any), and the biological system, nanoparticle-membrane interactions constitute a key initial step and play a key role for the subsequent biological response. Clarifying key factors controlling membrane binding and destabilization of nanoparticles is therefore key for the successful development of the latter towards therapeutics.

In the present project, membrane interactions will be investigated for mesoporous silica nanoparticles, which offer opportunities in combating challenging infections. For example, both low molecular weight and macromolecular drugs can be readily incorporated into such nanoparticles, allowing large drug loads due to their large specific surface area. In addition, silica nanoparticles can be designed to display needle-like surfaces, which may be used to effectively "puncture" bacterial membranes by "needle-like" actions. Within the project, factors determining membrane interactions of "spiky" mesoporous silica nanoparticles will therefore be investigated by previously developed model lipid...
membranes, in combination with various biophysical techniques, such as QCM-D, FTIR-ATR, and DLS. Results from such biophysical studies, e.g., on effects of membrane composition, structure and charge of the silica nanoparticles, and effects of co-administration of such particles with other potent antimicrobial agents, notably antimicrobial peptides, will be correlated to biological results on antimicrobial effects and cell toxicity for selected systems.

**Supervisor:** Martin Malmsten & Elisa Parra-Ortiz. Number of students: 1

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**Application of oxidative stress on lipid membranes as a new tool for developing new antimicrobial agents**

Inorganic nanoparticles are very attractive as antimicrobial agents ('nanobiotics'), notably due to the increasing resistance development against conventional antibiotics. Apart from scalability and versatility, such materials offer advantages related to responsiveness of antimicrobial and anti-inflammatory effects and the possibility of controlling them by a range of triggering factors. For instance, oxidative stress is known to be behind the antimicrobial activities of TiO$_2$ nanoparticles when activated by UV light. However, studies on the mechanisms underlying these activities remain scarce. Based on previous work done by our group on the oxidative destabilization of lipid membranes, and using different biophysical and surface-chemical techniques such as fluorescence spectroscopy, QCM-D, FTIR-ATR, and DLS, the present project will focus on the effects of TiO$_2$ nanoparticle-induced oxidation of lipid membranes, lipid degradation, and their consequences for membrane structure and stability. Any potential membrane selectivity that could allow more efficient antimicrobial activities along with reduced side effects will be also explored, for instance the combination with cationic peptide coatings. In a wider perspective, this project will contribute to the mechanistic foundation for the use of photocatalytic nanomaterials as triggerable antimicrobial agents.

**Supervisor:** Martin Malmsten & Elisa Parra-Ortiz. Number of students: 1

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**Application procedure and dates**

If you are interested in writing your thesis with the Surface and Colloid Chemistry Group, please write an email to one of the supervisors with more information about you. There is no deadline.
Toxicology and Drug Metabolism

www.pharmacy.ku.dk/research/toxicology-drug-metabolism/

We perform experimental research revealing the occurrence, fate, and toxicological and endocrine effects of xenobiotics, especially pharmaceuticals, with the aim of assessing their risks to humans and biota. We apply various in vitro, ex vivo and in vivo assays and advanced analytical techniques, such as LC-MS and mass spectrometry imaging.

Potential thesis supervisors

<table>
<thead>
<tr>
<th>Bjarne Styrishave</th>
<th>Christian Janfelt</th>
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<tr>
<td>Associate Professor</td>
<td>Associate Professor</td>
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<td><a href="mailto:bjarne.styrishave@sund.ku.dk">bjarne.styrishave@sund.ku.dk</a></td>
<td><a href="mailto:Christian.janfelt@sund.ku.dk">Christian.janfelt@sund.ku.dk</a></td>
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<td>Researcher Profile</td>
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<tr>
<th>Andreas Christopher Kretschmann</th>
<th>Catharina M. Lerche</th>
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<tr>
<td>Associate Professor</td>
<td>Clinical Associate Professor</td>
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<td><a href="mailto:andreas.kretschmann@sund.ku.dk">andreas.kretschmann@sund.ku.dk</a></td>
<td><a href="mailto:Catharina.Margrethe.Lerche@regionh.dk">Catharina.Margrethe.Lerche@regionh.dk</a></td>
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Examples of projects

**Endocrine disrupting pharmaceuticals**

Public awareness concerning endocrine disrupting drugs has increased the last few years, as these are presumed to affect reproductive ability and to increase the occurrence of hormone-dependent cancers. Endocrine disrupting drugs are, however, generally much less potent than physiological hormones, and therefore there is doubt as to whether or not these substances can affect humans.

Recent research indicate that simultaneous exposure to a cocktail of endocrine disrupting drugs, each at a concentration below the effect level, might result in a significant additive or synergistic effect. The present project wishes to uncover interactions between selected hormone-disturbing substances in various in vitro test systems and/or animal experiments with selected endpoints, including hormonal activity, changes in aromatase activity and the impacts of endocrine disrupting drugs on endogenous hormone metabolism.

**Supervisor:** Bjarne Styrihaye, No of students: 2-3

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**Endocrine toxicity of drug enantiomers and metabolites**

Increasing evidence exists that certain pharmaceuticals disturb the human hormone system and may contribute to endocrine related diseases like infertility, obesity and different types of cancers. It is well known that enantiomers of drugs can differ strongly in their biological activity. Furthermore, drug metabolites formed in the body can be active and possess higher activity than the parent compound. Very little is known about how the endocrine disrupting potency of a drug depends on its enantiomeric form and its metabolic products.

The focus of this project are chiral drugs like azole fungicides, which are used for the treatment of severe systemic and superficial fungal infections. The goal of this project is to elucidate the endocrine toxicity of azole enantiomers and metabolites through pharmacokinetic and –dynamic studies. The practical work includes enzyme and cell based in vitro assays as well as in vivo experiments. A large part of the project is the development of analytical chemical methods for the identification and quantification of enantiomers and metabolites in different biological matrices with enantioselective HPLC-MS/MS.

**Supervisors:** Andreas Kretschmann, Bjarne Styrihaye, Claus Cornett. No. of students: 1-2

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**Development of a microfluidic assay for testing the endocrine disrupting potential of pharmaceuticals**

Increasing evidence exists that certain pharmaceuticals disturb the human hormone system and may contribute to endocrine related diseases like infertility, obesity and different types of cancers. It is well known that enantiomers of drugs can differ strongly in their biological activity. Furthermore, drug metabolites formed in the body can be active and possess higher activity than the parent compound. Very little is known about how the endocrine disrupting potency of a drug depends on its enantiomeric form and its metabolic products.

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**Supervisor:** Bjarne Styrihaye, No of students: 1-2
**Toxicology and Drug Metabolism**

The goal of this project is to elucidate the endocrine toxicity of azole enantiomers and metabolites through pharmacokinetic and -dynamic studies. The practical work includes enzyme and cell based *in vitro* assays as well as *in vivo* experiments. A large part of the project is the development of analytical chemical methods for the identification and quantification of enantiomers and metabolites in different biological matrices with enantioselective HPLC-MS/MS.

**Supervisors:** Andreas Kretschmann. No. of students: 1-2

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**Pancreatic infections: Local and systemic antibiotics in infected walled-off pancreatic necrosis.**

Severe acute pancreatitis is characterized by organ dysfunction and necrosis of the pancreas. Mortality is high, up to 20%. Infection in the pancreas is a serious complication and is associated with high mortality, up to 20%. After 3-4 weeks the necrosis becomes encapsulated a so-called walled-off necrosis (WON). The primary treatment is systemic antibiotics. However, little is known about the penetration of antibiotics into the necrosis and the ability of antibiotics to stop the infection. Several factors may influence the activity of the antibiotics, such as the fibrous capsule surrounding the necrosis, the size and the physic-chemical milieu of the necrosis. Using 2D-DESI-imaging and LCMS/MS, this project aims to investigate the distribution of the most commonly used antibiotics in pancreatic necrosis. The purpose is to identify the most effective treatment, thereby decreasing mortality and morbidity in patients suffering from pancreatic necrosis.

**Supervisors:** Bjarne Styrishave, Christian Janfelt. No. of students: 1-2

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**Danida project: Green Resource Innovations For Livelihood Improvement (GRILI)**

Medicinal plants as green resource products (GRPs) are used as traditional medicine in Tanzania, and are key components for primary health care and livelihoods of more than 50% of the inhabitants. Unfortunately, many herbal products are adulterated with drugs, such as antibiotics, antimalarials and mild analgesics. The present study aims to investigate the adulteration of herbal drugs from Tanzania, by analysing the presence of different drug classes in herbal medicines collected from markets and health providers in Tanzania. Samples will be collected and extracted in Tanzania and transported to Denmark, where the samples will be analysed. The project included approximately 3 months of field work in Tanzania.

**Supervisors:** Bjarne Styrishave. No. of students: 1-2
# Mass spectrometry imaging of drugs in tissue sections from mice

Using a new technique with mass spectrometry, Desorption Electrospray Ionization Imaging (DESI-MS), it is possible to image the distribution of compounds on a surface. In this way, we can follow a drug dosed to a mouse, creating images of the mouse that show where in the body the drug goes, and how it is metabolized. In this project, a mouse will be dosed with a drug, and subsequently the whole mouse or single organs (brain, liver and kidney) will be cut in thin slices which are then analysed with DESI-MS. The aim of the project is to image where the drug goes and in which doses we can see the drug and its metabolites. The project will be planned in collaboration with pharmacologists or medicinal chemists.

**Supervisors:** Christian Janfelt. **No. of students:** 2

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# Mass spectrometry imaging of natural compounds in cannabis

The use of medical cannabis is increasing worldwide, and recently, the Danish government has sanctioned a 4-year pilot programme for the prescription of medical cannabis to Danish patients. More than 500 natural compounds have been isolated from Cannabis Sativa, including the medically important cannabinoids, terpenes and flavonoids. For a deeper understanding of this complex composition, and to ensure products of high and consistent quality, better analytical tools are needed. The aim of this project is to apply mass spectrometry imaging to characterize the distribution of active compounds in Cannabis Sativa leaves, to study the compound synthesis in the plant during flowering and the impact of environment and growth conditions on compounds of interest in the plant.

**Supervisors:** Christian Janfelt. **No of students:** 2

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# High-resolution MALDI mass spectrometry imaging for studies in drug delivery

A new laser-based mass spectrometry imaging setup has been installed, which enables mass spectrometry imaging at the cellular level. The technique will be used to study the delivery of drugs across biological membranes and barriers in ex-vivo and possibly in-vivo animal experiments. High resolution mass spectrometry images showing the distributions of drugs and other exogenous compounds relative to endogenous compounds such a membrane lipids will provide information about the efficacy and mechanism of new drug formulations. The project will be planned in collaboration with one of the Drug Delivery groups at the Department of Pharmacy.

**Supervisors:** Christian Janfelt. **No of students:** 2
### Mass spectrometry imaging in development of skin cancer treatment

The capabilities of DESI and MALDI MSI to image the distribution of endogenous compounds together with a drug and its metabolites make them ideal in the study of skin penetration of drugs. This project takes place in collaboration with Department of Dermatology, Bispebjerg Hospital, which develops new treatments for skin cancer. One approach is to ablate channels in the skin in order to be able to perform local, topical chemotherapy of skin cancer. In this project MALDI imaging and LC-MS will be used to optimize the delivery of one or more chemotherapy agents by imaging of tissue sections from different depths in the treated skin.

**Supervisors:** Christian Janfelt. **No of students:** 2

### DNA damage in the urine after UVR-exposure

Thymine dimer is the major form of DNA damage that happens when ultraviolet radiation penetrates the skin. Nucleotide excision repair (NER) is the main pathway for the repair of thymine dimers. The importance of this process is illustrated by the very high risk of developing skin cancer in individuals with disorders in which NER is defective. NER removes thymine dimers from DNA and subsequently they are excreted in the urine. The aim of this study is to investigate the effect of irradiation dose, exposed skin area, and skin type on the amount of excreted thymine dimers. The study involves irradiation of healthy volunteers, collection of urine samples and LC-MS. The study is part of SCIN-CAG (read more).

**Supervisors:** Catharina Lerche. **No. of students:** 1

### Pharmacological photoprotection

Sun exposure is the primary risk factor for keratinocyte cancer and despite massive prevention efforts, Danish incidences have risen to an estimated 38,500 per year. Pharmacological photoprotection is the concept of using pharmacological compounds before or after exposure to environmental carcinogens e.g. ultraviolet radiation. There is increasing evidence that compounds (e.g. nicotinamide and NSAIDS and less known plant- and marine- derived compounds), may be useful in keratinocyte cancer prophylaxis. The aim is to discover compounds that delay or even reduce photocarcinogenesis. Pharmacological compounds will be tested in well-established UVR-induced murine models. Laboratory Animal Science certificate is needed for this master project (FELASA A/B/D). The study is part of SCIN-CAG (read more).

**Supervisors:** Catharina Lerche. **No. of students:** 1
### Vitamin D-metabolite distribution in the skin analyzed by mass spectrometry imaging

Vitamin D plays a key role in the maintenance of calcium/phosphate homeostasis and elicits biological effects that are relevant to immune function and metabolism. It is predominantly formed through UVB exposure in the skin by conversion of 7-dehydrocholesterol (7-DHC). Melanin in the skin absorbs UVB irradiation and plays a major role in the protection against skin cancer, higher concentrations of melanin gives a better protection. Vitamin D is formed in all skin types, so the distribution of 7-DHC must be closer to the skin surface than melanin. Mass spectrometry imaging (MSI) enables the ability to gain spatial information of various molecules with spectra being mapped to individual pixels.

The aim of this study is to investigate the vitamin D-metabolite distribution in the skin using high mass resolution instrumentation and relate the findings to melanin in the skin.

**Supervisors:** Catharina Lerche and Christian Janfelt. No. of students: 1

### Application procedure and dates

If you are interested in writing your thesis with the Toxicology and Drug Metabolism group, please write an email to one of the supervisors with more information about you. There is no deadline.
The research focus of the Vaccine Design and Delivery Group is advanced drug delivery. The group uses *in vivo* imaging (e.g., NIR, MRI, and SPECT/CT) to guide and optimize the design of new nanoparticle-based delivery systems for vaccines and nucleic acid-based therapeutics to improve therapy. The research in the group is highly interdisciplinary. The team comprises international researchers of various backgrounds, including pharmacists, biologists, biochemists, physicists, and biotechnologists.

"Biopharmaceuticals like vaccines and nucleic acid-based therapeutics are challenging from a pharmaceutical perspective, because they are highly complex products, which can only be understood via solid fundamental science. Using systematic knowledge-based quality-by-design approaches, combined with advanced physicochemical and biopharmaceutical assessment, and molecular imaging, we design new delivery systems for biopharmaceuticals to optimize their stability, efficacy, and safety" says Professor and Group Leader, Camilla Foged.

The overall research goal is to improve disease prevention and treatment in the fields of infectious and inflammatory diseases, and cancer. The group is addressing drug delivery challenges from bench-to-bedside, via international collaborations, using state-of-the-art technologies. This has fostered innovative solutions and high-impact publications in drug delivery.
### Potential thesis supervisors

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<thead>
<tr>
<th>Camilla Foged</th>
<th>Aneesh Thakur</th>
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<tr>
<td>Professor</td>
<td>Assistant Professor</td>
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One of the primary goals of the Vaccine Design and Delivery Group is to gain new fundamental knowledge that can facilitate the design, optimization and development of novel delivery systems capable of delivering loaded biopharmaceuticals to the intended target site(s). The Vaccine Design and Delivery Group addresses the complex challenges associated with the formulation and targeted delivery of vaccines and nucleic acid-based therapeutics.

### Researcher Profile

**Camilla Foged**

- **Occupation**: Professor
- **Email**: camilla.foged@sund.ku.dk

**Aneesh Thakur**

- **Occupation**: Assistant Professor
- **Email**: aneesh.thakur@sund.ku.dk

### Examples of projects

**Microfluidics-assisted design of next-generation mRNA vaccines - a novel tool for fighting cancers and challenging infectious diseases**

There is an unmet medical need to develop novel vaccines against the so-called “difficult targets” such as AIDS, TB and cancer. One promising strategy is the use of vaccines based on mRNA that encode antigenic proteins from pathogens or tumor cells. Using microfluidics, we will develop multifunctional nanoparticle-based vaccine that both delivers mRNA encoding antigen and induces CTL responses. The efficacy and safety of the mRNA vaccines will be tested in animal models of infection and cancer.

**Supervisors**: Aneesh Thakur and Abhijeet Lokras
### Magnetic resonance imaging-assisted design of a thermostable and self-administrable tuberculosis vaccine for inhalation

**Liposomes**

Tuberculosis (TB) is caused by Mycobacterium tuberculosis, which enters the lungs through the respiratory mucosa. The objectives of the project is to develop a dry powder-based vaccine against TB and using MR imaging, to define the specific areas in the lungs, which are optimal for vaccine deposition, efficacy and safety. Using a benchtop aerosol generator, PreciseInhale, we will deliver the dry powder liposome-adjuvanted vaccine formulation in mice lungs and evaluate the safety and pulmonary distribution using mass spectrometry imaging. The immunogenicity and efficacy of the dry powder vaccine will be tested in animal models of Tuberculosis challenge.

**Supervisor:** Aneesh Thakur

### Design and investigation of nanoparticles for targeted delivery of small interfering RNA (siRNA)

**LPNs**

Small interfering RNA (siRNA) holds a promising therapeutic potential for treating a variety of diseases via gene silencing. However, the physicochemical properties of siRNA often limit its therapeutic efficacy rendering it unfavourable for efficient intracellular delivery. We have developed lipidoid-polymer hybrid nanoparticles (LPNs) and demonstrated safe and efficient intracellular delivery of siRNA. In this project, new generation of lipidoid-based LPNs will be evaluated for their transfection efficiency, safety, and therapeutic effect in animal models of acute inflammation.

**Supervisors:** Aneesh Thakur and You Xu

### Biomimetic surfactant phospholipid liposomes: Elucidating the effect of liposome surface charge and depot effect on pulmonary immunity

**Biomimetic liposomes**

The ability to induce airway mucosal immunity is an essential property of future subunit vaccines because several pathogens, *e.g.*, respiratory viruses, enter into the human body *via* the airways. It is well known that protection against these pathogens requires activation of the mucosal immune system, which can only be primed *via* mucosal vaccine administration. However, little is known about how to design safe nanoparticle-based subunit vaccines optimal for the induction of airway mucosal immunity. In this project, the requirement of surface charge and depot effect of liposomes will be evaluated in primary immune cells and animal models by incorporating pulmonary surfactant phospholipids and proteins in the formulations.

**Supervisor:** Aneesh Thakur

### Application procedure and dates

If you are interested in writing your thesis with the Vaccine Design and Delivery group, please write an email to [camilla.foged@sund.ku.dk](mailto:camilla.foged@sund.ku.dk) with more information about you. Places are given on a first come, first served basis.