Department of Drug Design and Pharmacology
Faculty of Health and Medical Sciences
University of Copenhagen

Master Thesis 2016 - 2017
Department of Drug Design and Pharmacology
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Dear Master's thesis student

The time is nearing when you have to decide on your Master Project. Maybe you have known for a long time in which area you want to do your project, maybe you enjoy several fields, and have not yet made up your mind. I hope you will find inspiration in this catalogue to help guide you to the right project. You are always welcome to speak to potential supervisors about a Master Project.

Please, note that as your thesis project is often part of a larger ongoing project, research in the coming 1 ½ year may lead to thesis-projects changing from the descriptions in this catalogue.

When you have made up your mind, it is a good idea to contact the supervisor to reserve a space, as each supervisor has a limited number of thesis-places. Sometimes you will have both a supervisor and a co-supervisor, who will guide and help you with your project.

You must also decide whether you want to do the project alone or together with another student. Consider the pros and cons for yourself. The supervisor can help advice you, as it will also depend on the nature of the project.

While being a Master student at Department of Drug Design and Pharmacology, you will be part of a research group/section and participate in various activities with the group. You will hopefully experience that you go from being a student to being a researcher – enjoying a stimulating and challenging work environment.

Best wishes

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Biostructural Research

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Master project: Within ionotropic glutamate receptors or nicotinic acetylcholine receptors

Are you interested in some of these research areas?

• Important receptors in our central nervous system and diseases such as Alzheimer’s disease and epilepsy
• How potential new drugs bind to the receptors
• Drug design and how receptor selectivity is achieved

Do you want to get experience with some of these methods?

• Recombinant expression of proteins in bacteria or insect cells
• Purification of proteins in mg amounts
• Determination of ligand binding affinities using isothermal titration calorimetry
• Determination and analysis of protein structures using X-ray crystallography and computer programs.

If yes, then a project within ionotropic glutamate receptors or nicotinic acetylcholine receptors is the right one for you.

You are always welcome to contact us and discuss possibilities. You will have great impact on the project and which methods you want to focus on. We can provide you with examples of previous master projects.

Titles of recent master projects:
• Expression and purification of the kainate receptor subunit GluK5 ligand binding domain
• Structural studies of acetylcholine binding protein as a model system for nicotinic acetylcholine receptors
• Structural basis for understanding the functional role of the ligand-binding-domain of the GluD2 receptor. Studies of the thermodynamic properties involved in the binding of D-serine to a novel GluD2-construct
• Investigations of the binding mode of the allosteric modulator NS1376 at the AMPA receptor GluA2

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The histone demethylase KDM5B (Kristensen et al., 2012) is known to be involved in several cellular processes including DNA repair (Li et al., 2014). It is also implicated in the development of several kinds of cancer and is therefore an important putative drug target (Højfeldt, Agger, & Helin, 2013).

It is a multidomain protein the comprise functionalities such as lysine demethylation (Yamane et al., 2007), post translationally modified lysine recognition (Klein et al., 2014; Zhang et al., 2014) and DNA binding (Tu et al., 2008). The domain structure is outlined below.

KDM5Bs ARID domain binds a known DNA motif and the CxxC domain has been shown to bind to unmethylated CpG islands. The PDH1 domain has been shown to bind to unmethylated H3K4 and the PHD3 domain has affinity for all methylation states of H3K4. Taken together it is likely that KDM5B has affinity of nucleosomes and other large complexes such as the NuRD complex. The structure of a putative KDM5B:nucleosome complex emphasizing PHD:H3K4 interactions and the NuRD complex is shown below.

The aim of the project is to study the structural background for the interplay between KDM5B and NuRD/nucleosomes. This will be sought achieved using transient expression of various components in HEK293 cells, followed by purifications and biophysical studies using Small Angle X-ray Scattering, Electron microscopy and protein crystallography.

Dependent on the length of the project it will be focused on specific components and involve expression, protein/complex purification and at least one biophysical technique.

References: See http://drug.ku.dk/teaching/bachelorormaster/biostructural-research/

Contact information: Professor Michael Gajhede, mig@sund.ku.dk
Computational Drug Design
Identify and optimise receptor ligands; Keys to physiological functions & drug design

Computational Drug Design Integrated With Experimental Studies
Our GPCR Computational Drug Design group, in the Biostructural Research Section builds computer 3D structure models that rationalise observed data and generate hypotheses for new ligand structures and experiments. Collaborators in the Medicinal Chemistry Section synthesise ligands and the Experimental Pharmacology Section provides in vitro pharmacological evaluation and performs functional studies in rodents.

Target-based methods
- Receptor structure modelling
- Receptor-ligand docking
- Virtual (compound) screening
- Structure-based optimisation
- Binding residue mutant design

Docking of a ligand into the binding site of a receptor target structure provides a model of their molecular interactions, guiding further medicinal chemistry optimisation and pharmacological validation by mutagenesis.

Ligand-based methods
- Conformation analyses
- Pharmacophore modelling
- Database searches for commercial ligand analogs
- Structure-activity relationships

Pharmacophore elements represent the ligand features important for target interaction, and are used to identify new ligands with other chemical structures.

Project 1: Identify Orphan Receptor Ligands; Keys to Physiological Functions

We use computational methods to identify, endogenous ligands (orange) that link the receptor to a physiological system, tool compounds (pink) for pharmacological characterisation, and G protein inhibitors (yellow) for dissection of intracellular signalling pathways.

Background: About Bone third of the human GPCRs are so called orphan receptors, meaning that their endogenous ligand (and function) is unknown. Recently, the Gloriam group received funding from EU and the Lundbeck Foundation, respectively, to launch 5- and 7-year projects to characterise orphan receptors from in silico to in vivo.

Significance: Characterisation of orphan receptors can unravel unknown physiological signalling systems and present new druggable targets, ligands and mechanisms.

Contact information: www.GloriamGroup.org or email david.gloriam@sund.ku.dk
Project 2: Optimise Serotonin Receptor Agonist Selectivity; Tracers for Disease and Drug Effects

Recently, two related serotonin receptor crystal structures were published. Now we can model the 5-HT$_{2A}$ receptor, and dock reference ligands. Ligand analogs can be designed to form new interactions with the receptor to increase selectivity.

**Background:** The serotonergic receptor, 5-HT$_{2A}$, is responsible for the effect of many psychedelics, such as LSD, and clinically targeted to treat schizophrenia and other psychoses, cluster headaches, and glaucoma.

**Significance:** Selective agonists can be used as tracers in brain imaging to monitor clinical conditions and drug effects.

**Contact information:** Read more at www.GloriamGroup.org or email david.gloriam@sund.ku.dk
Cytochromes P450 enzymes in Drug Metabolism and Cancer Therapy

Aim: To study how drugs compounds are metabolized by or inhibit cytochromes P450 (CYP) enzymes.

Background: In humans, CYP enzymes are involved in several different transformations, e.g. the elimination of drug compounds and the synthesis of hormones. The main function of CYP enzymes is to oxidize compounds.

Oxidation of Drug Compounds
CYP mediated drug metabolism of a new compound is important to consider, e.g. to understand potential toxic effects or bioavailability. Thus, it is important to understand what metabolites that the CYP enzymes generate.
It is very often difficult to predict what metabolites CYP generate (see figure, center, for an example). To help in this process our group has developed the SMARTCyp program, which can suggest the most likely CYP metabolites for a drug compound (Try it on: www.farma.ku.dk/smartcyp).

Involvement in Cancer
Cytochrome P450 enzyme are involved in the formation of several hormones and is therefore a potential drug target in cancer. Abiraterone (see figure, right) is an example of a marketed drug compound that is used in the treatment of prostate cancer. We have over the past years gained expertise in the design of compounds that inhibit CYP enzymes. We currently use these methods to design new inhibitors.
**MSc projects**

The student will get the opportunity to work with the newest approaches in computational chemistry or crystallography to rationalize *how drug compounds are metabolized* or to *design new inhibitors for cancer treatment*. Any combination of topic and method shown below can be applied to the project.

<table>
<thead>
<tr>
<th>Cytochrome P450 topic</th>
<th>Understanding of cytochrome P450 drug metabolism: What metabolites are generated</th>
<th>Design of new inhibitors of cytochrome P450 enzymes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods used in the project</strong></td>
<td>Methods in computational chemistry like docking, molecular dynamics, quantum mechanics</td>
<td>X-ray crystallography, testing of potential inhibitors in assays</td>
</tr>
</tbody>
</table>

**We can offer**

A research project with international collaborations, both in academia and industry. The group also develops the SMARTCyp software for predictions of CYP metabolism.

**Contact information:** Lars Olsen (lo@sund.ku.dk)
Protein fibrillering – strukturel indsigt som basis for nye lægemidler?

Problemstilling:
Proteineres struktur kan ændre sig på en meget uønsket måde, som får dem til at samles i meget store, smukke og symmetriske samlinger af 1000’r og atter 1000’r af proteiner, kaldet fibriller. Men hvor smukke de end er, så er de forbundet med et utal af uheldige omstændigheder: Sådanne fibriller spiller en central rolle i en stribe neurodegenerative sygdomme som f.eks. Alzheimers og Parkinson’s sygdom, og i den farmaceutiske industri er det et stort problem hvis proteinbaserede lægemidler fibrillerer, både fordi fibrillerne har tabt protein-aktiviteten, og fordi fibrillerne kan stimulere en uønsket immunologisk respons. Der er altså god grund til at ønske at forstå hvad det er der sker, når proteiner fibrillerer, så man kan udvikle inhibitorer af processen.

Lidt flere detaljer:


Konkrete projekter: Vi arbejder med alpha-synuclein (relateret til parkinsons og alzheimers), glucagon like peptide 2 (relateret til Chrons disease og osteoperose), insulin, og isolerede peptider fra bl.a. amylin (diabetes). Vi forsøger at forstå de konkrete strukturelle forandringer, samt den celle-toksiske effekt af systemerne.
**Din rolle:**

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Design of new anti-cancer ligands: interactions between epigallocatechin gallate from green tea and the protein G3BP

Green tea is known to have beneficial effects that help limit development of cancer; new research shows for the first time that the active compound, epigallocatechin gallate (EGCG), from the plant binds specifically to the protein G3BP [1]. Interestingly, this protein is an established marker, which is used diagnostically for early identification of certain types of cancer. Our recent research has focused on structural studies of isolated G3BP protein domains, and results from this work have been accepted for publication [2]. A former master's student, who scored 12 for his thesis, is co-author on the paper. However, EGCG binds the intact G3BP protein and the suggested project aims at structural studies of the complex and further binding studies as a basis for future design of novel anti-cancer drugs. A master’s study on this project may e.g. involve one or more of the following components:

1) Optimize purification of full-length G3BP. Redesign- and subcloning of available expression constructs may be required.
2) Robotassisted HTP-crystallization screening, optimization and production of crystals for data collection.
3) Ligand binding studies using Isothermal Titration Calorimetry (ITC)

References:

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Novel types of Peptidomimetic Foldamers

Foldamers are oligomeric organic compounds that mimic or complement the three-dimensional structures (folding) of biopolymers. Such compounds have potential as pharmaceuticals due to their non-biodegradable nature, compared to the parent biopolymers, such as peptides, proteins, oligonucleotides, or polysaccharides.

In the Olsen group, we have had a keen interest in peptidomimetic oligomers for a number of years,[1] and recently achieved the first high-resolution structures of a novel type of foldamers called β-peptoids.[2] These results provide a very strong foundation for further exploration of these structures with the aim of developing functional materials, multivalent display scaffolds, or well-defined compounds for disruption of protein–protein interactions for biomedical applications. Thus, projects in the laboratory within this area will involve design, synthesis, and evaluation of entirely unprecedented oligomeric structures with potential in drug discovery programs. The M.Sc. student will, among other techniques, be performing solution- and solid-phase synthesis as well as NMR- and CD-spectroscopy.

The figure above shows examples of peptidomimetic backbone architectures compared to the canonical α-peptides.


Contact information: Christian Adam Olsen, cao@sund.ku.dk
Epigenetics – Histone Deacetylase (HDAC) Inhibitors

Epigenetic mechanisms are important for temporal and tissue-specific regulation of DNA transcription in our different cell types. An example of an epigenetic modification is acetylation of ε-amino groups of lysine residues in histone proteins. Histones are the proteins onto which our DNA is packaged in the cell nuclei. Therefore, DNA transcription is indirectly affected by the extent of acetylation, and thus, modulation of the activities of the enzymes that regulate this acetylation is a powerful way of affecting transcription.

Interestingly, inhibition of HDAC enzymes have proven to have potential in cancer treatment, and four compounds targeting HDACs have been approved by the United States Food and Drug Administration thus far.

In the Olsen group, we explore several avenues towards inhibition of HDAC enzymes with the aim of developing novel chemical entities with improved selectivity profiles across the class of eleven different HDAC isoforms. We explore both novel chemical functionalities with potential to bind the Zn$^{2+}$ ion present in the enzyme catalytic site,[1] as well as more elaborate cyclic peptide-based structures that interact with the HDAC protein surface.[2,3] The projects in the laboratory within this area will involve design, synthesis, and enzymological evaluation of novel HDAC inhibitors. The M.Sc. student will, among other techniques, be performing solution- and solid-phase synthesis as well as enzymatic inhibition assays and enzyme kinetics.

The figure shows examples of cyclic peptide HDAC inhibitors (left) and an NMR structure with structure-activity relationship findings added (right).


Contact information: Christian Adam Olsen, cao@sund.ku.dk
3-in-1: A novel approach to study membrane protein pharmacology

Membrane proteins make up about 25% of all proteins encoded by the human genome and are considered major drug targets. One type of membrane protein, the family of ligand-gated ion channels (LGICs), mediates crucial functions in the nervous system and has been implicated in numerous diseases. Most LGICs are molecular assemblies of more than one subunit, but conventional methods to study these proteins cannot easily address the contribution of individual subunits within such a protein complex. Recent advances in the field of molecular biology and chemical biology now allow us to overcome this limitation by using of inteins, a family of self-splicing proteins, to link together individual subunits into one large protein containing all subunits required for full LGIC assembly and function. This will allow us to individually manipulate a defined number of subunits within LGIC complexes and therefore enable us to elucidate the function and pharmacology of these medically relevant proteins in unprecedented detail.

Fig 1: Left: Example of the structure of a trimeric LGIC with subunits indicated by different colors and the ligand shown in red; Right: cartoon illustrating the use of (split)inteins in order to create a trimeric protein in which a defined number of subunits can be individually manipulated

The development of such a cutting-edge approach will be broadly applicable to numerous types of proteins and will no doubt provide the foundation of many future studies in different fields.

The project will be carried out in the newly-established Center for Biopharmaceuticals, which provides state-of-the-art facilities and a very vibrant and international environment. The project will be supervised by Assoc. Prof. Stephan A. Pless (Stephan.pless@sund.ku.dk). For more information please contact us or visit our website: www.theplesslab.com
Atomic basis for binding of a novel epilepsy drug

Epilepsy is a highly common neurological disorder, affecting about 1% of the worldwide population. The disease is often caused by mutations in genes encoding for membrane proteins called ion channels. Retigabine, is a first-in-class drug targeting voltage-dependent potassium channels by acting as a channel opener. In close collaboration with groups in Canada and the US we have recently established the atomic contributions of the potassium channel to the interaction with retigabine (Kim et al., 2015, Nature Communications). However, it remains unclear which moiety of retigabine is crucial for the interaction with the channel. This project aims to use a series of retigabine analogues to perform a structure-activity relationship (SAR) study with regards to retigabine binding to potassium channels. The project will therefore include pharmacological components, as well as basic electrophysiological aspects and is expected to provide unprecedented insight into the novel and unique mechanism by which retigabine binds to potassium channels.

The project will be carried out in the newly-established Center for Biopharmaceuticals, which provides state-of-the-art facilities and a very vibrant and international environment. The project will be supervised by Assoc. Prof. Stephan A. Pless (Stephan.pless@sund.ku.dk). For more information please contact us or visit our website: www.theplesslab.com

Fig 1: Left: Hypothetical model of the potassium channel bound to retigabine; Right: Retigabine (top) and one of its analogues (bottom) containing a single-atom change (highlighted in red), as an example of a analogue that will be used to determine the atomic details of the drug-channel interaction.
Experimental Pharmacology

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Neurobiological basis for the pro-cognitive effect of nicotinic receptor ligands

One year master thesis project.
At the section for Experimental Pharmacology under the faculty of Health Sciences, University of Copenhagen we conduct research to better understand the neurobiological basis for brain function, particularly in relation to cognition.

Nicotinic receptors are important for several forms of memory as well as synaptic plasticity, and are accordingly being avidly pursued as molecular targets to treat cognitive dysfunction in diseases such as Alzheimer’s and schizophrenia (Thomsen et al. 2010, Curr Pharm Des).

The aim of the project is to study the molecular effects in the rodent brain after exposure to nicotinic ligands in combination with cognitive training paradigms.

The project will use affinity purification and Western blotting to look at nicotinic receptor levels and protein-protein interactions as well as other relevant molecular outputs. The project also involves setting up functional assays to assess the functionality of nicotinic receptors in the brain tissue.

The project will be conducted in collaboration with the medicinal company Lundbeck A/S, where another Master student will conduct the behavioural experiments from which the brain tissue for the present project will be obtained.

The project is intended to start as soon as possible. The project is intended as a Master thesis for students in Human or Molecular Biology, Biomedicine, Pharmacy or students with a similar background.

If interested, please send a motivated application letter, CV (including potential lab experience), recommendations, as well as a grade transcript to the following email address: morten.s.thomsen@sund.ku.dk

For further information please contact:
Morten Skøtt Thomsen
Associate Professor, Ph.D.
Molecular pharmacology

Molecular pharmacology is used to investigate cloned receptors and transporters, including their interaction with ligands and their molecular mechanism-of-action. Usually we apply a combination of techniques such as molecular biology (e.g. cloning and mutagenesis), cell culture and pharmacological assays (e.g. concentration-response curves and development of novel assays).

Pharmacological testing

Most receptors and transporters belong to families of targets for which the endogenous ligand activate several subtypes. For example, 24 glutamate receptors and 5 glutamate transporters have been identified. Therapeutically, it is often desired to only activate/inhibit one or few of the subtypes to e.g. avoid side-effects. By testing ligands on the receptor/transporter subtypes individually expressed in cell lines, it is possible to determine the potency, efficacy and subtype selectivity of the ligands, and thereby generate structure-activity-relationships. Such studies are performed in close collaboration with medicinal chemists and computational chemists to rationally generate subtype selective compounds with improved potency/selectivity for the target of interest.

Screening for new lead structures

For some targets it is desired to discover new lead structures which can then be developed into novel pharmacological tool compounds as described above. For these receptor/transporter targets we perform pharmacological screening of compound libraries using either a general library of diverse compounds available in the group or focused target libraries generated by e.g. chemogenomics or virtual screening. Such projects will typically involve optimization of pharmacological assays to enable high-throughput screening assays before actually engaging in the screening.
Investigations of binding sites and mechanism-of-action

Often it is of interest to get increased insight into the ligand binding site and mechanism-of-action. Combined with computational chemists we generate models of the binding sites and subsequently test these models by generation of mutations which are predicted to e.g. influence ligand binding or subtype selectivity. Such information can be applied to structure-based design of novel ligands with improved pharmacological properties. Along the same lines we investigate the mechanism-of-action of e.g. agonist induced receptor activation by introducing mutations predicted to influence receptor activation.

MSc project examples

• Pharmacological characterization of ligands on cloned receptors and transporters
• Screening of compound libraries for novel pharmacological lead structures
• Development of novel pharmacological assays
• Generation and characterization of mutated receptors and transporters

Please contact one of the supervisors to discuss more concrete projects possibilities. We also have a strong network with Danish companies and foreign universities and can facilitate projects outside University of Copenhagen.

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Pretargeted chemistry: Organic chemistry in man

Positron emission tomography (PET) companion diagnostic imaging can be used to select patients and monitor therapy. To date, there are no technologies available that allow for the direct in vivo monitoring of slow clearing targeting vectors as antibodies. These targeting vectors are crucial to diagnose or treat patients. Therefore, a possibility to follow the fate of these particles would help clinicians to tailor treatment.

This project aims to develop a technology that closes the aforementioned gap and develop a method for the direct in vivo monitoring of slow clearing targeting vectors. In this regard, a pretargeting approach will be applied that separates the targeting from the actual monitoring process. As a result, clinical acceptable patient radiation burden and a higher image quality will be achieved (Figure 1).

Pretargeted Chemistry Concept: A tagged nanomedicine such as a mAb is administered and allowed to bind to the target as the first step. Subsequently, a fast-clearing, short-lived radiolabeled imaging probe is administered. The imaging probe binds then to target-bound mAbs, enabling pretargeted imaging (Figure 1b). PET scan snapshots at multiple time points provide long-term imaging information. This strategy reduces the absorbed radiation dose resulting in a boost in target-blood ratios, as the nanomedicine can be imaged at a time point when the blood concentration of unbound nanomedicine has lowered to an acceptable level.

Requested qualifications:
- Organic chemistry basics
- Interest in evaluation studies
- Basics in pharmacokinetics
- Fun at interdisciplinary studies

This work is a part of a greater EU H2020 project located in Vienna, Mainz, Eindhoven and Copenhagen. The suitable candidate may have the possibility to stay abroad for a short timeframe.

Figure 1: a) Single-photon emission computed tomography (SPECT) images of a patient with a carcinoma in the left parotic region after the administration of a radiolabeled mAb ($^{186}$Re-bivatuzumab). The dark background and the contrast in the heart and in major blood vessels demonstrate the effect of a large amount of radioactivity circulating in blood up to 3 days post-mAb injection. This results in high patient radiation burden, which is limiting for approval by regulatory agencies. b) General scheme of a pretargeting in vivo click imaging approach. First step tumor pretargeting (days); second step pretargeted chemistry (hours). This approach circumvents the radionuclide dilemma, ultimately resulting in acceptable patient radiation doses and in a superior imaging contrast.

Contact information: Matthias Herth for further information (matthias.herth@sund.ku.dk)

Synthesis and defragmentation of known small-molecule Keap1 inhibitors.

About the Bach group: Our overall goal is to develop biological active small-molecule inhibitors against key CNS proteins involved in excitotoxicity and oxidative stress. We evaluate the ‘drug-gability’ of selected targets, and aim at developing new high-quality chemical probes useful for pharmacological studies and for identifying new therapeutic principles against ischemic stroke and related diseases.

‘Fragment-based drug discovery’ (FBDD) is a core theme of our research. We screen our library of fragments (i.e. small substructures of druglike molecules) using very sensitive biophysical methods, such as SPR and Ligand-based NMR. Promising and validated hits are optimized into lead molecules by medicinal chemistry and biostructural studies.

The Project - Background: Low levels of reactive oxygen species (ROS) are produced during cellular homeostasis, but are easily neutralized by endogenous antioxidants. However, during an ischemic stroke the levels of ROS exceed the capacity of these endogenous defence molecules resulting in oxidative stress. The transcription factor nuclear erythroid-related factor 2 (Nrf2) induces transcription of antioxidant response elements, but is neutralized by the regulator protein Keap1. Inhibition of the Keap1/Nrf2 protein-protein interaction leads to translocation of Nrf2 from the cytosol to the nucleus forming a transcription factor complex that induces expression of detoxifying antioxidant enzymes and thus protects the brain against ischemic stroke and related diseases. Existing Keap1/Nrf2 inhibitors are often covalent inhibitors (e.g. dimethyl fumarate, Tecfidera®), with the inherent risk of off-target effects. A few non-covalent Keap1 inhibitors now exist, but they are often low potent and/or do not enter the brain.

a) Oxidative stress inhibits the Keap1-Nrf2 interaction leading to nucleus-translocation of Nrf2 and transcription of antioxidant enzymes.

b) Non-covalent Keap1 inhibitors (examples).
**Project Aims:** The goals of this project are: 1) Synthesize known non-covalent inhibitors of Keap1; 2) Defragment known inhibitors, i.e. split the larger inhibitors into fragments, in order to evaluate the binding efficiency of these.

- The results from this project will lead to useful tool compounds for establishing future screening assays in the group, and facilitate further structure-activity relationship (SAR) studies and discoveries of novel non-covalent Keap1 inhibitors.

**Notes:** As a Master student you will be part of the ongoing research at the actual stage for the start of the master project, guided by a post doc or PhD student involved in the project. For the student the present project will involve literature study, experimental organic synthesis, spectroscopic characterization and structure-activity studies. Furthermore, the molecular pharmacology and computer modeling relevant for the project can be followed.

**Contact information:** For further information, please contact Anders Bach, anders.bach@sund.ku.dk, +45 21288604.
MSc Project in Medicinal Chemistry

Q: Are you interested in organic / medicinal chemistry?
A: Join us to uncover the diseases of the brain!

Q: Why target the glutamatergic neurotransmitter system?
A: The neurotransmitter glutamate (Glu) is involved in important neuro-physiological processes such as memory and learning, motor functions, and neural plasticity and development. Therefore, it is believed that brain diseases such as Alzheimer’s disease, Huntington’s disease, amyotrophic lateral sclerosis, epilepsy, depression, anxiety, schizophrenia and cerebral stroke may be directly related to disordered glutamatergic neurotransmission. To study the detailed function of the Glu receptors and transporters, we develop subtype selective ligands. In collaboration with pharmacologists our synthesized compounds are investigated carefully both in-vitro and in-vivo.

Contact the Chemical Neuroscience Group at:
lebu@sund.ku.dk - Lennart Bunch
drug.ku.dk/research/mcr/chemical_neuroscience_group

Department of Drug Design and Pharmacology
Faculty of Health and Medical Sciences University of Copenhagen Denmark

Info:
Duration: 30-60 ECTS points
Start: As agreed to

Project outline:
Retro-synthetic analysis
Literature study
Experimental organic chemistry
Report writing / publication
Unraveling the γ-hydroxybutyric acid (GHB) high affinity binding site: Is it just Fantasy...

γ-Hydroxybutyric acid (GHB) is a neuromodulator working alongside the main inhibitory neurotransmitter -aminobutyric acid (GABA) in the brain. GHB is also a prescribed drug (XyremTM) for treatment of narcolepsy and alcoholism (AlcoverTM). In yet another situation GHB is a drug of abuse known as a “date rape drug” or “Fantasy”. In spite of GHB being a prescribed drug, the specific neuropharmacological actions remain to be elucidated. GHB have both low- and high-affinity binding sites and whereas the GABAB receptor, representing the low-affinity site, is well characterized for mediating several actions of GHB, major functional roles of GHB seem to be related to specific high-affinity sites. The molecular identities of the high-affinity sites have for long been under investigation without success. Recently a distinct population of extrasynaptic GABA receptors was identified as a high affinity target for GHB. These findings provide a unique base for further investigations and advancements in the GHB field.

The aim of the overall project is to clarify the localization of this binding site, and understand in detail the architecture and mode of action of GHB at relevant extrasynaptic GABA receptors, which could lead to the basis for potential GHB-antidotes and drugs.

This project will cover design and synthesis of potential selective ligands to be used for exploring the architecture and function of the identified binding site. The ligands will cover ligands for structure-activity studies but also labeling ligands, such as fluorescent and photoaffinity. These studies are done in close collaboration with colleagues mastering molecular modelling and molecular pharmacology at The Department of Drug Design and Pharmacology.


As a Master student you will be part of the ongoing research at the actual stage for the start of the master project, guided by a post doc or PhD student involved in the project. For the student the present project will involve literature study, experimental organic synthesis, spectroscopic characterisation and structure-activity studies. Furthermore, the molecular pharmacology and computer modelling relevant for the project can be followed.

For further information, please contact Bente Frølund, bfr@sund.ku.dk, build. 30, room 203
Neuropharmacological investigations of $\text{GABA}_\text{A/C}$ receptors and ligands.

**Background**

GABA is the most important inhibitory neurotransmitter in the central nervous system, and disorders of the GABAergic neurotransmission are presumably important in a number of neurological and psychiatric diseases. GABA released from nerve terminals gives rise to high (mM) but brief (ms) local, synaptic concentration transients which, at further distance from the release site, gradually evolves into low but sustained or slowly varying extrasynaptic concentrations. Both synaptic and extrasynaptic GABA receptors are adapted to respond reliably to the GABA concentration profile which they are exposed to.

**Topics for investigation**

The ability of ligands for GABA receptors to selectively interact with synaptic or extrasynaptic GABA neurotransmission in different brain structures is essential for their in vivo pharmacological profile. In order to contribute to development of such ligands, we study model compounds with affinity for the ionotrophic GABA receptors involved. Functional selectivity depends on the interaction between ligands and receptor but also (especially for orthosteric ligands) on the interplay with the local GABA concentration profile. To investigate and understand these mechanisms, it is necessary to take kinetic aspects into account.

**Methods**

Using patch-clamp electrophysiology, we study the kinetics of interaction of orthosteric ligands with recombinant $\text{GABA}_\text{A}$ and $\text{GABA}_\text{C}$ receptor subtypes expressed in cell lines, including the interplay with different GABA concentration-time profiles relevant for synaptic and extrasynaptic receptors. We use kinetic (computer) modelling of ligand-receptor interactions to analyze and interpret the experimental data as well as to suggest further relevant experiments. Finally, we use electrophysiology in brain slices to investigate how ligands affect synaptic and extrasynaptic neurotransmission in functional neuronal networks and to improve our basic understanding of the mechanisms involved.

A suitable project for a master thesis could be based on patch-clamp studies in recombinant receptors, and/or kinetic modelling. Depending on preliminary results and the time available, further techniques may be involved.

**Contact information:**

Uffe Kristiansen,  
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Structure-based medicinal chemistry towards subtype-selective kainate receptor ligands

Why? The GluK2 and GluK3 kainate-type subunits are two out of more than ten ionotropic glutamate receptor subunits present in the brain. It is well known that glutamate receptors play an important physiological role and also are implicated in a long list of neurological diseases currently without optimal treatment. But not much is known about the physiological functions and the therapeutic potential of GluK2- and GluK3-containing receptors. In order to study the function of such receptors there is a need for compounds selectively blocking GluK2- and GluK3-containing receptors. This is what we would like to come up with. Would you like to be a part in this?

Structure-based design
When we decide which target compounds would be interesting/relevant to synthesize in your project, we combine 1) structural information, such as X-ray structures of the agonist binding site of a glutamate receptors co-crystallized with an antagonist (see the above model), 2) molecular modelling studies and 3) available structure-affinity relationships (SAR). Depending on your background and interest it might be relevant for you to carry out the design yourself. Design your target compounds on a rational basis?

Organic synthesis
Selected target compounds will be synthesized. We aim for simple and convergent retrosynthesis strategies that allows us to easily introduce different substitutents late in the syntheses. Would you like to spend time in the lab trying to make the syntheses work? And to purify and characterize the isolated products using NMR- and MS-techniques?

Examples of lead structures

<table>
<thead>
<tr>
<th>R</th>
<th>Native AMPA*</th>
<th>GluK1</th>
<th>GluK2 §</th>
<th>GluK2*</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>0.95</td>
<td>0.15</td>
<td>-</td>
<td>0.33</td>
</tr>
<tr>
<td>o-OH</td>
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<td>0.62</td>
<td>-</td>
<td>0.09</td>
</tr>
<tr>
<td>m-OH</td>
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<td>0.52</td>
<td>-</td>
<td>0.10</td>
</tr>
<tr>
<td>p-OH</td>
<td>2.1</td>
<td>2.1</td>
<td>-</td>
<td>0.56</td>
</tr>
</tbody>
</table>

Pharmacology and structure-activity relationship
When the target compounds are synthesized they will be evaluated pharmacologically in house and by our collaborators. Your contribution will expand the SAR and hopefully disclose how subunit selectivity can be controlled.

*: Ki values in μM obtained in receptor binding studies
§: not yet tested

Type of projects available
It will be possible to set up exciting Master thesis projects as well as projects for bachelor students or international exchange students.

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Molecular and Cellular Pharmacology

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Studies of disease pathways and potential drug targets in chronic inflammatory diseases

Chronic inflammatory diseases, like Rheumatoid Arthritis (inflammation in joints) and Multiple Sclerosis (inflammation in CNS), are autoimmune diseases where the immune system attacks the organisms’ own tissue. It is still not known why these diseases develop, and why specific organs are affected, but both genetic and environmental factors are important.

From genetic studies we have recently identified two proteins linked to development of disease in an experimental model for Rheumatoid Arthritis (Collagen Induced Arthritis). The proteins are transcription factors and are believed to be involved in bone remodeling, but potentially also in regulation of immune cell activity.

In a model for Multiple Sclerosis (Experimental Autoimmune Encephalomyelitis), we are studying a specific tyrosine kinase, which is important for activities of the cytoskeleton, in addition to expression of cell surface adhesion molecules.

The aim of these projects is to understand how the proteins described above are parts in the pathology of disease and whether any of the molecules could be used as drug target for treatment of autoimmune diseases.

Methods:
- Experimental mouse models
- Western Blotting and Real Time PCR for gene expression
- In vitro immune assays for activation of lymphocytes/macrophages
- Flow cytometry for studies of immune cell populations
- Bone assays (development of osteoclasts and osteoblasts)
- DNA sequencing, gene typing, to reveal genetic differences
- Bioinformatics to predict consequences of genetic polymorphisms
- Immunohistochemistry

For further information, please contact Åsa Andersson, (asa.andersson@sund.ku.dk)
Section for Molecular and Cellular Pharmacology.
The NeuroMet group - www.neuromet.dk

The mammalian brain has a high energy demand and consumes glucose as the main energy substrate. Neurons are the major consumers of glucose due to the cost of electrical activity. Besides neurons, the brain consists of a mixture of glial cells such as oligodendrocytes, microglial and astrocytes, all of which are involved in protection of the neurons and maintaining brain homeostasis. Particularly astrocytes are unique in their functional ability to support neuronal metabolism and neurotransmission by providing essential substrates to the neurons. This astrocyte-neuron relationship has been extensively studied in the NeuroMet group both under healthy and diseased conditions.

Hypometabolism in early Alzheimer’s disease (The MetAD project)

Alzheimer’s disease (AD) is the most common form of dementia accounting for over 50% of all dementia cases in the western world. It is a neurodegenerative disorder characterized by neuro-pathological changes and progressive cognitive decline. One of the earliest changes is the decline in brain glucose uptake which can be observed several decades before the first cognitive symptoms appear. Changes in expression and regulation of key enzymes in glucose metabolism and mitochondrial dysfunction contribute to the reduction in cerebral glucose metabolism. Due to its early nature, glucose hypometabolism has in recent years been proposed as a critical contributor to the pathogenesis of AD.

In the NeuroMet group we are currently investigating this early AD related brain hypometabolism using an AD mouse model and AD patient derived stem cells differentiated into neurons and astrocytes. We are overexpressing the astrocyte specific enzyme pyruvate carboxylase (PC) in both models thereby improving the oxidative capacity of astrocytes. Due to the tight metabolic relationship between astrocytes and neurons this will lead to an improved neuronal metabolism.

Our aim is to provide evidence that improving neuronal metabolism early in the course of AD we can delay the progression of the disease.

Master of Science projects

As a master’s student on the MetAD project you will be working with mapping of the metabolic differences between control and disease model using either the differentiated stem cells or tissue from the AD mouse model. Moreover, you will be involved in generating models overexpressing PC and determine the metabolic effect of this overexpressing.

Methods

You will be using ex-vivo $^{13}$C $^{1}$H nuclear magnetic resonance spectroscopy and mass spectrometry in the mapping of metabolic pathways in the mouse model and in the differentiated stem cells. Furthermore, mitochondrial function is determined using Seahorse Extracellular Flux Analyzer. HPLC and GC are routinely used combined with biochemical assays, protein biochemistry, molecular biology and fluorescence-based assays and imaging techniques.

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Natural Product Research

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High-resolution bioassays coupled with HPLC-HRMS-SPE-NMR for identification of T2D drugs and/or antimicrobials from natural sources

Copenhagen Small-Molecule NMR Center houses state-of-the-art NMR equipment for hyphenated HPLC-HRMS-SPE-NMR experiments (left-hand figure below) – and we are leading experts in high-resolution bioassays coupled with HPLC-HRMS-SPE-NMR (left-hand figure above).

A typical project will involve:
• Collection of plants, seaweed, fungi, etc - followed by extraction of bioactive metabolites
• High-resolution screening and HPLC-HRMS-SPE-NMR analysis of bioactive constituents
• Structure elucidation and pharmacological characterization of active molecules

Peptidomics – new bioactive peptides from nature
Peptides are recognized as important drug leads, and plants and animals have developed a variety of different peptides as toxins and signaling molecules. Peptidomics is a new discipline that aims at exploring the chemical and pharmacological properties of the peptidome, e.g., the low molecular mass subset of the proteome.

A typical project will involve:
• Collection of plants, fungi, insects, etc - followed by development of peptide extraction methods
• Screening for bioactive peptides followed by isolation and structure elucidation

Antidiabetic and antimicrobial properties of plants and their endophytic metabolites
Endophytes are microorganisms living within plants without having any negative effects on the host. Endophytes constitute a rich source of new bioactive drug leads, and endophytes can be isolated and cultured in large scale as a sustainable production platform for bioactive molecules.
A typical project will involve:

- Collection and surface sterilization of plant material followed by brushing on growth media
- Isolation and characterization of the endophytic microorganisms
- Assessment of optimal growth conditions for production of bioactive metabolites
- Isolation and structure elucidation of bioactive metabolites

Contact information: Professor Dan Stærk, ds@sund.ku.dk
Herbal products for management of type-2 diabetes?

PEOPLE AND PLANT MEDICINE PROGRAMME
Natural Products Research

Type-2 diabetes
More than half a million people in Denmark have type-2 diabetes. 750 000 others have pre-diabetes. It is thus a big health problem in our country. To a degree it is possible to control type-2 diabetes with exercise and diet, but medication might be necessary to control the disease. We want to develop herbal products for management of type-2 diabetes. Many plants are used around the world for treatment of diabetes. We will evaluate these plants and find the best that really work. Our goal is to develop products for the Danish market.

Targets
Type-2 diabetes is a complex disease with several drug targets: The pancreatic digestive enzymes, α-glucosidase and α-amylase. Inhibition of these enzymes slows the absorption of glucose from the food preventing a peak in blood glucose after a meal. GLP-1 signals to the pancreas to release more insulin. DPP-IV is an enzyme, which converts GLP-1. Inhibition of DPP-IV thus increases the level of GLP-1. Insulin sensitivity and insulin uptake are other therapeutic options. About 30 % of the glucose excreted in the urine is reabsorbed in the kidneys. If we can inhibit the SLGT-2 sodium/glucose transporter, we can lower the blood glucose.

T2D Pharmacology platform
We are expanding our assays to cover the drug targets of type-2 diabetes. It might be possible to do in vivo testing as well. Structure elucidation of active compounds is done in collaboration with the NMR-group. For certain assays it might be possible to use HPLC-SPE-NMR-HRBioassay.

Types of project
Your project could be:
Testing of plant extracts (from all over the world) for activity, and identification of the active compounds.
You could also work on the implementation of a new assay.
In many of the projects you will be linking up with a PhD-student.

Contact information: Anna K Jäger, anna.jager@sund.ku.dk
or come to my office, room 038 on the ground floor of Building 30.
You are always welcome – it might be clever to make an appointment
Specialeprojekter hos Prof. John Nielsen

Proteomimetics and bioactive peptoids
Making analogues of amino acids, peptides and proteins. Small-molecule mimetics.

UC2016: Changing the World
Synthesis and function of bioactive compounds targeting ATPases (antifungal targets)

IMI – New Drugs for Bad Bugs
Yeah, we need new drugs now!! Come help us make them ;)

Innovation, Technology and New Methodologies
New synthetic methods, new technology in synthesis and screening and innovation in academic research

Contact information: Professor John Nielsen, john.nielsen@sund.ku.dk
Optimization studies of biologically active peptides and peptidomimetics

Introduction to AMPs: Multidrug-resistant bacteria constitute an increasing world-wide problem, and therefore a major challenge for the pharmaceutical industry is to develop novel therapeutic antibiotics and device efficient systems for their delivery. Antimicrobial peptides (AMPs) and peptidomimetics constitute potential antibacterial drug leads with the advantage that they possess reduced tendency toward resistance development. Peptidomimetics incorporating unnatural residues in the amino acid sequence exhibit enhanced stability towards enzymatic degradation and display lower toxicity than natural AMPs. Below projects related to this challenge are described:

Synergy of AMPs and peptidomimetics: Possible synergy between AMPs, peptidomimetics and/or conventional antibiotics will be investigated, e.g. for E. coli. Here, design and solid-phase peptide synthesis (SPPS) of an array of AMPs and peptidomimetics will be followed by investigation of stability and evaluation of activity with focus on detecting synergistic effects.

Antimicrobial nanomedicine: Focus will be design and synthesis of an array of AMPs followed by formulation of these into a drug delivery system intended for preventing or treating infections. The aim is to understand the mechanisms of interaction with and transport through eukaryotic and/or prokaryotic cell membranes by using either bacterial or human cell culture models as well as model vesicle lipid bilayers mimicking either bacterial or human membranes. The methods applied also comprise calorimetry and different types of microscopy.

Modulation of inflammation: Sepsis, an infection-induced inflammatory syndrome, is the most common life-threatening complication in patients admitted to intensive care units. Besides exerting direct antimicrobial effects some host-defense peptides (HDPs) also modulate the host immune system by affecting release of pro- and anti-inflammatory factors as well as of reactive oxygen species (ROS). Thus, the concept of modulation of the innate immune system by peptides is a well-known natural regulatory process that may be exploited as a non-antibiotic strategy for enhancing clearance of bacteria and/or limiting dangerous inflammation. Based on our mimics of HDPs that exert potent immunomodulatory activities, e.g. via formylpeptide receptors (FPPs) on neutrophils, a number of analogues will be designed and synthesized (and maybe tested in collaboration with Swedish partners in extended projects).

Introduction to CPPs: Certain peptides enable transport of therapeutic peptides or even large macromolecules and particles (delivery systems) across cell membranes. These are known as cell-penetrating peptides (CPPs).

Cell-penetrating peptides for drug delivery: The present project concerns the exploitation of CPPs to achieve transmembrane delivery of e.g. antibacterials, and it involves design and solid-phase synthesis (SPPS) of a small library of atom-labelled CPPs followed by synergistic and mechanistic studies of the interaction between these CPPs and cell membranes. This include quantitation of uptake as well as qualitative methods (e.g. confocal microscopy) to determine the localization of CPPs within the cells. In addition, stability towards enzymatic degradation and toxicity studies may be included.
Contact information:

**Supervisor:** Henrik Franzyk, henrik.franzyk@sund.ku.dk (ILF)

**Co-supervisor(s):** Anna K. Jäger, anna.jager@sund.ku.dk (ILF), Dan Stærk, ds@sund.ku.dk (ILF), or Hanne M. Nielsen, hanne.morck@sund.ku.dk (IF)
Udvikling af peptid-baseret antibiotika

Antimikrobielle peptider produceres af alle levende organismer som en del af naturen’s egen første forsvarslinje mod sygdomsfremkaldende mikroorganismer. Der kendes over 1000 naturligt forekommende antimikrobielle peptider, isoleret fra bl.a. pattedyr, amfibier, insekter og planter. I modsætning til traditionelle antibiotika, som blokerer en biokemisk proces inde i cellen, ødelægger antimikrobielle peptider bakteriens cellemembran indenfor få minutter.

Indenfor de sidste par år har der været en stigende interesse i antimikrobielle peptider, pga. af deres mulige terapeutiske anvendelse. Der er dog tre problemer med antimikrobielle peptider: kort halveringstid, toksicitet og pris.

Tidligere har vi identificeret peptid-baserede forbindelser med rigtig god antimikrobiel aktivitet mod klinisk relevante bakterier.


![Figur: Peptider og Peptoider]

Målet er at komme frem til en kandidat med god antibakteriel aktivitet og lav aktivitet overfor røde blodlegemer.

Det eksperimentielle specialearbejde vil gå ud på følgende:
1. Design og syntese af nye active antibakterielle peptidanaloger ved fast-fase peptidsyntese
2. Peptiderne karakteriseres ved analytisk HPLC og MALDI-TOF MS/LC-MS
3. Analoger der ikke er > 95% rene oprenses ved præparativ HPLC
4. Du tester den antimikrobielle aktivitet af analogerne i samarbejde med vores partnere i Danish Centre for Antibiotic Research and Development.
5. Den hæmolitiske aktivitet testes overfor røde blod celler.

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Pharmacotherapy

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Master Thesis  Project 2017 – Example of an Translational Pharmacotherapy Project

The research within Pharmacotherapy is focused on optimisation of drug therapy with regard to safety and effectiveness of drugs at the individual patient level.

The Pharmacotherapy section consists of three research groups: Clinical Pharmacy, Pharmacometrics and Metabolomics. The following project is an example of a project which includes elements from all groups: Clinical practice, PK-modelling and drug analyses.

Title: Vancomycin therapy in critically ill patients:

Hypothesis: The hypothesis is that including a pharmacist (who has a thorough understanding of pharmacokinetics) in the team will improve the outcome of the dose adjustment procedure, further including a population PK-model in the dose-adjustment procedure, will support tailoring the dose to the individual patient, leading to improved therapy.

Objective: The overall objective is to improve vancomycin therapy in the critically ill by introducing pharmacist assisted Therapeutic Drug Monitoring (TDM).

Aims:
1. Building a population PK model of vancomycin in critically ill patients based on own data and data from literature.
2. Elaboration of a new pharmacist assisted TDM procedures.
3. Implementation of the procedure.
4. Evaluation of the therapeutic outcome (approximated as serum concentration of vancomycin within the recommended range) before, during and after implementation.

Background: Results from observational studies on vancomycin therapy at the ICU 4131, Copenhagen University Hospital, have shown that vancomycin therapy is not optimal. Implementation of new practical procedures and new dose regimen in order to improve the therapy resulted in improvement of the precision of the practical procedures; however the therapeutic outcome judged by the proportion of measured vancomycin concentrations being within the recommended range worsened. Proportion of vancomycin concentrations within the recommended range decreased from 35% to 29%, and the proportion of sub-therapeutic concentrations increased from 40% to 46%. The proportion of vancomycin concentrations higher than the recommended max concentration remained constant at 25%. Since the new procedures included an increase in dose and the precision of the blood sampling and dosing procedures increased, the most probable explanation of the negative outcome is that the dose-adjustments were not adequately performed.

Content: A population PK model of vancomycin in critically ill patients will be constructed using data from literature – the model will be updated and thus improved regularly during the project with incoming results.
Based on the experience from the previous observational studies and the daily routines at the ICU a new TDM procedure for vancomycin will be developed. The work will include a review of 1) all practical single steps in the TDM procedure such as timing of dosing timing of blood sampling, 2) pharmacological aspects such as choice of dosing schedule (once daily vs. twice daily, infusion period), size of loading - and maintenance dose, choice of recommended range for vancomycin serum concentrations and 3) development of guidelines for dose-adjustments based on measured vancomycin serum concentrations.

Before during and after the implementation the therapeutic outcome (approximated as serum concentration of vancomycin within the recommended range) and the precision of the practical procedures will be evaluated. Evaluation during the implementation process will be performed using the PDSA method in order to be able to fine-tune the single steps of the TDM process.

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Master Thesis Project 2017 - Clinical Pharmacy/ Patient Oriented Pharmaceutics

Clinical pharmacy is defined as the area of pharmacy concerned with the science and practice of rational pharmacotherapy, with focus on the patient and society.

Research within the area is focused on elucidating factors affecting the patients' individual response drugs, with the aim of optimizing the individual patient treatment and safety by ensuring that drugs are given in the right dose, in the optimal formulation, at the right time to the right patient, in order to achieve the desired therapeutic effect without occurrence of side-effects and using the fewest possible resources.

Projects will be focused on:

• Optimisation of practical procedures related to prescription, dispensing and administration. Either with focus on improving the pharmacological treatment on improving therapy by adjustments and optimization of treatment, guidelines, procedures. These projects will be conducted in close collaboration with healthcare professionals or researchers at universities
• Evaluation of Clinical Trial Methodology. The projects will be conducted in close collaboration with clinical researchers at hospitals or with the medical industry or contract research organisations (CROs)

In order to be enrolled in a project involving patient contact, the students are normally required to have full command of the Danish language

Examples of recent projects:

• A clinical perspective of chronic non-malignant pain at a Danish multidisciplinary pain center; Clinical characteristics, treatment outcome and economic costs.
• Optimisation of the systemic vancomycin therapy in the critically ill patient
• Description of the opioid-laxative therapy at Nordsjaelands Hospital, Hillerød
• Method to obtain medication history and medicine review at an orthopaedic ward
• Influences on the pharmacokinetics of transdermal fentanyl in chronic cancer pain patients; a study of CYP3A4*22, CYP3A5*3 and other non-genetic factors relation to the observed variability
• Possible discrepancies between the current drug development processes and the Market access needs
• Risk-Based Monitoring; Implementation of Risk-based Approaches in a First-in-Human Study
• Investigating Focus and Outcome of Monitoring at a Study Site in Denmark
• Consistency between protocols and publications of Danish academic clinical drug trials

Examples of possible projects in 2017 are given in a table on the homepage: http://drug.ku.dk/teaching/bachelorormaster/pharmacotherapy/

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Pharmacotherapy

The Pharmacotherapy group conducts research which generates, disseminates, and applies new knowledge that optimizes drug therapy.

Main area is within:

Translational Pain Research

The success of molecular biology and the new tools derived from molecular genetics have revolutionized pain research and its translation to therapeutic effectiveness. Bringing together recent advances in modern neuroscience Translational Pain Research covers the progress made toward bringing laboratory science to our understanding of pain phenomena in humans with the ultimate goal of providing optimal and safe drug treatments for promoting patient health.

The research focus is to improve the pharmacological and therapeutic properties of different analgesics to provide optimal and safe drug treatments. Research focuses on the influence of administration routes and delivery systems on the pharmacokinetic fate and pharmacodynamic behavior of analgesics in adults and children.

Examples of previous and current projects:

- Do polymorphisms in genes have an impact on morphine analgesia? A study conducted in paediatric cancer patients.
- Procedure-related pain in children in a Danish University hospital.
- Parents’ management of drugs in pediatric cancer outpatients.
- Structured interventions for management of pain following day-surgery in children.

Partners in Co-operation

All research projects are conducted in close co-operation with national as well as international researchers at other Universities and University Hospitals. At the moment we collaborate with Copenhagen University Hospital Rigshospitalet; Bispebjerg Frederiksberg University Hospital; Copenhagen University Hospital Herlev Gentofte in Denmark and University College Cork in Ireland.

Contact information: Janne Rømsing, jr@sund.ku.dk
Multi-dimensional data analysis and pattern recognition in pharmacology

On a daily basis critical decisions need to be taken with regard to pharmaco-therapeutic strategies in very complex patient disease situations. These decisions are taken on the basis of a vast amount of individual patient data that is available, ranging from biomarker information to metric or categorical physiological data. Still only few individual parameters are used as primary targets and guidelines for pharmacological intervention. Research in our group aims at developing and validating new computational methods that use all existing patient data to create specific disease profiles or patterns. It is hypothesised that these methods will be able to form clusters of subpopulations of patients and associations between different parameters that can be used to classify new patients, predict patient outcome and propose dosing strategy. The methods that will be used are, amongst others, correlation matrix analysis and machine learning methods (neural fuzzy network, genetic algorithm). Future projects may be in collaboration with industry or clinical centres (Novo Nordisk, Fertility clinic, Rigshospitalet; Clinical pharmacology/toxicology, Bispebjerg Hospital).

Figure 1 Example of a differential functional network of mice treated with Angiotensin II, showing significant co-segregation (edges) of parameters (nodes) with correlation coefficients in red

Example thesis title:
“Functional network and correlation matrix method for advanced data analysis. Applied to an animal study”
“Development of Novel Computational Methods in Systems Pharmacology”

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Population pharmacokinetic/pharmacodynamic (PK/PD) modelling

Describing the plasma concentration-time profile (pharmacokinetics, PK) and understanding the quantitative link to therapeutic response (PK/PD) of a drug is of paramount importance for selection of the optimal dosage and frequency to treat patients and minimise unwanted adverse events.

PK/PD modelling (also referred to as pharmacometrics or quantitative pharmacology) is the science of developing simplified computer-based models that provide useful mechanistic understanding of the processes involved in drug disposition and corresponding therapeutic effect. An example is shown in the figure below where we sought to find the optimal dose combination of gabapentin and morphine to treat postoperative pain.

Population PK/PD modelling is an alternative to conventional statistical analysis, that allows for an analysis of the differences in therapeutic response that are observed between individuals in addition to prediction of study trial outcome with different dosage regiments. This makes PK/PD modelling a strong analytical tool that plays a growing role in drug research & development in the pharmaceutical industry and in planning and execution of clinical studies.

An example of a current project available: Human experimental pain models and analgesic effects

Opioid analgesia can be explored with quantitative sensory testing (QST) and more objective assessments as EEG recordings of brain activity. However, the relation between these different dynamic measures is still not well understood. Thus, we want to look in to drug effects on several pain metrics by using PKPD modeling. This project is done as a collaboration between University of Copenhagen, Aalborg Hospital and University of South Australia.
Other projects are available within projects where we have collaborations with Rigshospitalet, Bispebjerg Hospital, Mech-Sense Centeret Aalborg Sygehus, Australian Centre for Pharmacometrics at University of South Australia, Lundbeck or NovoNordisk.

Examples of previous Master Student projects:
- Investigation of synergistic effects of morphine and gabapentin in a model of postoperative pain in the rat, 2014
- Determination of gastric emptying and small intestine transit time in dogs by paracetamol and sulfapyridine absorption modelling using nonlinear mixed-effects pharmacokinetics. Collaboration with NovoNordisk 2014
- Population modeling of the analgesic and antihyperalgesic effects of buprenorphine, 2015
- Modelling on Effect of High-dose Target-controlled Naloxone Infusion on Pain and Hyperalgesia in Patients following Groin-Hernia-Repair, ongoing 2015-16

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